The Handbook of Peri-Operative Medicines

This Handbook has been supported and funded by:





The Handbook of Peri-Operative Medicines

This handbook was developed and project managed by Sophie Blow, Advanced Clinical Pharmacist at St James' University Hospital, Leeds Teaching Hospitals NHS Trust.

The project steering group comprised Richard Adams (Rotherham NHS Foundation Trust), Katharina Floss (Oxford University Hospitals NHS Foundation Trust), Claire Frank (Betsi Cadwaladr University Health Board) and Sukeshi Makhecha (Royal Brompton & Harefield NHS Foundation Trust).

The project was funded by the UK Clinical Pharmacy Association (www.ukcpa.org).

The information contained in this Handbook has been compiled by surgical pharmacists from across the United Kingdom, all of whom are members of the UKCPA Surgery & Theatres Group.

List of contributors

Richard Adams Rotherham NHS Foundation Trust Azhar Ahmed City Hospitals Sunderland NHS Foundation Trust Assana Assadi Haghi St George's University Hospitals NHS Foundation Trust Neetu Bansal Central Manchester University Hospitals NHS Foundation Trust Leeds Teaching Hospitals NHS Trust Sophie Blow Lindes Callejas-Diaz City Hospitals Sunderland NHS Foundation Trust Vicki Caton Southport and Ormskirk Hospital NHS Trust **Kiranjeet Dhillon** Northampton General Hospital NHS Trust Robert Elliot-Cooke Royal Free London Hospital NHS Foundation Trust Katharina Floss Oxford University Hospitals NHS Foundation Trust Claire Frank Betsi Cadwaladr University Health Board Louise Graham University Hospital Southampton NHS Foundation Trust Andrew Green Newcastle Upon Tyne Hospitals NHS Foundation Trust Lynne Harris County Durham and Darlington NHS Foundation Trust Marium Javed Heart of England NHS Foundation Trust Alanna Johnston Kings college Hospital NHS Trust Zainab Khanbhai Royal Brompton & Harefield NHS Foundation Trust Kate Lawson Royal Brompton & Harefield NHS Foundation Trust Esther Lim Newcastle Upon Tyne Hospitals NHS Foundation Trust Helen Lindsay NHS Greater Glasgow and Clyde Sukeshi Makhecha Royal Brompton & Harefield NHS Foundation Trust Lynne Merchant Kings college Hospital NHS Trust Sinéad Murphy Central Manchester University Hospitals NHS Foundation Trust Dr Helen Murray Spire Cambridge Lea Hospital John Navis Leeds Teaching Hospitals NHS Trust Christina Nurmahi University Hospital Southampton NHS Foundation Trust Royal National Orthopaedic Hospital NHS Trust Anina Patel Sophie Ridsdale Leeds Teaching Hospitals NHS Trust Elena Roberts Betsi Cadwaladr University Health Board Amandeep Setra University College London Hospitals NHS Foundation Trust Rekha Shah West Hertfordshire Hospitals NHS Trust Priti Sharma Newcastle Upon Tyne Hospitals NHS Foundation Trust

| Christopher Smillie | Newcastle Upon Tyne Hospitals NHS Foundation Trust |
|----------------------|---|
| Paul Smith | Southend University Hospital NHS Foundation Trust |
| Suzanne Smith | Chesterfield Royal Hospitals NHS Foundation Trust |
| Sushma Solanki | Northampton General Hospital NHS Trust |
| Sarah Tinsley | Mid Cheshire NHS Foundation Trust |
| Jennie Toft | Royal Brompton & Harefield NHS Foundation Trust |
| Charles Walker | Leeds Teaching Hospitals NHS Trust |
| Lesley van der Walle | Papworth Hospital NHS Foundation Trust |
| Majella Warnock | Altnagelvin Hospital |
| Katie Warren | The Royal Marsden NHS Foundation Trust |
| Dale Weerasooriya | Kings College Hospital NHS Trust |
| Jennifer Whatton | Lancashire Teaching Hospitals NHS Foundation Trust |
| Emma Wilson | Aintree University Hospital |
| Verity Woodhall | Newcastle Upon Tyne Hospitals NHS Foundation Trust |
| Danielle Wragg | North Bristol NHS Trust |
| Jonathan Yates | Royal Alexandra Hospital, NHS Greater Glasgow and Clyde |
| | |

Acknowledgements

The UKCPA Surgery & Theatres Group is grateful to individuals and organisations that have provided advice and information to support the development of the Handbook of Peri-Operative Medicines.

Correspondents in the pharmaceutical industry have provided information of products and formulations.

Each author is grateful to the numerous doctors, nurses and pharmacist colleagues who have provided feedback and suggestions.

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Foreword

Until now there has been no national guideline in existence for the use of medicines in the peri-operative period. This has resulted in varying practices across the country for the management of patients' regular medicines during this time.

Many individual NHS Trusts have devised their own local guidelines to provide guidance to medical, nursing and pharmacy staff. However, the lack of a unifying national guidance and support resource has resulted in a range of practices relating to the same medicines but that vary according to location and local preference. Such practice induces an element of risk, confusion and ambiguity across a multitude of treatment centres.

The variation in practice is something recognised in the recent Carter review¹ which identified that a reduction of such variations will improve patient care and safety through compliance to national guidance.

The Handbook of Peri-operative Medicines has been developed collaboratively by clinical pharmacy experts working in the area of Surgery, to address the need for a national resource of guidance and support for healthcare professionals working in this area. It will remove the need for individual local guidelines and will ultimately reduce variations in patient care and improve outcomes for patients undergoing surgery.

The Handbook of Peri-operative Medicines has been developed in a format similar to that of other resources used for information on medicines management, such as the Renal Drug Handbook and the Handbook of Drug Administration via Enteral Feeding Tubes. The Handbook contains information on how medicines are to be managed in the peri-operative period, a time when a patient is nil by mouth and often experiences interruption of medication regimens that are important for the treatment of other non-surgical comorbidities. It contains information pertaining to the risks and benefits of omitting, changing and continuing therapy during this period, and where possible how those risks can be managed.

¹ Lord Carter. 2015. Review of Operational Productivity in NHS Providers. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/434202/carterinterim-report.pdf

Preface

Welcome to the first edition of The Handbook of Peri-Operative Medicines. The information contained in this book has been compiled from a wide range of sources and from surgical pharmacists of all surgical specialties from across the United Kingdom, all of whom are members of the UKCPA Surgery & Theatres Group.

The Handbook aims to provide guidance on the management of medicines in the peri-operative period. When patients are admitted for surgery many are receiving medicines for co-morbidities that are unrelated to their surgery, the management of which is as important as the surgical intervention to ensure complete post-operative recovery. Many medicines can be taken up to two hours before surgery with a sip of water. However, owing to potential interactions with anaesthetic agents adjustment of dose according to the operative schedule must be considered. When not possible due to the nature of the procedure or an increased anaesthetic/surgical risk due to drug therapy, it is necessary to omit a patient's regular medicine for the shortest time possible.

Sophie Blow August 2016

Using the monographs

Drug name:

Generic name is listed alongside any approved brands.

Indication(s):

A brief account of common indications. Where an indication is unlicensed, or used off label, this will be stated.

Risks associated with surgery:

Advice in the peri-operative period: Advice on whether a medication needs to be omitted in the peri-operative period, and how to safely do this. Where dose changes are required these will be listed. Where advice between manufacturers and national practice differs, specialist national guidance has been consulted and a UKCPA consensus given. When the use of a medicine increases the risk of peri-operative complications, (e.g. bleeding, clotting) this is specified with the risk specific information to allow speciality teams to make decisions based on an individual patient basis.

Special Instructions:

Includes information on formulation considerations and issues with absorption, where variations in bioavailability exist between preparations this will be listed. Information on interactions with anaesthetic agents are listed (if exist) in addition to interactions with medicines commonly used in the peri-operative period e.g. opiates.

References:

Every monograph has been compiled using a standard set of nationally recognised resources. These include;

Electronic Medicines Compendium

British National Formulary. London; BMJ Publishing Group/RPS Publishing

Drugdex database, Micromedex Inc. USA

National Institute for Health and Care Excellence (NICE) clinical guidelines

UKMI

Stockley's Drug Interactions

Martindale. The Complete Drug Reference. Pharmaceutical Press

In addition personal communications with drug company and literature searches through Medline and Embase (search strategies available on request) were made for all monographs.

Acarbose

Approved Brands:

| | Glucobay® | | |
|-------------------------------------|--|--|--|
| Indication(s) | The treatment of Type 2 diabetes mellitus alone, or in combination with other oral hypoglycaemic agents ^{1,2} . | | |
| Risks associated with surgery | None known or anticipated ² . | | |
| Advice in the | | | |
| peri-operative period | Morning Surgery | | |
| period | Omit morning dose if nil by mouth, restart when next dose is due once eating and drinking ³ . | | |
| | Afternoon Surgery | | |
| | Take as normal prior to surgery, restart when next dose is due once eating and drinking ³ . | | |
| Special Instructions | None | | |
| References | 1. British National Formulary Available at: <u>www.bnf.org</u> [Accessed: 2 July 2015]. | | |
| | Bayer PLC. (2015). Glucobay tablets – Summary of Product Characteristics (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/4236</u> [Accessed: 2 July 2015] | | |
| | Management of adults with diabetes undergoing surgery and elective procedures: improving standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: <u>http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm</u> [Accessed 16th February 2016] | | |

Alfuzosin

Approved Brands:

Xatral ®

| Indication(s) ¹ | Hypertension | |
|---|---|--|
| | Benign Prostatic Hyperplasia (BPH) | |
| Risks associated with surgery | IFIS (Intraoperative Floppy Iris Syndrome) – Meta-analysis ³ examined the comparative incidence of IFIS was examined across a range of alpha-blockers, with alfuzosin use demonstrating the second highest IFIS incidence. | |
| Advice in the peri-operative period | The incidence of IFIS in a population of patients having undergone cataract surgery was examined ² suggesting it is reasonable to withhold alfuzosin prior to cataract surgery to decrease the risk of IFIS. | |
| portou | It is advisable to stop all alpha-1 adrenergic blockers ^{2,5} prior to cataract surgery. No specific recommendations surrounding timescales are available however it is reasonable to advise temporary withdrawal of alfuzosin for two weeks prior to cataract surgery ⁴ . | |
| Special Instructions | If alfuzosin is withheld peri-operatively, blood pressure should be closely monitored upon restarting treatment, owing to the risk of hypotension ⁷ . | |
| | Prolonged release formulations should not be crushed for administration via enteral feeding tubes post-operatively owing to the risk of inappropriate absorption and early onset of adverse effects ⁶ . | |
| | If indicated for the treatment of BPH (Benign Prostatic Hyperplasia), alfuzosin may be stopped following an effectual TURP (Transurethral Resection of Prostate), subject to a successful TWOC (Trial Without Catheter). | |
| References | Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. | |
| | Haridas, A., Syrimi, M., Al-Ahman, B., et al. Intraoperative floppy iris syndrome (IFIS) in patients receiving tamsulosin or doxazosin-a UK-based comparison of incidence and complication rates, 2013. Graefes Arch Clin Exp Ophthalmol; 251(6): 1541-5. | |
| | Chatziralli, I.P., Sergentanis, T.N. Risk factors for intraoperative floppy iris syndrome: a meta- analysis, 2011. Opthalmol; 118(4): 730-5. | |
| | Chang, D.F., Campbell, J.R. Intraoperative floppy iris syndrome associated with tamsulosin (Flomax), 2005. J Cataract Refract Surg; 31: 664 – 73. | |
| | Schwinn, D.A., Afshari, N.A. Alpha (1)-adrenergic receptor antagonists and the iris: new mechanistic insights into Floppy Iris Syndrome, 2006. Surv Ophthalmol; 51: 501 – 12. | |
| | Aventis Pharma Ltd. Summary of Product Characteristics (SPC): Xatral XL, 2014 [Online]. Available from: URL: <u>www.medicines.org.uk</u> | |
| | Roehrborn, C.G. Alfuzosin: overview of pharmacokinetics, safety, and efficacy of a clinically uroselective alpha-blocker, 2001. Urology;58(6 Suppl 1):55-63; discussion 63-4. | |

Aspirin

| Indication(s) | Approved Brands: Micropirin® Nu-Seals® Disprin® (dispersible preparation) Secondary prevention of thrombotic cerebrovascular or cardiovascular disease ^{1,2} . Prevention of graft occlusion following coronary bypass surgery ^{1,2} . |
|-------------------------------------|--|
| Risks associated with surgery | Risks associated with drug continuation during surgery: Increased risk of bleeding complications during surgical procedures ^{1,3} . There is an average increase in surgical blood loss of 2.5-20% associated with aspirin therapy; no increase in surgical mortality is linked to the increase in bleeding ⁴ . Mortality linked directly to massive surgical blood loss in patients maintaining antiplatelet therapy is \leq 3% ⁴ . |
| | Risks associated with stopping therapy: Aspirin can prevent perioperative vascular complications, in particular cardiac and thromboembolic complications⁴. The stress response of surgery leads to increased sympathetic tone and dehydration raises blood viscosity, both increasing the risk of vascular ischemic events⁵. Patients with a history of cardiovascular or cerebrovascular disease in primary care who stop taking low dose aspirin are at significantly increased risk of non-fatal myocardial infarction compared to those who continue such treatment^{4,6}. Discontinuation of aspirin preoperatively is associated with increased risk of adverse cardiac events. This risk is highest for patient with coronary stents⁵. Acute withdrawal of antiplatelet agent produces a rebound effect; resulting in enhanced pro-thrombotic effects⁴, resulting in increased platelet adhesiveness⁵. Patients who are at high risk of event (e.g. cardiac, MI, VTE) if aspirin is withheld: ≤6 weeks after MI, percutaneous coronary interventions (PCI), bare metal stents (BMS), CABG ≤12 months following drug eluting stent Patients who are at intermediate risk of event (e.g. cardiac, MI, VTE) if aspirin is withheld: ≤12 months following drug eluting stent, high risk stents, low ejection fraction, diabetes. Patients who are at low risk of event (e.g. cardiac, MI, VTE) if aspirin is withheld: ≤12 months following drug eluting stent, high risk stents, low ejection fraction, diabetes. Patients who are at low risk of event (e.g. cardiac, MI, VTE) if aspirin is withheld: ≤6 months after MI, PCI, BMS, CABG, stroke ≤12 months following drug eluting stent, high risk stents, low ejection fraction, diabetes. Patients who are at low risk of event (e.g. cardiac, MI, VTE) if aspirin is withheld: ≥6 months after MI, PCI, BMS, CABG, stroke ≥12 after the above if complications. |

| | Aspirin |
|---|---|
| Advice in the peri-operative period | The risk of withdrawing aspirin therapy in the perioperative period is generally higher than that of maintaining therapy ³ . However, each patient must be assessed on an individual basis, pending co-morbidities ^{2,3} . |
| Ponod | Continue pre-operatively and throughout the perioperative period unless the risk of bleeding is considered to be high or the consequences of bleeding are significant ^{3,4,5} . |
| | In patients taking aspirin for secondary prevention, the risks and benefits of continuing aspirin in the perioperative should be discussed with the patient, surgeon, cardiologist or neurologist. |
| | The European society of Anaesthesiology recommends that aspirin can be continued in patient receiving neuraxial anaesthesia ⁷ . |
| | If withdrawal is necessary it is advised to stop aspirin 5-10 days prior to surgery ^{3,4,5} . Platelets have a life span of approximately 10 days however platelet aggregation is partially restored 4 to 5 days after stopping aspirin ⁵ . If antiplatelet therapy is discontinued it should be for the shortest time possible ⁶ . |
| Special Instructions | Aspirin permanently inactivates the platelet enzyme cycloocygenase, the effect of which is only reversed by the generation of new platelets ⁶ . |
| 1150 001013 | Patients on dual antiplatelet therapy are at a higher risk of bleeding; where possible elective surgery should be delayed until the second antiplatelet can be safely stopped. When surgery cannot be delayed and the patient's thrombotic risk is high, the continuation of both agents should be discussed with the surgeon, anaesthetist and cardiologist. These patients should be considered on an individual basis ^{5,6} . |
| | There is no evidence to support bridging therapy during the period of antiplatelet withdrawal ⁵ . |
| References | 1. SPC 2. BNF |
| | 3. Hall R, Mazer D. Antiplatelet drugs: A Review of Their Pharmacology and Management in the Periopeative Period. <i>Anaesthesia-analgesia</i> 2011; 112 (2) : 292-318) |
| | Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. <i>BJA</i> 2007; 99 (3): 316-28. |
| | Rodriguez LAG, Cea-Soriano L, Martin-Merino <i>Et al.</i> Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. <i>BMJ</i> 2011; 343; d4094. |
| | Bauer W and Ng L. Guidelines for the Perioperative Management of Antiplatelet Therapy. Evidenced-based guidelines for Preoperative Assessment Units 2012. 41- 49. |
| | Patrono C, Bagigent C, Hirsh J, Roth G. Antiplatelet Drugs: American Collage of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). CHEST 2008; 133; 199s-233s |
| | Gogarten W, Vandermeulern E, Van Aken H et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiology 2010; 27: 999-1015 |

Azathioprine

Approved brands:

| | Approved Brands. |
|---|--|
| | IMURAN® |
| Indication(s) | Immunosuppressive regimes |
| | Prophylaxis of transplant rejection |
| | Alone or in combination with steroids in: |
| | Rheumatoid Arthritis |
| | Severe inflammatory intestinal disease (Crohn's or Ulcerative Colitis) |
| | Systemic Lupus Erythematosus |
| | Dermatomyositis and polymyositis |
| | Auto-immune chronic active hepatitis |
| | Pemphigus vulgaris |
| | Polyarteritis nodosa |
| | Auto-immune haemolytic anaemia |
| | Chronic refractory idiopathic thrombocytopenic purpura |
| | Severe refractory eczema (unlicensed) |
| | Primary sclerosing cholangitis |
| | Primary biliary cirrhosis |
| Risks associated | The following risks have been associated with individuals taking azathioprine in the peri-operative period; |
| with surgery | Infection: sepsis, abdominal sepsis, wound infection, systemic infections^{3,6} |
| | Impaired hepatic function |
| | Changes in renal function |
| | Gastroduodenal ulceration/bleeding |
| | Pancreatitis |
| | Bone marrow suppression |
| Advice in the peri-operative period | Each patient should be individually assessed for continued prescribing in the peri-operative period as post-operative infections and healing rates are affected by comorbidities. The decision to withhold Azathioprine is dependent on the condition the drug is being used to treat. The withdrawal of azathioprine on the patient's quality of life and management of their chronic condition should be taken into consideration. |
| | Azathioprine should be withheld on the day of surgery and restarted once renal function is normal, usually within the first 3 days post-operatively when all oral medicines are restarted ⁴ . Other suggested regimes include withdrawal one week prior to surgery and reintroduction 2 weeks post op ⁷ . |

| | Azathioprine | | |
|--------------|--------------|---|--|
| | | nsider stopping immunosuppressive therapy if a patient develops a significant temic infection. The pre-operative use of azathioprine in patients with Crohn's ease increases the risk of short-term post-op complications ³ . | |
| | | Complications after elective abdominal surgery for Crohn's disease have not been associated with steroid dose, immunosuppressive therapy, or infliximab use ⁶ . | |
| Special | Dos | Dose reduction in renal and hepatic impairment? Monitor for signs of bone marrow suppression and hepatotoxicity. Withdraw immediately if jaundice occurs. (See SPC for monitoring advice) ^{1,2} . | |
| Instructions | | | |
| References | 1. | Actavis UK Ltd, SPC Azathioprine (September 2015) | |
| | 2. | Aspen UK, SPC Imuran (azathioprine) (August 2014) | |
| | 3. | M. Coscia, G. Vitali, S. Laureti, L. Gentilini, F. Ugolini, A. Calafiore, F. Rizzello, P. Gionchetti, C. Calabrese, M. Campieri, G. Poggioli. <i>Risk of short-term postoperative complications in patients treated with azathioprine for Crohn's disease</i> . A single center experience. Poster presentations: Clinical: Therapy and observation (2012). | |
| | 4. | Kumar A, Auron M, Aneja A, Mohr F, Jain A, Shen B. <i>Inflammatory bowel disease:</i> perioperative pharmacological considerations. Mayo Clin Proc. 2011 Aug;86 (8):748-57. | |
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| | 6. | Colombel JF, Loftus EV Jr, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, Harmsen WS, Schleck CD, Sandborn WJ. <i>Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy.</i> Am J Gastroenterol. 2004 May;99 (5):878-83. | |
| | 7. | Juan Salvatierra Ossorio, Magdalena Peregrina-Palomares, Francisco O'Valle Ravassa and Pedro Hernandez-Cortes (2011). <i>Perioperative Management of Non-Biological and Biological Therapies in Rheumatic Patients Undergoing Orthopedic Surgery</i> , Challenges in Rheumatology, Dr. Miroslav Harjacek(Ed.) | |
| | 8. | Azathioprine. BNF 69. Last accessed 10/02/2016 | |
| | 9. | NICE. Ulcerative colitis: management. June 2013. Last accessed on 10/02/2016. | |
| | 10. | NICE. Crohn's disease: management. October 2012. Last accessed on 10/02/2016. | |

Benzodiazepines (hypnotics & anxiolytics)

International Approved Drug Name(s) (approved brands):

| Alprazolam (Xanax®) | Midazolam (Hypnovel®) |
|---------------------------------|-----------------------|
| Clobazam (Frisium®) | Nitrazepam (Mogadon®) |
| Clonazepam (Rivotril®) | Oxazepam |
| Diazepam (Diazemuls®, Tensium®) | Temazepam |
| Flurazepam (Dalmane®) | Zaleplon (Sonata®) |
| Lorazepam (Ativan®) | Zolpidem (Stilnoct®) |
| Loprazolam | Zopiclone (Zimovane®) |
| Lormetazepam (Dormagen®) | |

Indication(s) All of the benzodiazepines can be used for insomnia and anxiolysis but exact licensed indications vary (please refer to BNF or product literature).

Clobazam and clonazepam are licensed for treatment of epilepsy.

Diazepam, lorazepam and midazolam are also licensed for the management of Status Epilepticus, for conscious sedation and treatment of febrile convulsions.

The benzodiazepine-like zaleplon, zolpidem and zopiclone are licensed for treatment of insomnia.

Risks associated with surgery

Continuation of benzodiazepines and benzodiazepine-like drugs during surgery is associated with an increased sedative effect, and risk of cumulative CNS depression. This risk can be minimised by adjusting anaesthetic and other peri-operative sedative drugs.

Some benzodiazepines are licensed as premedication or induction agents for anaesthesia. Anaesthetists are trained in use of benzodiazepines and combination with other anaesthetic/ sedative medicines^{16,17}.

Long-term use of benzodiazepines was linked to increased postoperative confusion in one study²⁵. Another study²⁶ though did not find association of benzodiazepines with postoperative delirium.

Sudden discontinuation of benzodiazepines and benzodiazepine-like drugs is associated with withdrawal symptoms including confusion, toxic psychosis, convulsions, delirium and rebound effects. Doses should be reduced gradually^{2,3,5,6,7,8,21,22,23}.

Withdrawal symptoms can occur within a day after stopping short-acting benzodiazepines, such as alprazolam, lorazepam, lormetazepam, oxazepam and temazepam^{1,11,12}.

Withdrawal symptoms from zolpidem and zopiclone are unlikely if treatment duration has been less than 4 weeks $^{\rm 14,15}$.

If a benzodiazepine is used for control of epilepsy, it must not be suddenly discontinued without putting an alternative treatment plan in place¹. Please also refer to [introductory section on antiepileptic drugs].

Discontinuation of benzodiazepines in psychiatric patients with panic disorders should be avoided $^{\rm 24}. \,$

| Advice in the peri-operative | Establish indication for benzodiazepine/ benzodiazepine-like drug use to determine risk from missing doses. | |
|------------------------------|---|--|
| period | Benzodiazepines/ benzodiazepine-like drugs for night sedation can be safely administered the evening before surgery. | |
| | If prolonged period of nil-by-mouth or reduced enteral absorption expected, convert to a benzodiazepine that can be administered via parenteral route. Consult specialist literature (e.g. Psychotropic drug directory) or local Medicines Information Department for equivalent doses. | |
| | Anaesthetist needs to be made aware of type and dose of benzodiazepine the patient usually takes to adjust anaesthetic accordingly if necessary. | |
| | Patients who are discharged on the day of surgery after having received an anaesthetic and who usually take benzodiazepines/ benzodiazepine-like drugs should be advised of the potential of enhanced drowsiness and psychomotor effects. | |
| Special | Interactions with anaesthetic agents: | |
| Instructions | Benzodiazepines and benzodiazepine-like drugs provide an additive effect when co-administered with drugs depressing the central nervous system such as sedatives and anaesthetics ^{2,3,5,6,7,8,10,11,12,18,21,22,23} . Benzodiazepines can cause respiratory depression ^{2,3,5,6,7,8,10,11,12} . | |
| | An additive effect with neuromuscular blocking agents has been observed ^{7,20} . | |
| | Premedication with diazepam can lead to prolonged effects of ketamine ⁴ and to reduced haemodynamic effects of ketamine ¹⁸ . | |
| | Diazepam has been reported to increase plasma levels of bupivacaine ¹⁹ . | |
| | Single-dose intravenous fentanyl has been shown to reduce metabolism of midazolam ²⁷ . | |
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Benzodiazepines

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- Oxazepam tablets BP 10 mg Summary of product characteristics, Actavis, last revised 09/2014, accessed on medicines.org.uk [Accessed: 5th May 2015]
- 12. Temazepam tablets 20 mg Summary of product characteristics, Sandoz Ltd, last revised 03/2015, accessed on medicines.org.uk [Accessed: 5th May 2015]
- Sonata® Summary of product characteristics, Meda AB, last revised 12/2014, accessed on medicines.org.uk [Accessed: 5th May 2015]
- Stilnoct® 5 mg film-coated tablets Summary of product characteristics, Sanofi/Aventis Pharma Ltd, last revised 09/2014, accessed on medicines.org.uk [Accessed: 5th May 2015]
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Carbamazepine

Approved Brands:

Tegretol®

Carbagen®

| Indications(s) | Focal and secondary generalised tonic-clonic seizures. |
|-------------------------------------|--|
| | Primary generalised tonic-clonic seizures |
| | Trigeminal neuralgia |
| | Prophylaxis of bipolar disorder unresponsive to lithium |
| | Treatment of alcohol withdrawal (unlicensed) |
| | Diabetic neuropathy (unlicensed) ¹ |
| Risks associated with surgery | Abrupt withdrawal of any anticonvulsant drug in a responsive epileptic patient may precipitate seizures or status epilepticus. Do not discontinue abruptly due to risk of increased seizure frequency ² . |
| with Surgery | Carbamazepine may antagonise the effects of non-depolarising muscle relaxants (e.g. atracurium/pancuronium). Subsequently doses may need to be increased and patients monitored closely for a more rapid recovery from neuromuscular blockade than expected ³ . |
| | Concurrent use of Carbamazepine and Tramadol may result in decreased tramadol efficacy and increased seizure risk ⁴ . |
| | Concurrent use of Granisetron and selective serotonergic agents may result in increased risk of serotonin syndrome ⁴ . |
| Advice in the peri-operative | In patients with a history of well-controlled epilepsy, it is vital that efforts are made to avoid disruption of antiepileptic medication peri-operatively. |
| period | Elective Surgery: |
| | Patients should be advised to take their regular medications on the morning of surgery and regular dosing should be re-established as early as possible post-operatively surgery ⁵ . |
| | Suppositories are licensed for short-term use as replacement therapy (maximum period recommended: 7 days) in patients for whom oral treatment is temporarily not possible, for example in post-operative or unconscious subjects. |
| | When switching from oral formulations to suppositories the dosage should be increased by approximately 25% (the 125 and 250mg suppositories correspond to 100 and 200mg tablets respectively). Where suppositories are used the maximum daily dose is limited to 1000mg (250mg QDS at 6 hour intervals). |
| | No clinical data is available on the use of suppositories in indications other than epilepsy ⁶ . |

Carbamazepine

| For patients where swallowing is compromised, carbamazepine suspension can |
|--|
| be used and is suitable for enteral tube administration ⁷ . The oral bioavailability of |
| carbamazepine tablets and suspension are reportedly equivalent, although the rate of |
| absorption for the suspension is quicker ¹ . When changing a patient's therapy from oral |
| tablets to the suspension; the dose conversion is the total daily dose of tablets taken |
| divided into smaller, more frequent doses. The oral suspension should be shaken well |
| before administration ² . To convert to the liquid preparation from modified release (MR) |
| tablets, divide the total daily dose by 4 to give the liquid dose required, e.g. 400mg MR |
| tablets twice daily = 200 mg four times a day of liquid ⁷ . |
| |

Special Instructions

Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer's product¹.

Administration via an enteral tube:

There is data to suggest that the liquid preparation may adsorb onto the enteral tube and reduce the dose administered. Diluting with an equal volume of water immediately prior to administration appears to prevent this⁶. Flush the tube with 100 mL of the diluent after administration². The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultations with the patient, taking into account factors such as seizure frequency and treatment history.¹

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- Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.</u> medicinescomplete.com on 14/01/2016

Catechol-O-Methyltransferase (COMT) Inhibitors International Approved Drug Name(s) (approved brands): Entacapone (Comtess®) Tolcapone (Tasmar®) Levodopa+ carbidopa + entacapone (Stalevo®: Sastravi®) - see levodopa preparations for advice Indication(s) Adjunct to co-beneldopa or co-careldopa in Parkinson's disease with 'end of dose' motor fluctuations. Tolcapone is only indicated when other inhibitors of peripheral catechol-Omethyltransferase are inappropriate and under specialist supervision¹. **Risks** COMT-inhibitors are ineffective when given without levodopa. Hence many of the risks associated with surgery are due to the levodopa component of treatment. associated with surgery COMT-inhibitors may potentiate the action of other drugs metabolised by COMT. e.g. adrenaline, noradrenaline. Due to limited clinical experience recommendation is to exercise caution 2,3,4,5 Omitted doses of COMT-inhibitors will reduce the effectiveness of prescribed levodopa preparations and therefore increase the risk of 'end-of-dose' motor fluctuations. Combination products onlv^{6,7,8,9,10,11,12} Continuation of a COMT-inhibitor with levodopa may increase the risk of central nervous system effects, these include; alterations in mental status, dyskinesias, dizziness. hallucinations. dvstonia. confusion. somnolence and insomnia. Continuation of COMT-inhibitors can increase both the risk of haemodynamic compromise and risk of arrhythmias. Abrupt withdrawal of a COMT-inhibitor combined with levodopa may lead to an increase in Parkinson's symptoms or precipitate withdrawal syndromes which have been associated with fatalities, e.g. neuroleptic malignant-like syndrome. Omitted doses of combination products of COMT-inhibitors may increase the risk of complications associated with Parkinson's disease, e.g. motor instability leading to falls, respiratory complications, and dysphagia. Advice in the It is essential to ensure that all medications are administered immediately prior to surgery. peri-operative period Minimise the 'nil-by-mouth' period and restart usual oral medication as soon as possible post-operatively.7 **Post-operatively:** If a patient is unable to swallow, COMT-inhibitors can safely be omitted in the short-term. However, if prescribed as a combination product with levodopa then the

levodopa element must be replaced (see levodopa preparations).

Catechol-O-Methyltransferase (COMT) Inhibitors

Longer-term, if a patient is to be tube-fed or is struggling to swallow solid oral dosage forms, then entacapone (Comtess®) can be dispersed to aid administration (unlicensed; see special instructions).

| Special | Swallowing difficulties/enteral feeding considerations | |
|--------------|--|--|
| Instructions | Comtess® (data not available for other brands)¹³: Place tablet in an oral syringe and add 10ml of water. It will slowly disintegrate over 5 minutes. Flush tube well as dispersal may be incomplete. Feeding tube may be stained orange. | |
| | | |
| | NB: Crushing tablets to a dry powder may stain skin or clothing. | |
| | • Administration of entacapone must be at the same time of day as levodopa- containing medication. | |
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Ciclosporin

Approved Brands:

| Neoral® | Capsorin® |
|------------|-----------|
| Sandimmun® | Capimune® |
| lkervis® | Vanquoral |
| Deximune® | |

Indication(s) Transplantation:

Solid organ transplantation and bone marrow transplantation¹

Non-Transplantation:

Endogenous uveitisnephrotic syndrome Rheumatoid Arthritis Psoriasis Atopic dermatitis¹

Unlicensed:

Severe acute ulcerative colitis (UC)²

| Risks associated with surgery | Risks associated with drug continuation during surgery: Risk of Infections (opportunistic infections) Renal Toxicity Hepatotoxicity ¹ |
|---|--|
| | Risks associated with stopping therapy: |
| | Risk of UC flare |
| | Risk of organ rejection |
| Advice in the peri-operative period | To maintain therapeutic drug levels, administer the oral dose $4 - 7$ hours before surgery and continue therapy during the peri-operative period. There is no evidence to support the need to discontinue therapy before or immediately after surgery ^{3,4} . |
| | Carefully observe patients peri-operatively for deterioration of renal function and opportunistic infections ³ . A dose reduction may be required if there are signs of renal impairment, infection, hepatotoxicity ¹ . |
| | Monitor BP and ciclosporin levels daily during the perioperative period ^{1,5} . |
| | Monitor magnesium and potassium levels ¹ . |
| | Avoid concomitant administration of NSAIDs due to the increased risk of nephrotoxicity ¹ . |

| | Ciclosporin |
|-------------------------|--|
| Special Instructions | Consider medication interactions as ciclosporin is extensively metabolised in the liver. Levels may be affected by inducers or inhibitors of hepatic enzymes, particularly cytochrome P450 isoenzyme CYP3A4 ⁶ . |
| | Refer to special warnings, monitoring and precautions stated in the summary of product characteristics. Any changes in therapy require a clinical decision from the physician and surgeon responsible for the treatment of the patient ⁷ . |
| | Consider dose equivalences when switching routes of administration. Where possible maintain patients on the oral formulation they have been stabilised on due to differences in bioavailability, and encourage brand prescribing ⁸ . |
| | Due to variations between brands resulting in changes in blood-ciclosporin concentration, patients need to be maintained on a single brand. |
| | When administering the oral solution via an enteral feeding tube, monitor drug levels closely as the solution may adhere to the feeding tube. Do not use grapefruit juice to dilute the oral solution for patients with swallowing difficulties ⁸ . |
| References | Novartis Pharmaceuticals UK Ltd. (2016). Neoral Soft Gelatin Capsules – Summary of Product Charecteristics (SPC) – (eMC). Available from <u>https://www.medicines.org.uk/emc/</u> <u>medicine/1307</u> [Accessed 22nd March 2016] |
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Approved Brands:

Plavix®

Grepid®

Indication(s) Situations whe

Situations when used for the prevention of atherothrombotic events:

- In established peripheral arterial disease
- Within 35 days of myocardial infarction
- Within 6 months of ischaemic stroke
- In percutaneous coronary intervention in patients not already on clopidogrel (in combination with aspirin)
- In non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention (in combination with aspirin) for up to 12 months
 - ► For 1 month following elective percutaneous coronary intervention with placement of a bare-metal stent
 - ► For 12 months following percutaneous coronary intervention with placement of a bare-metal stent for an acute coronary syndrome
 - ► For 12 months following percutaneous coronary intervention with placement of a drug eluting stent (longer duration than 12 months if a high risk of developing late stent thrombosis)
- In ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy (in combination with aspirin) for at least 4 weeks
- In transient ischaemic attack for patients with aspirin hypersensitivity or intolerance (unlicensed)
- In acute ischaemic stroke for patients with aspirin hypersensitivity or intolerance (unlicensed)

When used for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation:

 In patients who have at least one risk factor for vascular events, have a low bleeding risk and for whom warfarin is unsuitable (in combination with aspirin)

Risks associated with surgery

General Surgery

Clopidogrel has a short half-life (4 hours) but platelet inhibition is irreversible. It therefore exerts its effect for the lifespan of the platelet (approximately 7-10 days). Its effect is corrected only by production or transfusion of new platelets, not by decreased plasma clopidogrel concentrations^(3,4). The daily turnover of platelets is approximately 10%. Following discontinuation of clopidogrel, platelet function is gradually increased with complete recovery within 7 – 10 days. Haemostatic competence is unlikely to require restoration of all platelets' function and may recover within 5 days when 50% of platelet function is obtained⁽⁵⁾.

There is a distinct lack of randomised controlled trials comparing the effects of withdrawing versus continuing clopidogrel in the perioperative period.

Clopidogrel prolongs bleeding time and therefore presents a possible increased risk of bleeding if it is continued in patients undergoing surgical procedures⁽¹⁾. In addition to perioperative blood loss, increased bleeding caused by anaesthetic procedures such as the possibility of epidural haematomas with neuraxial techniques and nasal bleeding after intubation must also be taken into account⁽⁶⁾. Patients taking antiplatelets have more difficult intraoperative control of bleeding but most studies found transfusion rates and reoperations are not increased. Bleeding problems occurred more often on dual antiplatelet therapy and moderate to high risk operations⁽⁷⁾. Reviews have also concluded preoperative exposure to clopidogrel results in excess bleeding risks but without significant differences in all cause mortality⁽⁸⁾. It should be taken into account certain surgical procedures have high bleeding risks independent of the presence of antiplatelet medication and others may be associated with increased morbidity and mortality if bleeding occurs⁽⁹⁾.

The stress response to surgery includes an inflammatory, hypercoagulable and hypoxic state. There is an increase in plasma clotting factors alongside decreased fibrinolysis⁽¹⁰⁾. Sympathetic activation promotes shear stress on arterial plaques, vascular reactivity leading to vasospasm and platelet activation all of which may trigger adverse cardiovascular outcomes⁽¹¹⁾. Stopping clopidogrel is also associated with an increase in thrombotic events due to rebound effect on platelet activation⁽¹²⁾. In patients with a history of acute transient ischaemic attack (TIA) or minor ischemic stroke (CVA). stopping clopidogrel is unlikely to have a large rebound thrombotic effect with significant complications⁽¹³⁾. In 90 days following a TIA there is the highest risk of stroke (10%) and cardiac events (2.6%)⁽¹⁴⁾. In the 90 days following a CVA there is a 4-8% risk of stroke recurrence⁽¹⁴⁾ and a 2-5% risk of fatal cardiac event⁽¹⁵⁾. As patients with atrial fibrillation derive a modest benefit from antiplatelets it can be concluded that preoperative discontinuation of clopidogrel will not impact the overall outcome⁽¹⁶⁾. When non aspirin antiplatelets such as clopidogrel are substituted with aspirin or placebo for 10 days prior to surgery there is no difference in terms of perioperative thrombotic or bleeding events in the 30 days post procedure. However, this study was underpowered (<50%) due to premature termination of recruitment limiting the reliability of the results⁽¹⁷⁾.

Cardiac Surgery

Exposure to clopidogrel within five days prior to coronary artery bypass graft (CABG) surgery is associated with a

- Greater risk for haemorrhage⁽¹⁸⁾
- 2 5 fold increase in the risk of re-exploration and 30 100% increase in the chest drain blood $\mbox{loss}^{(19)}$
- 50% higher incidence in major bleeding and a 70% higher incidence in transfusion requirements⁽²⁰⁻²²⁾

In CABG surgery it is important to minimise perioperative bleeding especially mediastinal bleeding that can cause pericardial tamponade⁽²²⁾.

Cessation of clopidogrel 5 – 7 days before cardiac surgery is at the expense of a 1% increase in the risk of myocardial infarction while awaiting surgery⁽²¹⁾. There is no significant difference in mortality, postoperative myocardial infarction or stroke rates when clopidogrel is continued or stopped for CABG⁽²³⁾ but stopping is associated with reduced bleeding, blood transfusion and reoperation rates^(7,24,25).

Cardiac Stents

Patients undergoing non cardiac surgery soon after insertion of cardiac stents (bare metal or drug eluting) are at risk of major adverse cardiac events. These are mainly coronary stent related cardiac adverse events but bleeding adverse events have also been reported. The type of cardiac stent has not been shown to influence outcomes^[26]. Complication rates range from 2.6%⁽²⁶⁾ to 44.7%⁽²⁷⁾ with a mortality rate of 4.9%⁽²⁷⁾ to 20%⁽²⁸⁾. The adverse event rate is doubled in patients with recently implanted stents (<35 days) than in those whom stents were inserted >90 days before the operation⁽²⁷⁾. There is an inverse relationship between time from stent insertion and complications. The majority of cardiac complications occur in patients operated on within 6 weeks of implantation of bare metal stents or 12 months for drug eluting stents. Patients that experience adverse events continue dual antiplatelet therapy throughout surgery. Pre-operative dual antiplatelet therapy is not associated with a lower rate of adverse events in these patients⁽⁸⁾.

Emergency non-cardiac surgery in patients with recently inserted bare-metal and drug-eluting cardiac stents is independently associated with major adverse cardiac and bleeding events. The rate of major adverse cardiac events was 17.9% for patients undergoing emergency procedures after drug-eluting stents and 11.7% with bare metal stents versus 4.7% in patients undergoing non-emergency surgery after drug-eluting stent and 4.4% after bare-metal stent, respectively⁽²⁹⁻³¹⁾.

Premature discontinuation of dual antiplatelet therapy is the leading independent predictor of major adverse cardiac events relating to stent thrombosis ⁽³²⁻³⁴⁾ with an incidence of 30.7% in comparison to those patients who continue on dual antiplatelets (0%)⁽²⁶⁾. Rebound platelet reactivity after discontinuation of antithrombotic therapy is thought to lead the increased thrombotic risk in stented patients undergoing surgery⁽³⁵⁾. The rate of major adverse cardiac events is nearly doubled when dual antiplatelet therapy is stopped more than 5 days before non cardiac operations in patients with coronary stents⁽³⁶⁾.

In retrospective studies, patients with bare metal or drug eluting stents undergoing a variety of surgical procedures with varying degrees of risk continued dual antiplatelet therapy. Despite an increased risk for oozing and diffuse haemorrhage there was been no clear association between dual antiplatelet therapy and bleeding or transfusion requirements ^(26,29,30,37,38).

| Advice in the | Elective/General Surgery |
|---------------|--|
| neriod | Where possible postpone the elective surgery until; |
| | The duration of treatment with clopidogrel is complete |
| | \bullet The patient is 90 days post transient ischaemic attack and ischaemic stroke $^{(14)}$ |
| | When being used post myocardial infarction, postpone surgery for minimum of 6 weeks but ideally 3 months after myocardial infarction ⁽³⁹⁾ |
| | Little evidence is available and recommendations derive mostly from expert opinion. |

Decisions must be made on an individual patient basis. A multidisciplinary approach is needed to consider the indication for clopidogrel and the consequences of treatment cessation. The risks of bleeding should be weighed against the risk of ischaemic or thrombotic events if clopidogrel is discontinued.

Discontinuation of clopidogrel is unnecessary in procedures that are not highly invasive and have a low bleeding risk or haemostasis is controllable. In general, clopidogrel monotherapy when taken for secondary prevention provides cardiovascular benefit that outweighs the bleeding risk and should be continued during most procedures^(32,40). Stopping clopidogrel preoperatively should be considered an exception on an individual basis and only when undergoing procedures with high risk from bleeding or expected major bleeding complications (e.g. closed space procedures transurethral prostatectomy and intraocular or intracranial procedures)^(7,32).

Risks associated with stopping therapy:

If clopidogrel's antiplatelet effect is not desirable and it needs to be stopped it should be $5^{(41,42)} - 7^{(1,2,7,43)} - 10^{(44,45)}$ days before surgery. Neuraxial anaesthesia requires clopidogrel to be stopped for a minimum of 7 days^(46,47). No randomised controlled trials have assessed the optimal timing or how bleeding and thromboembolic outcomes⁽²²⁾ are affected. When used in atrial fibrillation or for primary prevention of cardiac or cerebrovascular events it can be stopped without major consequence^(16,32). In patients with a history of acute transient ischaemic attack or minor ischaemic stroke stopping clopidogrel is unlikely to have a large rebound thrombotic effect with significant complications⁽¹³⁾.

Replacement with reversible antiplatelet or antithrombotic agents that have a short duration of action such as unfractionated or low molecular weight heparin, salicylate derivatives or non steroidal anti inflammatory drugs have not been prospectively validated and are not recommended⁽⁴⁵⁾.

Post-Operatively:

Clopidogrel should be reinstated as soon as possible when haemostasis is stable taking into account that the effects cannot be reversed. It is not recommended to administer clopidogrel when spinal or epidural catheters are in place. There should be 6 hours after block performance or catheter removal before it is administered⁽⁴⁷⁾. Maximum platelet inhibition is observed after 3 - 7 days following a 75mg dose⁽⁴⁶⁾.

Cardiac Surgery

Clopidogrel should be withheld between 5^(22,48,49) and 7^(19,50,51) days before CABG (coronary artery bypass graft) if clinical circumstances permit.

For patients with a high risk of ischaemic events or when CABG is indicated urgently and a 5 day interruption in clopidogrel is not feasible a preoperative platelet transfusion and/or administration of antifibrinolytic drugs such as tranexamic acid should be considered⁽²²⁾.

Stopping clopidogrel within 3 days of operation does not result in increased bleeding or use of blood products compared with stopping clopidogrel 5 days or more before operation⁽⁵²⁾.

The use of aprotinin (unlicensed) is controversial and evidence is conflicting. Aspirin and clopidogrel can be continued until CABG without increasing postoperative bleeding and transfusion requirements when prophylactic low dose aprotinin is also given ⁽⁵³⁾. Conversely, in cardiac surgery it has been associated with serious renal, cardiac and cerebral events⁽⁶⁴⁾. Its use is therefore not recommended and other safer agents such as tranexamic acid should be used instead ^(22,45).

Cardiac Stents

Elective surgery should be delayed following cardiac stent placement until completion of mandatory dual antiplatelet therapy and re-endothelialisation of the vessel surface is completed.

Bare metal stents:

Following bare metal stent implantation, the majority of guidelines recommend deferring surgery for at least $4^{(32-34,55,56)}$ weeks (range $2^{(57)} - 6^{(9,22,58,59)}$ weeks) and optimally $12^{(59)}$ weeks.

Drug eluting stents:

In patients with drug eluting stents, delaying surgery at least $12^{(9,32-34,55-59)}$ months post stent insertion is consistently recommended but $6^{(22,36)}$ months is also advised⁽⁶⁰⁾.

The need for urgent surgery in regards to timing and pathology should be balanced against the excessive risk of stent thrombosis. The decision for surgery should be made on an individualised case by case basis based on a review of the risks and benefits ⁽⁵⁹⁾. In general, patients required to undergo urgent surgery soon after cardiac stent insertion that cannot be deferred should continue on dual antiplatelet therapy wherever possible unless the risk of bleeding outweighs the benefit of preventing stent thrombosis^(22,61).

It is important to note it is preferable to delay elective surgery soon after stent placement rather than proceeding with surgery whilst maintaining dual antiplatelet therapy⁽⁸⁾.

Guidelines provide specific algorithms for perioperative management of dual antiplatelets following stent insertion stratifying options in terms of bleeding and thrombosis risk^(32,33,43,62). In procedures with low to moderate bleeding risk surgeons should be encouraged to operate whilst maintaining dual antiplatelet therapy as the risk of stent thrombosis outweighs the risk of procedure associated bleeding^(7,16,34,36). Continuation of aspirin and clopidogrel is not consistently associated with increased perioperative bleeding or transfusion requirements, whereas premature discontinuation of antiplatelet agents is a significant contributor in most cases of stent thrombosis.

If the intervention has a high haemorrhagic risk or is closed space surgery and clopidogrel must be discontinued then it should be temporarily withheld for $5^{(7,32,36,57,63)} - 7^{(1,2,32)} - 10^{(9,22,45,59)}$ days pre-operatively⁽⁶⁰⁾. In these cases continue aspirin as monotherapy where possible. Aspirin should only be discontinued when the bleeding risk outweighs the potential cardiac benefits ^(34,41,59). See the aspirin monograph for further information.

Bridging therapy could be considered for patients who are unsuitable to remain on clopidogrel and/or aspirin but require antiplatelet therapy until surgery due to a very high risk of stent thrombosis. Intravenous reversible glycoprotein inhibitors such as eptifibatide⁽⁶⁴⁾ or tirofiban⁽⁶⁵⁾ have been reported as successful but there is also conflicting evidence suggesting otherwise⁽⁶⁶⁾. There is no high quality evidence these agents will reduce the risk of stent thrombosis after discontinuation of oral antiplatelets and further high quality research is required to support their use^(32,33,41). The use of low molecular weight or unfractionated heparin for bridging is an ineffective substitution for dual antiplatelet therapy⁽⁶³⁾ and should be avoided⁽⁴¹⁾. It should only be started for venous thromboprophylaxis post procedure⁽³²⁾ as it cannot provide

antiplatelet effects, increases the risk of bleeding^(34,51) and there is no evidence to support its efficacy preventing acute stent thrombosis⁽⁶⁷⁾.

Restarting clopidogrel post-operatively:

Dual antiplatelet therapy should be resumed as soon as possible when adequate haemostasis has been secured usually between $24^{(59)} - 48^{(41)}$ hours after surgery. If there is a high risk of postoperative bleeding, restarting should be delayed until this risk has diminished. The removal of any indwelling catheters should have occurred. It may be advantageous to restart clopidogrel with a loading dose (300mg) to ensure a rapid return of antiplatelet activity and protection against stent thrombosis which usually presents early in the post operative period. However, whether a loading dose is beneficial in preventing perioperative thrombotic events or is accompanied by an unacceptably greater potential for bleeding complications is currently not known⁽⁶⁸⁾.

Overall, a multidisciplinary team review and consensus decision between the cardiologist, haematologist, surgeon, anaesthetist and the patient is essential ^(7,32,33,51,59). Potential haemorrhagic or thrombotic complications should be anticipated as appropriate ⁽³²⁾. This may include platelet transfusion and/or other procoagulant interventions⁽⁵⁹⁾, continuous cardiac monitoring in a critical care environment with regular review by cardiologists focusing on recognition of myocardial ischaemia/ infarction⁽⁶⁸⁾ and the possibility of stent thrombosis leading to rapid triage in an interventional catheterisation laboratory to reduce morbidity and mortality⁽⁶⁹⁾.

Special Instructions

Clopidogrel is a prodrug that requires first pass metabolism by cytochrome P450 enzymes in the liver and can only be administered orally. Variable absorption and first pass metabolism including CYP2C19 gene variation contribute to a high variability in clopidogrel response⁽⁷⁾. Absorption and metabolism of clopidogrel can also be affected by surgery^(62,70).

Administration via enteral tubes:

Specific information regarding administration of tablets or oral solution (special) through enteral feeding tubes is not available. There is likely to be alterations in pharmacokinetics if clopidogrel tablets are crushed but this is unlikely to cause any adverse effects. The tablets do not disperse readily in water. They can be crushed and dispersed with 10 mL of water and flushed down an 8Fr nasogastric feeding tube without blockage^(71,72).

Jehovah's Witnesses:

1.

In patients who refuse or have contraindications to blood transfusion, e.g. Jehovah's witnesses, consider discontinuing antiplatelet therapy despite its risks⁽⁷⁾.

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Combined Oral Contraceptives (COCs)

Low Strength combined oral contraceptives:

Contain ethinylestradiol 20micrograms

Standard strength combined oral contraceptives:

Contain oestrogen at the following strengths:

Ethinylestradiol at 30, 35 or 40micrograms

Mestranol 50 micrograms

Estradiol 1mg, 1.5mg, 2mg and 3mg.

| Approved Brand | Oestrogen | Progesterone | Formulation |
|---|----------------------------|------------------------|-------------|
| | Low Strength Pr | reparations | |
| Gedarel® Mercilon® | Ethinylestradiol | Desogestrel | Tablet |
| Femodette® Millinette® Sunya® | Ethinylestradiol | Gestodene | Tablet |
| Loestrin 20® | Ethinylestradiol | Norethisterone acetate | Tablet |
| | Standard Strength | Preparations | |
| Gedarel 30/150® Marvelon® | Ethinylestradiol | Desogestrel | Tablet |
| Yasmin® | Ethinylestradiol | Drospirenone | Tablet |
| Femodene ED® Millinette 30/75® Katya 30/75® Triadene® | Ethinylestradiol | Gestodene | Tablet |
| Levest® Microgynon 30® Microgynon 30 ED Ovranette® Rigevidon® Logynon® TriRegol® Logynon ED® | Ethinylestradiol | Levonorgestrel | Tablet |
| Loestrin 30® Brevinor® Ovysmen® Norimin® BiNovum® Synphase® | Ethinylestradiol | Norethisterone acetate | Tablet |
| Cilest® | Ethinylestradiol | Norgestimate | Tablet |
| Zoely® | Estradiol (as hemihydrate) | Nomegestrol acetate | Tablet |
| Qlaira® | Estradiol valerate | Dienogest | Tablet |
| Norinyl-1® | Mestranol | Norethisterone acetate | |

Combined Oral Contraceptives (COCs)

| Indication(s) | Contraception |
|---|--|
| | Menstrual symptoms |
| Risks associated with surgery | There is an increased risk of venous thromboembolic disease and ischemic stroke in users of combined oral contraceptives ¹⁻⁷ . In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors such as obesity and thrombophilia status ^{7,8} . |
| | The type of progesterone used in the combined oral contraceptive also carries risk of venous thromboembolism (VTE). The following combined oral contraceptives were associated with a significantly higher risk of venous thromboembolism: |
| | • Gedarel 20/150® and 30/150® |
| | • Mercilon® |
| | Marvelon® |
| | • Femodette® |
| | Millinette 20/75 and 30/75® |
| | • Sunya 20/75® |
| | • Femodene® |
| | • Katya 30/75® |
| | Femodene ED® |
| | • Triadene® |
| | • Yasmin® |
| | Compared with Levest®, Microgynon 30®, Ovranette®, Rigevidon®, Microgynon 30 ED®, Logynon®, TriRegol®, Logynon ED® 4, 5,8,9,10,11. |
| | Overall there is a 2.5-fold increased risk of postoperative VTE in COC users as per the SIGN guidelines ¹¹ .Data suggest that COCs containing the 'third generation' progesterone's gestodene or desogestrel are associated with an increased risk of venous thromboembolism (VTE) when compared with those containing the 'second generation' progesterone's levonorgestrel or norethisterone ^{12,13} . |
| | There is even less available data for the vaginal ring which contains ethinylestradiol and etonogestrel. A national registry-based study reported that compared to non-users of oral-contraceptives the use of the vaginal ring did increased the risk of VTE ¹² . Other studies suggest the risks of VTE are similar to that of combined oral contraceptives ^{16,17} . |
| Advice in the peri-operative period | Oestrogen containing contraceptives (oral and transdermal) should be discontinued at 4 (minimum) to 6 weeks prior to major elective surgery and all surgery to the lower limbs or surgery which involves prolonged immobilisation of a lower limb. This allows adequate alternative contraceptive arrangements to be made – such as a progesterone-only contraceptive, if appropriate. |
| | Oestrogen containing contraceptives should normally be recommenced at the first menses occurring at least two weeks after full mobilisation ^{7,8,11,12,18,19} . |

| Special Instructions | surę as t | Where it is not possible to stop the combined oral contraceptive e.g. emergency surgery, appropriate anti-thrombotic measures are needed post-operatively such as thromboprophylaxis with unfractionated or low molecular weight heparin and graduated compression hosiery⁸. Where the duration available to stop combined oral contraceptives is less than the recommended four to six weeks please refer to the individual pharmacokinetics of the contraceptives and assess against individual patient risk. | | | |
|-------------------------|--------------|---|--|--|--|
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Coumarins and Phenindione

International approved drug name(s) (approved brands):

Warfarin (Marevan®)

Acenocoumarol (Sinthrome®)(Acenocoumarol®)

Phenindione

Indications^{1,2,3}

The following indications and target INRs for adults take into account recommendations of the British Society of Haeamatology guidelines on oral anticoagulation with warfarin – fourth edition⁷. The guidelines have recommendations for warfarin and have been extrapolated for use with the other vitamin K antagonists (Acenocoumarol and phenindione).

| INDICATIONS FOR ANTICOAGULATION | INR Target | INR Range |
|--|------------|-----------|
| Atrial Fibrillation/atrial flutter | 2.5 | 2.0 - 3.0 |
| Atrial arrhythmias for ablation | 2.5 | 2.0 - 3.0 |
| Atrial Fibrillation for cardioversion (NB. INR $2.5 - 3.0$ for at least 3 weeks before and 4 weeks post cardioversion). | 2.5 | 2.0 - 3.0 |
| Cardiomyopathy | 2.5 | 2.0 - 3.0 |
| Mitral Valve Disease (with additional thrombotic risk factors - AF, history of systemic embolism or an enlarged left atrium) | 2.5 | 2.0 - 3.0 |
| Bioprosthetic valve: | | |
| Mitral position – 3 months duration | | |
| • History of systemic embolism (at least 3 months anticoagulation) | 2.5 | 2.0 - 3.0 |
| Left atrial thrombus at surgery (anticoagulation until clot resolved) | 210 | 210 010 |
| Other prothrombotic risk factors such as AF, low ventricular ejection fraction. | | |
| Aortic Valve Mechanical Prosthesis (St Jude) no history of thromboembolic complications | 3.0 | 2.5 - 3.5 |
| Mechanical Prosthetic Heart Valve (other than St Jude) | 3.5 | 3.0 - 4.0 |
| Deep Vein Thrombosis (DVT): | 2.5 | 2.0 - 3.0 |
| Pulmonary Embolism (PE): | 2.5 | 2.0 - 3.0 |
| Recurrence of DVT/ PE when off warfarin | 2.5 | 2.0-3.0 |
| Recurrence of DVT/PE when on warfarin and within the rapeutic range of $2.0-3.0$ | 3.5 | 3.0 - 4.0 |
| Acute arterial embolism proceeding to embolectomy (consider long term treatment) | 2.5 | 2.0-3.0 |
| Antiphospholipid syndrome | 2.5 | 2.0 - 3.0 |

* According to individual patient risk assessment, including position of valve, history of VTE, left atrial thrombus, other risk factors, e.g. atrial fibrillation

Coumarins and Phenindione

| Risks associated with surgery | Increased bleeding risk |
|-------------------------------------|--|
| Advice in the peri-operative | There is no specific advice relating to other vitamin K antagonists (phenidione and coumarin) – therefore advice is that of warfarin |
| period | • Stop anticoagulant 5 days before to allow INR to fall to less than 1.5 ^{2,3} |
| | Treatment dose LMWH should be given to those patients that require bridging (see below) as the INR falls below the patients therapeutic range⁴ |
| | Warfarin can be resumed where appropriate, approximately 12-24 hours (the evening of or the next morning) after surgery if haemostasis is secure and deemed appropriate³ |
| | For all other invasive procedures local protocol should be followed² as to whether warfarin can be continued |
| | • Dental surgery – The risk of significant bleeding in patients on oral anticoagulants and with a stable INR in the therapeutic range 2-4, is low. The risk of thrombosis if anticoagulants are discontinued may be increased. Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental treatment. An appreciation of the surgical skills of primary care dentists and the difficulty of surgery, particularly when INR levels approach ⁴ , is also important when assessing the risk of bleeding. Individuals, in whom the INR is unstable, should be discussed with their anticoagulant management team ⁴ . |
| | Peri-operative bridging therapy: (1,2,3,4) |
| | Pre-operative bridging carries a low risk of bleeding but the use of post-operative bridging requires careful consideration due to the high risk of bleeding therefore post-operative bridging should not be started until at least 48 h after high bleeding risk surgery. |
| | Patients with low risk AF (no prior stroke or TIA) do not require bridging therapy. |
| | Patients with a bileaflet aortic Mechanical Heart Valve (MHV) with no other risk factors do not require bridging. |
| | Patients with a VTE greater than 3 months and less than one year may be suitable for prophylactic dose LMWH. |
| | Patients with a VTE less than 3 months ago, patients with AF and previous stoke or TIA or multiple other risk factors, and patients with a mitral MHV and with recurrent VTE should be considered for bridging therapy with therapeutic dose LMWH. |
| | In patients who are receiving bridging anticoagulation with therapeutic dose LMWH the last dose of LMWH should be administered 24 hours before surgery. |
| Special | Emergency surgery |
| Instructions | For surgery that requires reversal of warfarin and that can be delayed for 6–12 h, the INR can be corrected by giving intravenous vitamin K^4 . |
| | For surgery that requires reversal of warfarin and which cannot be delayed, for vitamin K to have time to take effect the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery ⁴ . Contact haematology for further advice. |

If the patient has swallowing difficulties or an Enteral Feeding Tube⁶

- Use liquid preparation where available or disperse the tablets in water immediately prior to administration.
- Where possible give the warfarin dose during a break in the feeding regimen; when this is not possible, ensure that the timing of feed and dose are kept as stable as possible.

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| | Dihydropyridine | (Calcium Channel Blockers) | |
|-------------------------------------|---|--|--|
| | International Approved Drug | Name (approved brands): | |
| | Amlodipine (Istin®) | Nicardipine (Cardene®) | |
| | Felodipine (Vascalpha®) | Nifedipine (Adalat®) | |
| | Lacidipine (Motens®) | Nimodipine Nimotop®) | |
| | Lercanidipine (Zandip®) | | |
| Indication(s) | Nifedipine, nicardipine, amlodipine, and felodipine: treatment of angina or hypertension. All are valuable in forms of angina associated with coronary vaso | | |
| | Lacidipine, and lercanidipine | treatment of hypertension only. | |
| | Nimodipine: vascular spasm foll | owing aneurysmal subarachnoid haemorrhage⁵. | |
| | Nifedipine: Raynauds phenonen | non ⁶ . | |
| Risks associated with surgery | | nced additive hypotensive effects, this may result when anaesthetics such as enflurane and isoflurane ³ . | |
| Advice in the | Peri-operatively: | | |
| peri-operative period | Continue treatment to prevent rebound hypertension and coronary vasospasm ^{1,10} . There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of angina. ⁵ | | |
| | To continue with caution if eject | ion fraction is below 40%. ¹⁰ | |
| | contribute to a patient developing increases with increased dose a | I blockers may cause a reflex tachycardia which may ng atrial fibrilation. The incidence of reflex tachycardia and will generally be observed when the medication on removal of the medication, reflex tachycardia will | |
| | For hypertensive patients with a of the first line treatment option | ortic regurgitation, calcium channel blockers are one ${\rm S.}^{\rm 8}$ | |
| | Post-operative coronary byp | ass surgery: | |
| | Dihydropyridines such as amloo pressure is controlled on beta b | ipine can be stopped post cardiac surgery if blood locker and ACE inhibitor ^{4,10} . | |
| Special Instructions | term management of hypertens | edipine are not recommended for angina or long- ion; their use may be associated with large variations hycardia which can cause complications such as ischaemia. ⁷ | |
| | Swallowing difficulties/ente | ral feeding considerations: | |
| | | hypotension if converted from a long acting preparation refore not recommended, switch to amlodipine ² . | |

Dihydropyridine (Calcium Channel Blockers)

Felodipine is long acting (MR) preparation so cannot be crushed: switch to amlodipine².

For angina control whilst nil by mouth a GTN patch or infusion could be considered. IV nicardipine is licensed for specialist use for indications such as post-operative hypertension.

Metabolism:

Liver impairment; consider dose reductions for amlodipine and felodipine ⁵. Use of lacidipine results in a greater antihypertensive effect⁵. In cirrhosis the clearance of nimodipine is reduced, monitor blood pressure⁵.

Renal impairment: dose reduce lercanidipine⁶ and nifedipine.

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|------------|-----|--|
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| | | |
| | | |

| | Dipeptidylpeptidase-4 (Gliptins) | (DPP-IV) Inhibitors | |
|---|--|---|--|
| Indication(s) | International Approved Drug Name: Alogliptin (Vipidia®) Linagliptin (Trajenta®) Saxagliptin (Onglyza®) Sitagliptin (Januvia®) Vildagliptin (Galvus®) | Combination products: Vipdomet® (alogliptin with metformin) Jentadueto® (linagliptin with metformin) Komboglyze® (saxagliptin with metformin) Janumet® (sitagliptin with metformin) Eucreas® (vildagliptin with metformin) ther alone or in combination with insulin or | |
| Risks associated with surgery | Potential for hypoglycaemia, especially if also taking another antidiabetic drug or insulin ^{1,2,3,4,5,6} . | | |
| Advice in the peri-operative period | Pre-operatively: Continue^{2,3,4,5,6,7}. DPP IV inhibitors can be safely continued throughout the peri-operative period. Post-operatively: Continue. However, if a patient is receiving variable rate insulin infusion stop oral and do not recommence until eating and drinking normally7. Combination products: For advice on combination products follow metformin monograph | | |
| Special Instructions | Be aware that an unconscious or sedated patient may not exhibit all the signs of hypoglycaemia. | | |
| References | Available at: <u>http://www.medicines.org.uk</u> Boehringer Ingelheim Ltd. (2016). Trajent (SPC) - (eMC). Available at: <u>http://www.medicines.org.uk</u> T June 2016] AstraZeneca UK Ltd (2016). Onglyza table | w.bnf.org [Accessed: 17 June 2016]. ummary of Product Characteristics (SPC) - (eMC). /emc/medicine/28513 [Accessed 17 June 2016] a tablets - Summary of Product Characteristics adicines.org.uk/emc/medicine/25000 [Accessed ts - Summary of Product Characteristics (SPC) - .org.uk/emc/medicine/22315 [Accessed 17 June | |

Dipeptidylpeptidase-4 (DPP-IV) Inhibitors (Gliptins)

- Merck Sharp and Dohme (2016). Januvia tablets Summary of Product Characteristics (SPC) - (eMC). Available at: <u>http://www.medicines.org.uk/emc/medicine/19609</u> [Accessed 17 June 2016]
- Novartis Pharmaceuticals UK Ltd. (2016). Galvus tablets Summary of Product Characteristics (SPC) - (eMC). Available at: <u>http://www.medicines.org.uk/emc/</u> medicine/20734 [Accessed 17 June 2016]
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Dipyridamole

Approved brands:

Persantin® Indication(s) Secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin¹. An adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves¹. **Risks** Risks associated with drug continuation during surgery: associated Post procedural haemorrhage and intraoperative haemorrhage with surgery Risks associated with stopping therapy: Ischemic event Advice in the There is no data on the safety of dipyridamole if continued in the peri-operative period. Factors to consider in deciding whether to continue or hold dipyridamole reflect a peri-operative balance between the risk of bleeding and risk of ischemic events. period If discontinued, the drug should be stopped at least two days before surgery². Dipyridamole has antiplatelet and vasodilator properties and has a half-life of 10 hours. It is typically used in combination with Aspirin³. Perioperative management should weigh the risk and benefits including the possibility of increased risk of bleeding caused by the combination of aspirin and dipyridamole therapy.4 **Special** Patients on dual antiplatelet therapy at are higher risk of bleeding and higher risk of discontinuation. These patients should be considered on an individual basis⁴. Instructions Swallowing difficulties / enteral feeding considerations: Suspension is available. Alternatively, dipyridamole capsules can be opened and contents dispersed in water for administration. The granules should not be crushed. Enteral feeding tubes should be flushed well as there is a potential for the granules to block feeding tubes⁵. Metabolism: Metabolism of dipyridamole occurs in the liver predominantly by conjugation with glucuronic acid to form a monoglucuronide¹. Renal excretion is very low $(1 - 5\%)^1$. **Counselling points:**

Preferably taken after meals to avoid gastrointestinal side effects¹.

Dipyridamole

Side effects¹:

Adverse reactions at therapeutic doses are usually mild. Vomiting, diarrhoea and symptoms such as dizziness, nausea, dyspepsia, headache and myalgia have been observed. These tend to occur early after initiating treatment and may disappear with continued treatment.

As a result of dipyridamoles vasodilating properties, there is the potential for hypotension, hot flushes and tachycardia. Worsening of the symptoms of coronary heart disease such as angina and arrhythmias have been noted.

Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioodema have been reported. In very rare cases, increased bleeding during or after surgery has been observed

Surgery related Interactions:

Dipyridamole increases the plasma levels and cardiovascular effects of adenosine¹.

If a patient is taking dipyridamole and supraventricular tachycardia (SVT) occurs intra-operatively requiring treatment with adenosine, the initial post-operative dose of dipyridamole should be reduced.

Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs and counteract the anticholinesterase effect of cholinesterase inhibitors. Resulting in potential aggravation of myasthenia gravis.

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Direct Oral Anticoagulants

*This group of agents have previously been referred to as NOACs (novel oral anticoagulants)

| | International Approved Drug Name (approved brands): | | | | |
|---|--|--|---|---|--|
| | Apixaban (Eliquis® | 9) | Edoxaban (Lixiana | ®) | |
| | Dabigatran (Prada | xa®) | Rivaroxaban (Xare | lto [®]) | |
| Indication(s) | Prevention of stroke and systemic embolism in people with nonvalvular atrial fibrillation ^{2,4,5,6} . | | | | |
| | Treatment and pre | evention of deep vein th | rombosis and pulmona | ary embolism ^{2,4,5,6} . | |
| | | bus thromboembolism a se post-operatively) ^{2,3,5,} | | ement surgery in | |
| Risks associated with surgery | Risk of peri-operative thromboembolism: Risk stratification should be performed to assess the likelihood of thromboembolism if DOAC (direct oral anticoagulant) therapy is withheld. If there is a high likelihood of thromboembolism bridging therapy with LMWH should be considered. | | | inticoagulant) therapy | |
| | Risk of peri-operative bleeding due to continuation of therapy: Where there is insufficient time to allow the anticoagulant effect to wear off the increased ris bleeding should be assessed against the urgency of the intervention. | | | | |
| Advice in the peri-operative period | stopped 24 hours | The European Heart Rhythm Association (EHRA) ⁹ recommends that DOACs can be stopped 24 hours before procedures that do not have a clinically important bleeding risk e.g. ophthalmological and superficial dermatological procedures. | | | |
| period | For moderate and major surgical interventions it is recommended that direct oral anticoagulants are stopped during the peri-operative period, as there is a lack of evidence for the safety of surgery while on these agents. | | | | |
| | Each DOAC has a different half-life which are extended in worsening renal impairment, please see below for drug specific guidance. | | | | |
| | | | Procedure with low bleeding risk | Procedure with high bleeding risk | |
| | DOAC | Renal Function | 12-25% residual anticoagulant effect at time of surgery acceptable | <10% residual anticoagulant effect at time of surgery acceptable | |
| | | CrCl >50mL/min | These agents should be stopped 24 hours before procedure. | These agents should be stopped 2 days before procedure. | |
| | Edoxaban ^{4,8} | | No edoxaban to be taken on day of procedure. | No edoxaban to be taken on day of procedure. | |
| | (once daily preparation) | CrCl 15-50mL/min | These agents should be stopped 2 days before procedure. | These agents should be stopped 3 days before procedure. | |
| | | | No edoxaban to be taken on day of procedure. | No edoxaban to be taken on day of procedure. | |

Direct Oral Anticoagulants

| | | Procedure with low bleeding risk | Procedure with high bleeding risk |
|----------------------------------|---|---|---|
| DOAC | Renal Function | 12-25% residual anticoagulant effect at time of surgery acceptable | <10% residual anticoagulant effect at time of surgery acceptable |
| | CrCl >30mL/min | Rivaroxaban should be stopped 2 days before procedure (i.e. miss one dose). | Rivaroxaban should be stopped 3 days before procedure (i.e. miss two doses). |
| Rivaroxaban ^{3,8,9,10} | | No rivaroxaban to be taken on day of procedure. | No rivaroxaban to be taken on day of procedure. |
| (once daily preparation) | CrCl 15-30mL/min *Patients with a | Rivaroxaban should be stopped 3 days before procedure (i.e. miss two doses). | Rivaroxaban should be stopped 4 days before procedure (i.e. miss three doses). |
| | CRCI<15ml/min should not be receiving rivaroxaban - discuss with haematology | No rivaroxaban to be taken on day of procedure. | No rivaroxaban to be taken on day of procedure. |
| | CrCl >30mL/min | Apixaban should be stopped 2 days before procedure (i.e. miss two doses). | Apixaban should be stopped 3 days before procedure (i.e. miss four doses). |
| Apixaban ^{5,8,9,10} | | No apixaban to be taken on day of procedure. | No apixaban to be taken on day of procedure. |
| (twice daily preparation) | CrCl 15-30mL/min *Patients with a | Apixaban should be stopped 3 days before procedure (i.e. miss four doses). | Apixaban should be stopped 4 days before procedure (i.e. miss six doses). |
| | CRCI<15ml/min should not be receiving apixaban - discuss with haematology | No apixaban to be taken on day of procedure. | No apixaban to be taken on day of procedure. |
| | CrCl >50mL/min | Dabigatran should be stopped 2 days before procedure (i.e. miss two doses). | Dabigatran should be stopped 3-4 days before procedure (i.e. miss four- six doses). |
| Dabigatran ^{2,6,8,9,10} | | No dabigatran to be taken on day of procedure. | No dabigatran to be taken on day of procedure. |
| (twice daily preparation) | CrCl 30-50mL/min | Dabigatran should be stopped 3 days before procedure (i.e. miss four doses). | Dabigatran should be stopped 5-7 days before procedure (i.e. miss eight-twelve doses). |
| | | No dabigatran to be taken on day of procedure. | No dabigatran to be taken on day of procedure. |

| Special Instructions | Ons There is no direct reversal agent for these agents, if required in an emergency with local haemaphilia/haematology team for specific guidance. | | |
|-------------------------|---|---|--|
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| | 4. | SmPC: Lixiana accessed via emc.medicines.org.uk (Last update: 24/11/2015) | |
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| | 6. | NICE guidelines and technology appraisals via <u>www.nice.org.uk</u> (Apixaban, NICE TA275; Dabigatran, TA249; Edoxaban, TA355; Rivaroxaban, TA256) | |
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Donepezil Hydrochloride

| | Approved brands: |
|-------------------------------------|---|
| | Aricept® |
| | Aricept Evess® (orodispersible preparation) |
| Indication(s) | Mild to moderate dementia in Alzheimer's disease ¹ . |
| Risks associated | Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain ² . |
| with surgery | Due to its mechanism of action (cholinesterase inhibitor) donepezil is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia ² .Additive effects may be expected if donepezil is given with other anticholinesterases such as neostigmine, cholinergic drugs such as pilocarpine and neuromuscular blockers such as suxamethonium (succinylcholine) ³ . |
| | The clinical relevance of this interaction is unclear. One study has shown that the use of cholinesterase inhibitors was not associated with an increased risk of postoperative complications among older adults with dementia ⁴ . Case reports suggest treatment with donepezil led to prolonged post-operative muscle relaxation ^{5,6,7,8} . |
| | Donepezil has an elimination half-life of 70 hours ⁹ . In order to completely deplete body stores of donepezil treatment would need to be discontinued for at least three weeks ¹⁰ . There have been two case reports of patients suffering from mood changes, agitation, trouble sleeping and difficulty concentrating following the discontinuation of donepezil ⁹ . |
| | An increased risk factor for the development of post-operative delirium is dementia ¹¹ . Cholinergic enhancement with donepezil has been proposed to decrease the risk of delirium after hip surgery in elderly patients, but the results from small pilot studies have been disappointing ¹² . |
| Advice in the peri-operative period | Consideration should be given to the type of anaesthetic that will be used during surgery. Some types of anaesthesia (e.g. regional anaesthesia) do not involve the use of muscle relaxants ⁴ which removes the issue of potential interactions. |
| | Elective Surgery: |
| | The anaesthetist should be made aware that the patient is taking donepezil. |
| | Consider stopping donepezil three weeks prior to surgery if succinylcholine-type muscle relaxants are going to be used during anaesthesia. |
| | Stopping donepezil for this period of time may lead to a loss of cognitive function which is only partially regained when therapy is resumed ¹³ . Therefore, the decision to stop should be made on clinical grounds. |
| | Emergency Surgery: |
| | The anaesthetist should be made aware that the patient is taking donepezil and |

The anaesthetist should be made aware that the patient is taking donepezil and there is a potential for exaggeration of succinylcholine-type muscle relaxation during anaesthesia.

Donepezil should be continued.

Donepezil Hydrochloride

| Special Instructions | As a | above |
|-------------------------|------|--|
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| | Ref | erences checked but no relevant evidence identified: |
| | Mar | tindale: The complete drug reference, accessed at www.medicines.org.uk |
| | Nice | e.org.uk searched on 16th June 2015 |
| | - | al College of Anaesthetists website https://www.rcoa.ac.uk |

International Approved Drug Name (approved brands):

Pramipexole (Mirapexin®)(Mirapexin® Prolonged Release)(Oprymea®)(Oprymea® prolonged release)

Ropinirole (Adartrel®)(Eppinix XL®)(Ralnea XL®)(Raponer XL®)(Repinex XL®) (Requip®)(Requip XL®)(Ropilynz XL®)(Ropiqual XL®)

Rotigotine (Neupro®)

Indication(s) Pramipexole 1-6

Treatment of the signs and symptoms of idiopathic Parkinson's disease, alone or in combination with levodopa. Often used in combination with levodopa when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations).

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Ropinirole^{1,7-15}

Initial treatment of Parkinson's disease as monotherapy, to delay the introduction of levodopa

In combination with levodopa for treatment of Parkinson's disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur ("end of dose" or "on-off" type fluctuations).

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Rotigotine 1,16

Treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease alone or in combination with levodopa. Often used in combination with levodopa when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations).

Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS) in adults.

Risks associated with surgery When used alone, dopamine agonists cause fewer motor complications in long-term treatment compared with levodopa treatment but the overall motor performance improves slightly less. The dopamine agonists are associated with more psychiatric side-effects than levodopa¹.

Parkinson's patients are high risk surgical patients, due to their increased risk of aspiration pneumonia and post operative respiratory failure. Delaying or missing doses for any patient, medical or surgical, can have a significant impact on their disease management. Particular attention should be given when considering their medication management throughout the peri-operative period.

Risks associated with stopping therapy:17-28.

The half-life of dopaminergic agonists (Pramipexole, Ropinirole, Rotigotine) is variable. Delayed administration or missing doses of dopaminergic agonists for longer than 6-12 hours may significantly worsen a patient's symptoms. Risks associated include

| aspiration, speech problems, dysphagia, and falls. Rarely, neuroleptic malignant |
|--|
| syndrome or related withdrawal syndromes may also occur. These complications can |
| cause significant patient distress and are potentially fatal. |

Risks in continuing therapy:1-16,20,24-28

Direct stimulation of dopamine receptors can cause a theoretical risk of arrhythmias and also carry a risk of postural hypotension. The following adverse effects are also possible: nausea/vomiting, hallucinations, impulse control disorder and confusion.

However, if medication is stopped, the risk of worsening symptoms of Parkinson's disease is greater than compared to the risk of side effects if the medication is continued. It is advisable to continue parkinsonian drug therapy throughout the peri-operative period and any complications managed as appropriate by the anaesthetist.

Advice in the peri-operative period Parkinson's patients awaiting surgery should be prioritised and placed first on the list in order to minimise the length of time they need to be kept nil by mouth (NBM)^{23,28}. For prolonged periods of NBM (nil by mouth), please refer to the "special instructions" section detailed below.

All patients having surgery under general or regional anaesthetic require preoperative fasting. It is safe to continue oral medication therapies with sips of water (maximum 50mls) up to 2 hours before elective surgery. Continue oral Parkinson medications until the time of anaesthetic induction^{23,28}. Patients prescribed and established on transdermal patches (rotigotine/Neupro® transdermal patch) should have these left in situ throughout the peri-operative period at their established dose^{19,28}.

Regional anaesthesia is preferable as this will allow monitoring of Parkinson's symptoms peri-operatively. However, some motor symptoms of Parkinson's disease might make a general anaesthetic preferable. In exceptional circumstances oral medication can be administered intraoperatively. The anaesthetist should be aware of the effects of routinely used anaesthetic drugs on parkinsonism. Centrally acting dopamine antagonists should be avoided ^{19,23,28}.

Where possible the patient's established medication regime should be maintained. Treatment should be restarted as soon as oral tolerance tests allow. For non-abdominal surgeries, treatment could start after 2-3 hours ¹⁹post-operatively.

Patients who do not rapidly regain the ability to take their usual medication should be seen by a Parkinson's disease specialist or elderly care consultant at the earliest opportunity¹⁹.

Anti-emetics such as metoclopramide and dopamine should not be used in Parkinsonian patients.

Special If the total duration of surgery and NBM period will be > 6 hours consider the use of a rotigotine patch or other alternative medication regimens^{19,23,28}.

Surgery requiring a strict NBM period: e.g abdominal surgery

Rotigotine patches can be used when the patient is NBM ¹⁹.

See below for conversions.

Surgery requiring a period of NBM for a few hours: e.g non-abdominal surgery

Medication may be administered through an enteral tube with a minimal amount of water, commencing 2 hours after surgery¹⁹.

Surgery requiring subsequent admission to an intensive care unit:

Continue patient's usual régimen. If the patient is NBM (ie. intubated, sedated) then convert the patient to the equivalent dose of rotigotine (patch), based on their dopamine dose. No additional medication is required in cases where patients are intubated and sedated¹⁹.

Management of patients with swallowing difficulties or enteral tubes in situ^{29,30.}

| Medicine | Formulation | Recommendation | |
|-------------|------------------|---|--|
| | Tablets | Continue current regimen, plain release tablets will disperse in water. | |
| Prominovolo | (plain release) | | |
| Pramipexole | Modified Release | Convert to plain release tablets. | |
| | Tablets | Divide total daily dose into TDS regimen. | |
| | Tablets | Continue current regimen, plain release tablets will disperse in water. | |
| Popipirala | (plain release) | | |
| Ropinirole | Modified Release | Continue current regimen, plain release | |
| | Tablets | tablets will disperse in water. | |

If an enteral tube is not in place before the next dose of Parkinson's medication is due, prescribe rotigotine patch and review in 24 hours (see below for conversion tables). If symptom control sub-optimal contact specialist for advice.

Rotigotine conversion table when only using a dopamine agonist preparations^{16,19,23,31,32,34}

Rotigotine patches have proven effectiveness and feasibility of use in the perioperative period and are ideal in cases of dysphagia.

| Pramipexole (salt content) | Ropinirole | Controlled release Ropinirole | Rotigotine patch |
|----------------------------|--------------|-------------------------------|------------------|
| 0.125mg tds | Starter pack | 2mg/day | 2mg/24 hrs |
| 0.25mg tds | 1mg tds | 4mg/day | 4mg/24hrs |
| 0.5mg tds | 2mg tds | 6mg/day | 6mg/24hrs |
| 0.75mg tds | 3mg tds | 8mg/day | 8mg/24hrs |
| 1mg tds | 4mg tds | 12mg/day | 10-12mg/24hrs |
| 1.25mg tds | 6mg tds | 16mg/day | 14mg/24hrs |
| 1.5mg tds | 8mg tds | 24mg/day | 16mg/24hrs |

Notes:

 DO NOT cut patches – available as 2mg/4mg/6mg/8mg patches. More than one patch can be applied at any one time. Note 1mg/3mg are also available but these are not licensed for use in Parkinson's.

- · Max dose 16mg/24 hours
- Do not use the same site for 14 days.
- Treat each patient individually and adjust doses accordingly:
 - ▶ if increased stiffness/slowness observed, increase dose and review daily
 - ▶ if increased confusion/hallucinations observed, decrease dose and review daily

Rotigotine conversion tables when only taking levodopa preparations:^{16,23,33}

Before initiating rotigotine in a dopamine agonist naïve patient, exercise caution as it can cause nausea, vomiting, skin reaction, hypotension, hallucinations and increased confusion. Start with the lowest possible dose and titrate slowly in patients with dementia/delirium. Specialist opinion needs to be sought as soon as possible. Resume usual drug regime as soon as possible.

| Current levodopa regime | Rotigotine patch equivalent |
|--------------------------------|-----------------------------|
| Madopar or Sinemet 62.5mg BD | 2mg/24hrs |
| Madopar or Sinemet 62.5mg TDS | 4mg/24hrs |
| Madopar or Sinemet 62.5mg QDS | 6mg/24hrs |
| Madopar or Sinemet 125mg TDS | 8mg/24hrs |
| Madopar or Sinemet 125mg QDS | 10mg/24hrs |
| Madopar or Sinemet 187.5mg TDS | 12mg/24hrs |
| Madopar or Sinemet 187.5mg QDS | 16mg/24hrs |
| Madopar or Sinemet 250mg TDS | 16mg/24hrs |
| Madopar or Sinemet 250mg QDS | 16mg/24hrs |
| Stalevo 50/12.5/200 TDS | 6 mg /24 hours |
| Stalevo 100/25/200 TDS | 10 mg /24 hours |
| Stalevo 100/25/200 QDS | 14 mg /24 hours |
| Stalevo 150/37.5/200 TDS | 16 mg /24 hours |
| Stalevo 200/50/200 TDS | 16 mg /24 hours |

- DO NOT cut patches available as 2mg/4mg/6mg/8mg patches. More than one patch can be applied at any one time. Note 1mg/3mg are also available but these are not licensed for use in Parkinson's. Max dose 16mg/24 hours
- Controlled release levodopa preparations are equivalent to 2mg/24 hours of rotigotine.
- Do not use the same site for 14 days.
- Treat each patient individually and adjust doses accordingly:
 - if increased stiffness/slowness observed, increase dose and review daily if increased confusion/hallucinations observed, decrease dose and review daily

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Doxazosin

Approved Brands:

| | Cardura ® | | |
|-------------------------------------|---|--|--|
| Indication(s) ¹ | Hypertension Benign Prostatic Hyperplasia (BPH) | | |
| Risks associated with surgery | IFIS (Intraoperative Floppy Iris Syndrome) – Meta-analysis ² examined the comparative incidence of IFIS was examined across a range of alpha-blockers, in patients having undergone cataract surgery. The incidence of IFIS in the study population (n = 2028) was significantly higher in doxazosin patients (16 %; $p < 0.0001$) than control groups, with a higher complication rate associated with affected patients ² . | | |
| | Further studies ³ examined comparative incidence of IFIS across a range of alpha- blockers, with doxazosin use demonstrating an IFIS incidence similar to other alpha- blockers such as terazosin and alfuzosin ³ . | | |
| Advice in the peri-operative | It is reasonable to withhold doxazosin prior to cataract surgery to decrease the risk of IFIS ^{2,5} . | | |
| period | No specific recommendations surrounding timescales are available however it is reasonable to advise temporary withdrawal of doxazosin for two weeks prior to cataract surgery ⁴ . | | |
| Special Instructions | If doxazosin is withheld peri-operatively, blood pressure should be closely monitored upon restarting treatment, owing to the risk of severe hypotension ⁶ . Prolonged release formulations should not be crushed for administration via enteral feeding tubes post-operatively, owing to the risk of profound hypotension ⁶ . | | |
| | If indicated for the treatment of BPH (Benign Prostatic Hyperplasia), doxazosin may be stopped following an effectual TURP (Transurethral Resection of Prostate), subject to a successful TWOC (Trial Without Catheter). | | |
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Fentanyl

| | - | | | |
|---------------|--|---|--|--|
| | Transdermal patches (approved brands): | Buccal and Sublingual Tablets (approved brands): | | |
| | Durogesic® | Abstral® | | |
| | Fencino® | Breakyl® | | |
| | Fentalis® | Effentora® | | |
| | Matrifen® | Recivit® | | |
| | Mezolar® | Buccal Lozenges (approved brands): | | |
| | Opiodur® | Actiq® | | |
| | Osmanil® | Nasal spray (approved brands): | | |
| | Victanyl® | Instanyl® | | |
| | Yemex® | Pecfent® | | |
| | | | | |
| Indication(s) | The management of chronic intractable pain due to cancer in adults ^{1a} . | | | |
| | The management of chronic intractable pain in adults ^{1a} . | | | |
| | Long term management of severe chronic pain in children receiving opioid therapy from 2 years of age ^{1a} . | | | |
| | The management of breakthrough pain (BTP) in adults who are already receiving maintenance opioid therapy for chronic cancer pain ^{1b,1c,1d} . | | | |
| | Fentanyl injection is used as an adjunct to general anaesthetics, and as an anaesthetic for induction and maintenance. | | | |
| Risks | **As per strong opioids monograph | | | |
| associated | Minimise missed doses to avoid withdrawal if a patient is on chronic opioid therapy. | | | |
| with surgery | If patches are removed, a longer time to steady state concentration will result in delay of analgesia. | | | |
| | Interaction with postoperative analgesia regimes-take regular opioid use into consideration to prevent opioid toxicity or conversely prevent under dosing in those opioid tolerant. | | | |
| | Regular observations for signs of toxicity i.e, sedation scores, respiratory rates, blood pressure will ensure opioid toxicity is detected early. | | | |
| | Interactions ⁴ | | | |
| | There is some evidence that the presence of amiodarone possibly increases the risk of complications (atropine-resistant bradycardia, hypotension, decreased cardiac output) during general fentanyl-based anaesthesia, but other studies have shown no problems with fentanyl-based anaesthesia. | | | |
| | Seizures have rarely been associated with the use of propofol with alfentanil and/ or fentanyl. | | | |

Fentanyl

| • | A case of respiratory depression has been reported when intravenous lidocaine was |
|---|---|
| | given to a patient who had been receiving fentanyl and morphine. |

- Fentanyl has been given to patients taking MAOIs without problems, but case reports describe fatal hyperthermia in one patient and hypertension and tachycardia in another patient following concurrent use.
- Bradycardia has been reported when vecuronium was given with fentanyl in patients taking beta blockers and/or calcium-channel blockers.
- Patients taking carbamazepine alone or in combination with phenytoin appear to need more fentanyl than those not taking these antiepileptics.
- The analgesic effects of fentanyl might be increased by baclofen.
- Quinidine appears to increase the oral absorption and effects of fentanyl.
- Fluconazole negligibly increased and voriconazole slightly increased intravenous fentanyl exposure, whereas single-dose itraconazole had no effect. A fatality, possibly due to an interaction between fluconazole and transdermal fentanyl, has been reported, as has a case of opioid toxicity when itraconazole was used with transdermal fentanyl.
- In general the concurrent use of benzodiazepines with fentanyl in anaesthesia is synergistic but might also result in additive adverse effects, such as respiratory depression and/or hypotension.
- Two cases of serious respiratory depression have been described in patients receiving transdermal fentanyl, after clarithromycin was added.
- The serum concentrations and effects of transdermal fentanyl were decreased in two patients when they took rifampicin. Studies in healthy subjects have found that the bioavailability of oral transmucosal fentanyl is reduced by rifampicin.

Advice in the peri-operative period

**As per strong opioids monograph, additionally

Advice in the perioperative period will usually be to continue the fentanyl patch; however, this will be dependent on predicted postoperative analgesic requirements. Anaesthetic staff should always be made aware that patients are wearing a fentanyl patch preoperatively.

Transdermal preparations are considered not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because of the long time to steady state concentrations. However it is noted in some Trusts they are used as analgesic stepdown after major surgery or when oral routes are not available.

If it is necessary to remove a fentanyl patch it should be noted that drug concentrations will fall gradually, it takes 17 hours or more for the fentanyl serum concentrations to decrease 50%^{1a}.

If a patient is nil by mouth or has swallowing difficulties, fentanyl is available in a variety of different formulations which can be given during this period⁶.

Physicians should keep in mind the potential for abuse of fentanyl^{1d}.

Fentanyl

| Special | **As per strong opioids monograph, additionally | | | |
|--------------|---|--|--|--|
| Instructions | For advice on opioid dose conversions please contact pharmacy. | | | |
| | When replacing patches, apply to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of skin ^{1a} . | | | |
| | Sublingual tablets should be administered directly under the tongue at the deepest part. Sublingual tablets should not be swallowed, but allowed to completely dissolve ir the sublingual cavity without chewing or sucking. Patients should be advised not to ea or drink anything until the sublingual tablet is completely dissolved ^{1b} . | | | |
| | In patients who have a dry mouth water may be used to moisten the buccal mucosa before taking sublingual tablets ^{1b} . | | | |
| | Lozenges should be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximising the amount of mucosal exposure to the product. The lozenge should be sucked, not chewed, as absorption of fentanyl via the buccal mucosa is rapid in comparison with systemic absorption via the gastrointestinal tract ^{1c} . Water may be used to moisten the buccal mucosa in patients with a dry mouth ^{1c} . The lozenge should be consumed over a 15 minute period ^{1c} . | | | |
| | | | | |
| | Fentanyl has been reported to be effective in the treatment of postoperative shivering ³ | | | |
| References | Durogesic DTrans Transdermal Patch. Janssen-Cilag Ltd, September 2015. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 15.05.2016 | | | |
| | Abstral sublingual tablets. Prostraken, September 2015. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 15.05.2016 | | | |
| | Actiq lozenges. Teva Pharma B.V, September 2015. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 15.05.2016 | | | |
| | 1.d Pecfent nasal spray. Prostraken, September 2015. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 15.05.2016 | | | |
| | 2. British National Formulary. Accessed via www.medicinescomplete.com on 15.8.15 | | | |
| | 3. Martindale. Accessed via www.medicinescomplete.com on 17.05.16 | | | |
| | 4. Stockley's Drug Interactions. Accessed via www.medicinescomplete.com on 17.05.16 | | | |
| | 5. Micromedex. Accessed via www.micromedexsolutions.com on 21.05.2016 | | | |
| | Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.</u> <u>medicinescomplete.com</u> on 21.05.2016 | | | |
| | 7. Medline search via www.evidence.nhs.uk on 21.05.16 | | | |
| | 8. Embase search via www.evidence.nhs.uk on 22.05.16 | | | |
| | | | | |

GLP-1 analogues

| | International Approved Drug Name(s): Exenatide – available in both immediate release (Byetta®) and modified release (Bydureon®) preparations | | |
|-------------------------------------|--|--|--|
| | Liraglutide (Victoza®) Lixisenatide (Lyxumia®) | | |
| | Combination products: | | |
| | Xultophy® (insulin degludec with liraglutide) | | |
| Indication(s) | Treatment of type 2 diabetes mellitus in combination with other antidiabetic medications ¹ . | | |
| Risks associated with surgery | Risks associated with drug continuation during surgery: Potential for hypoglycaemia in patients who are also taking sulfonylureas ^{2,3,4,5} (risk is negligible as sulfonylureas are omitted prior to surgery – see sulfonylurea monograph) | | |
| | Risks associated with stopping therapy: Nil | | |
| Advice in the peri-operative | Pre-operatively: Continue ⁶ . | | |
| period | Post-operatively: GLP-1 analogue should be continued as usual, even if variable rate insulin infusion is commenced ⁶ . | | |
| | Combination product: for advice on Xultophy follow insulin degludec monograph | | |
| Special Instructions | Be aware that an unconscious or sedated patient may not exhibit all the signs of hypoglycaemia. | | |
| References | 1. British National Formulary Available at: www.bnf.org [Accessed: 7 January 2016]. | | |
| | AstraZeneca UK. (2015). Byetta solution for injection – Summary of Product Characteristics (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/19257</u> [Accessed: 7 January 2016] | | |
| | AstraZeneca UK. (2015). Bydureon powder and solvent for prolonged release suspension for injection – Summary of Product Characteristics (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/24665</u> [Accessed: 7 January 2016] | | |
| | Sanofi Aventis. (2014). Lyxumia solution for injection – Summary of Product Characteristics (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/27405</u> [Accessed: 7 January 2016] | | |
| | Novo Nordisk. (2015). Victoza solution for injection – Summary of Product Characteristics (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/21986</u> [Accessed: 7 January 2016] | | |
| | Management of adults with diabetes undergoing surgery and elective procedures: improving standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: <u>http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm</u> [Accessed 12 November 2015] | | |

| | H2-Receptor Antagonist | | |
|---|---|--|--|
| | International Approved Drug Name (approved brands): Cimetidine (Tagamet®) Famotidine Nizatidine Ranitidine (Zantac®)(Gavilast®) | | |
| Indication(s) | Treatment for non-steroidal anti-inflammatory drugs (NSAID) associated ulceration, benign gastric or duodenal ulcers ¹ . Treatment of functional dyspepsia ¹ . Treatment of postoperative ulcers and duodenal ulcers associated with <i>Helicobacter</i> <i>Pylori</i> ^{2,3} . | | |
| | Symptomatic relief of gastro-oesophageal reflux disease (GORD) and oesophageal reflux disease ^{2,3} . Prophylaxis of stress ulcers ¹ . | | |
| Risks associated with surgery | Risks associated with drug continuation during surgery: Masks symptoms of gastric cancer¹. There is a potential for psychiatric reactions in the elderly and very ill patients (confusion, depression, hallucination) ¹. Risks associated with stopping therapy: Potential for duodenal and gastric ulcers, functional dyspepsia and symptomatic GORD^{2,3}. NSAID associated ulceration¹. | | |
| Advice in the peri-operative period | Manufacturers of H2-receptor antagonists were unable to provide advice on their use in the perioperative period⁴. Avoid for 2 weeks prior to investigations for gastric cancers and <i>Helicobacter Pylori</i> or in patients who are undergoing endoscopic procedures¹. Can be used as pre-operatively to reduce gastric acid secretions, gastric pneumonitis and reduce the risk of GI bleeding ^{5,6,7,8,9}. When used concomitantly with H1-receptor antagonists, H2- receptor antagonists contribute to a reduced incidence of postoperative nausea and vomiting ⁷. In critically ill patients, H2-receptor antagonists are more effective than proton pump inhibitors at lowering gastrointestinal bleeding⁹. | | |

| Special Instructions | Pre-operatively: To prevent aspiration pneumonitis it is more effective to administer ranitidine 300mg orally 4 hours preoperatively than when administered 2 hours preoperatively¹⁰. Cimetidine reduces gastric secretion acidity when given 2-4 hours preoperatively¹¹. Post-Operatively: When used for post-operative ulceration, treatment should last for 4 weeks. A further 4 weeks treatment is possible if the ulcers have not fully healed^{2,3}. | | | | | | |
|-------------------------|--|--|--|--|------------|--|---|
| | | | | | | | |
| | | | | | References | 1. | British National Formulary Available at: www.bnf.org [Accessed: 22nd March 2016] |
| | | | | | | 2. | Aurobindo Pharma – Milpharm Ltd. (2015) <i>Ranitidine 150mg Tablets – Summary of Product Charecteristics (SPC)</i> – (eMC). Available from: <u>https://www.medicines.org.uk/emc/medicine/23245</u> [Accessed 12 th May 2016] |
| 3. | | | | | | Accord Healthcare Limited. (2012) <i>Cimetidine 400mg Tablets BP – Summary of Product Charecteristics (SPC) –</i> (eMC). Available from: <u>https://www.medicines.org.uk/emc/</u> medicine/25754 [Accessed 12 th May 2016] | |
| 4. | Personal correspondence with Chemidex Pharma regarding Tagamet® (5th May 2016) | | | | | | |
| | 5. | Trekova, NA. lavorovskii, AG. Shmyrin, MM. et al. (2002). Use of H2-receptor blocker famotidine (quamatel) in anesthesiology for cardiopulmonary bypass surgery. <i>Anesteziologiia i Reanimatologiia</i> . 1 (1), 16-19. | | | | | |
| | 6. | Clark, K. Lam, LT. Gibson, S. et al. (2009). The effect of ranitidine versus proton pump inhibitors on gastric secretions: a meta-analysis of randomised control trials. <i>Anaesthesia</i> . 64 (6), 652-657. | | | | | |
| | 7. | Doenicke, AW. Hoernecke, R. Celik, I. (2004). Premedication with H1 and H2 blocking agents reduces the incidence of postoperative nausea and vomiting. <i>Inflammation Research.</i> 53 (2), 154-158. | | | | | |
| | 8. | Hong, JY. (2006). Effects of metoclopramide and ranitidine on preoperative gastric contents in day-case surgery. <i>Yonsei Medical Journal</i> . 47 (3), 315-318 | | | | | |
| | 9. | Alshamsi, F. Belley-Cote, E. Cook, D. et al. (2016). Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta- analysis of randomized trials. <i>Critical Care</i> . 20 (120), 1-12. | | | | | |
| | 10. | Momose, K. Shima, T. Haga, S. et al. (1992). The effect of preoperative oral administration of ranitidine on pH and volume of gastric juice. <i>Masui. The Japanese Journal of Anaesthesiology.</i> 41 (9), 1482-1485. | | | | | |
| | 11. | Seraj, MA. El-Nakeeb, MM. Estafan, MY. et al. (1980). The preoperative use of cimetidine in reducing acidity of gastric secretion. <i>Middle East Journal of Anaesthesiology</i> . 5 (7), 445-455. | | | | | |

Hormone Replacement Therapy (HRT)

| Approved Brands | Oestrogen | Progesterone | Formulation | | |
|---|--------------------------------|-----------------------------|-------------|--|--|
| Conjugated Oestrogen alone | | | | | |
| Premarin | Conjugated Oestrogen | | Tablet | | |
| | Conjugated Oestrogens | with Progestogen | | | |
| Premique | Conjugated oestrogen | Medroxyprogesterone acetate | Tablet | | |
| Prempak-C | Conjugated oestrogen | Norgestrel | Tablet | | |
| Estradiol/Estradiol valerate alone | | | | | |
| Bedol | | | | | |
| Climaval | | | | | |
| Elleste-Solo | Estradiol | | Tablet | | |
| Progynova | | | | | |
| Zumenon | | | | | |
| Elleste-Solo MX | | | | | |
| Estraderm MX | | | | | |
| Estradot | Estradiol | | Patch | | |
| Evorel | Lottation | | 1 dtorr | | |
| FemSeven | | | | | |
| Progynova TS | | | | | |
| Oestrogel | Estradiol | | Gel | | |
| Sandrena | | | | | |
| Estradiol/Estradiol valerate with Progestogen | | | | | |
| Femoston | Estradiol | Dydrogesterone | Tablet | | |
| Angeliq | Estradiol | Drospirenone | Tablet | | |
| Climagest | | | | | |
| Climesse | | Norethisterone | Tablet | | |
| Clinorette | | | | | |
| Elleste-Duet | | | | | |
| Elleste-Duet Conti | Estradiol | | | | |
| Kliofem | | | | | |
| Kliovance | | | | | |
| Novofem | | | | | |
| Nuvelle Continuous | | | | | |
| Trisequens | | | | | |
| Evorel Conti | Estradiol | Norethisterone | Patches | | |
| Evorel Sequi | | | | | |
| Cyclo-Progynova | Estradiol | Norgestrel | | | |
| FemSeven Conti FemSeven Sequi | Estradiol | Levonorgestrel | Patches | | |
| | | | | | |
| Indivina Tridestra | Estradiol | Medroxyprogesterone acetate | Tablets | | |
| Hormonin | Estradiol, estriol and estrone | | Tablet | | |

Hormone Replacement Therapy (HRT)

Indication(s) Menopausal symptoms

Osteoporosis prophylaxis

(Progestogen component required for women with intact uterus)

Ethinylestradiol is also licensed for menstrual disorders, female hypogonadism and palliative treatment of prostate cancer.

Risks associated with surgery

HRT is associated with a 1.3-3 fold risk of developing VTE¹. This risk is especially increased in the first year of use and is also influenced by age and type of HRT;² in non-surgical patients, risk is as follows:

Oestradiol only HRT (after 5 years usage)

Women aged 50-59: incidence increases from 5 to 7 per 1000 women

Women aged 60-69: incidence increases from 8 to 10 per 1000 women

Combined HRT (after 5 years usage)

Women aged 50-59: incidence increases from 5 to 12 per 1000 women

Women aged 60-69: incidence increases from 8 to 18 per 1000 women

Level of risk associated with non-oral routes of administration of HRT has not been established, but may be lower for the transdermal route²⁻⁵. Non-oral HRT achieves plasma oestradiol concentrations that are thought to be similar to those observed in premenopausal women^{6.7,8}.

Risks associated with drug continuation during surgery:

In light of VTE risk, many sources advise stopping HRT 4-6 weeks before major surgery, particularly if there is a likelihood of prolonged immobilisation; it should be restarted only after full mobilisation^{1,2,9}. However, reviews to date have found no studies comparing withdrawal with continuation of HRT in the perioperative period and there is no compelling evidence to suggest any increased risk of perioperative VTE in HRT users, or that HRT should be discontinued in the perioperative period¹²⁻¹⁸.

Hurbanek found no association between perioperative hormone replacement and post-operative thrombosis in patients undergoing major orthopaedic surgery (hip and knee arthroplasty) and suggests that routine discontinuation of these medications preoperatively may be unnecessary in patients receiving appropriate pharmacologic antithrombotic prophylaxis¹⁹.

Risks associated with stopping therapy:

The risks and benefits of continuing with HRT should be discussed with the patient and consideration given to any changes in the quality of life that may result due to recurrence of menopausal symptoms if the HRT is discontinued^{4,12,20}. Other risk factors for VTE should be taken into consideration when making decision on whether to stop HRT^{10,14,15}.

| Advice in the peri-operative period | If the risk of VTE outweighs the benefits of continuation, HRT should be stopped 4-6 weeks pre-operatively and treatment should not be restarted until the patient is fully mobile ^{1,2} . | | | | |
|---|---|--|--|--|--|
| penou | Women who do not have other predisposing risk factors for VTE may continue with HRT ²¹ . | | | | |
| | HRT can be continued in the peri-operative period provided appropriate thromboprophylaxis such as LMWH with or without thromboembolic deterrent stockings are used ^{13,21} . This applies to patients requiring emergency surgery who are taking HRT; prophylaxis with unfractionated or low molecular weight heparin (LMWH) and graduated hosiery is advised ^{1,2,9} . | | | | |
| | If there is significant of a VTE during the perioperative period to warrant discontinuation of HRT, but there are concerns about rebound menopausal symptoms the patient may be switched to a non-oral HRT e.g. transdermal. | | | | |
| Special | Interactions: | | | | |
| Instructions | <u>HRT</u> + NSAIDs ²² | | | | |
| | The findings of one observational study raise the possibility that the risk of myocardia infarction might be higher with the concurrent use of NSAIDs and HRT. Further studies are needed. | | | | |
| References | Summary of Product Characteristics: (Angeliq, Climagest, Climaval, Climesse, Elleste- Solo/MX, Elleste-Duet/Conti, Estraderm MX, Estradot, Evorel/Conti/Sequi, ethinylestradiol, Femoston, Hormonin, Indivina, Kliofem, Kliovance, Novofem, Nuvelle Continuous, Oestroge Premarin, Premique, Prempak C, Progynova/Cyclo-Progynova, Sandrena, Tibolone, Tridestu Trisequens, Zumenon). Available from: <u>http://www.medicines.org.uk/emc/</u> [Accessed 29th October 2015] | | | | |
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| | | | | | |

Hormone Replacement Therapy (HRT)

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- 13. McLintok C. HRT, VTE and surgery: what is best practice? NZMJ 2002; 115 (1157); U65.
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Other sources referred to:

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- Snape S, Anjum I. Premedication and management of concomitant medication. Surgery 2008; 26 (9): 379382 – no additional information found
- Shiffman MA. Estrogen and Thromboembolic Disorders: Should patients stop hormones prior to cosmetic surger? Journal of Women's Health 2003; 12 (9): 853-5 – no additional information found.

Hydralazine

Approved Brands:

Apresoline ®

| Indication(s) ¹ | Moderate to Severe Heart Failure | | | |
|---|--|--|--|--|
| | Hypertensive Emergencies | | | |
| Risks associated with surgery | No specific issues noted | | | |
| Advice in the peri-operative period | Continue treatment with vasodilators ^{2,3} , hydralazine should be taken on the morning of surgery. | | | |
| Special Instructions | In the intra-operative period, if patients managed with hydralazine exhibit hypotension, adrenaline should not be used owing to the potential for tachycardia to occur with concurrent hydralazine and adrenaline use ⁴ . | | | |
| References | Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. | | | |
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| | continuing drugs around surgery, 1999. DTB; 37:862-64. | | | |

Hydroxychloroquine Sulfate

Approved Brands:

Plaquenil®

Quinoric®

| Indication(s) | Licensed indications: | | | | | |
|---|--|--|--|--|--|--|
| | Treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight. | | | | | |
| | Treatment of juvenile idiopathic arthritis (in combination with other therapies) ^{1,2} . | | | | | |
| | Other indications: | | | | | |
| | Treatment and prophylaxis of malaria, management of sarcoidosis and other skin disorders ³ . | | | | | |
| Risks associated | No association with increased risk of post-operative infection or wound healing complications ^{4,5,6,7,8} . | | | | | |
| with surgery | No increase in hemorrhagic complications found ⁶ . | | | | | |
| | There is a potential for additive effects with the conventional neuromuscular blockers used during surgery (single report with chloroquine) ⁹ . | | | | | |
| | Aminoglycoside antibiotics could potentiate its direct blocking action at the neuromuscular junction ¹ . | | | | | |
| | Limited evidence suggests that the failure rate of spinal anesthesia with bupivacaine may be markedly increased in patients who are receiving anti-rheumatic drugs and/or who drink alcohol ³ . | | | | | |
| | The interruption of treatment could risk an increase in symptoms of the underlying condition. | | | | | |
| | Active rheumatoid arthritis is associated with an increased risk of post-operative complications including infection, and may compromise participation in rehabilitation ^{5,7,10} . | | | | | |
| Advice in the peri-operative period | Continue treatment ^{4,5,6,7,10,11} . | | | | | |
| Special | Check post-operative renal function ⁵ and reduce dose in renal impairment ¹² . | | | | | |
| Instructions | Hydroxychloroquine has been known to cause hypoglycaemia. Patients with symptoms suggestive of hypoglycaemia should have their blood glucose levels checked and treatment reviewed ¹ . | | | | | |
| References | Summary of product characteristics Plaquenil-hydroxychloroquine sulfate 200mg FC tabs (last updated 12th March 2015) Available from: <u>https://www.medicines.org.uk/emc/ medicine/30066</u> [Accessed 9.8.15]. | | | | | |
| | 2. BNF (August 2015) [mobile app] Available from: Apple store [Accessed 9.8.15]. | | | | | |
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Hydroxychloroquine Sulfate

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Indoramin

Approve Brands:

| | Doralese ® | | | | | |
|---|---|--|--|--|--|--|
| Indication(s) ¹ | Hypertension Benign Prostatic Hyperplasia (BPH) | | | | | |
| Risks associated with surgery | IFIS (Intraoperative Floppy Iris Syndrome) There is a low, but significant risk of IFIS in patients taking Indoramin who undergo cataract surgery ⁵ . | | | | | |
| Advice in the peri-operative period | The incidence of IFIS in a population of patients having undergone cataract surgery was examined ² suggesting it is reasonable to withhold indoramin prior to cataract surgery to decrease the risk of IFIS. It is advisable to stop ^{2,4} all alpha-1 adrenergic blockers prior to cataract surgery. No specific recommendations surrounding timescales are available however it is | | | | | |
| Special Instructions | reasonable to advise temporary withdrawal of indoramin for two weeks prior to cataract surgery ³ . If indoramin is withheld peri-operatively, blood pressure should be closely monitored upon restarting treatment, owing to the risk of severe hypotension ⁶ . If indicated for the treatment of BPH (Benign Prostatic Hyperplasia), indoramin may be stopped following an effectual TURP (Transurethral Resection of Prostate), subject to a successful TWOC | | | | | |
| References | (Trial Without Catheter). Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. Haridas, A., Syrimi, M., Al-Ahman, B., et al. Intraoperative floppy iris syndrome (IFIS) in patients receiving tamsulosin or doxazosin-a UK-based comparison of incidence and complication rates, 2013. Graefes Arch Clin Exp Ophthalmol; 251(6): 1541-5. Chang, D.F., Campbell, J.R. Intraoperative floppy iris syndrome associated with tamsulosin (Flomax), 2005. J Cataract Refract Surg; 31: 664 – 73. Schwinn, D.A., Afshari, N.A. Alpha (1)-adrenergic receptor antagonists and the iris: new mechanistic insights into Floppy Iris Syndrome, 2006. Surv Ophthalmol; 51: 501 – 12. Issa, S. A., Hadid, O. H., Baylis, O., et al. Alpha antagonists and intraoperative floppy iris syndrome: A spectrum, 2008. Clin Ophthalmol; 2(4): 735-41. Amdipharm UK Ltd. Summary of Product Charcteristics (SPC): Baratol tablets, 2013 [Online]. Available from: URL: www.medicines.org.uk | | | | | |

| | Insulins |
|---|---|
| | Short Acting Insulins: |
| | Insulin: Actrapid®, Humulin S®, Insuman Rapid®, Hypurin Porcine Neutral, Hypurin Bovine Neutral |
| | Insulin Aspart: Novorapid® |
| | Insulin Glulisine: Apidra ® |
| | Insulin Lispro: Humalog® 100 and 200 Units |
| | Biphasic/Mix Insulin Products: |
| | Biphasic Insulin Aspart: Novomix 30® |
| | Biphasic Insulin Lispro: Humalog Mix 25®, Humalog Mix 50 |
| | Biphasic Isophane Insulin: Humulin M3®, Insuman Comb 15®, Insuman Comb 25®, Insuman Comb 50®, Hypurin® Porcine 30/70 Mix |
| | Intermediate Acting Insulins: |
| | Isophane Insulin: Humulin I®, Insulatard®, Insuman Basal®, Hypurin Bovine Isophane®, Hypurin Porcine Isophane® |
| | Long Acting Insulins: |
| | Insulin Degludec: Tresiba® |
| | Insulin Detemir: Levemir® |
| | Insulin Glargine: Lantus ® |
| | Insulin Zinc Suspension: Hypurin Bovine Lente® |
| | Isophane Insulin: Humulin I, Insulatard, Insuman Basal® |
| | Protamine Zinc Insulin: Hypurin Bovine Protamine Zinc® |
| Indication(s) | Diabetes Mellitus ¹ |
| Risks | Hyperglycaemia due to metabolic stress of surgery ² |
| associated with surgery | Hypoglycaemia from starvation before surgery can exacerbate catabolic effects of $\ensuremath{surgery}^2$ |
| | Poor glycaemic control could increase the risk of post-operative infection and impair wound healing ² |
| Advice in the peri-operative period | See separate table, overleaf for Pre and post-operative advice ² |
| Special Instructions | Blood glucose control may be erratic for a few days after procedure |

Insulins

References

1 British National Formulary Available at: www.bnf.org [Accessed: 2 Feb 2016].

Management of adults with diabetes undergoing surgery and elective procedures: improving 2 standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm [Accessed 16th February 2016]

| Management | | Day | Day o | of Surgery/whilst on a VRII | I |
|-------------------------------------|--|---------------------|---|---|--|
| of Insulin in the peri- | Insulin | prior to surgery | Patient for a.m. surgery | Patient for p.m. surgery | If VRIII is being used* |
| in the peri- operative period | 3, 4, 5, injections daily eg. 3 meal time injections of short acting insulin (Actrapid, Humulin S, Insuman Rapid, Apidra, Humalog, Novorapid, animal neutral) and once or twice daily background (Lantus, Levemir, Tresiba, Humulin I, Insulatard, Insuman Basal, Hypurin Bovine Lente or Protamine Zinc) or 3 injections of premixed insulin daily (Novomix 30, Humulog Mix 25 or 50, Humulin M3, Insuman Comb 15, 25 or 50) | No dose change | Basal Bolus Regime: Omit morning short acting insulin (if no breakfast eaten) and omit lunchtime dose Give 80% of long acting basal dose if usually taken in morning Premixed a.m. insulin: Halve the usual morning dose and omit lunchtime dose Check blood glucose on admission Resume normal insulin dose(s) in the evening if eating and drinking | Take usual morning insulin dose(s) Omit lunchtime dose Check blood glucose on admission Resume normal insulin dose(s) in the evening if eating and drinking | Stop short acting or premixed Insulins until eating and drinking normally, but continue long acting at 80% of the dose the patient usually takes |
| | Twice daily (Novomix 30, Humalog Mix 25 or 50, Humulin M3, Insuman Comb 15, 25 or 50 twice daily Lantus or Levemir) Twice daily | No dose change | Halve the usual morning dose Check blood glucose on admission Leave the evening meal dose unchanged | Halve the usual morning dose Check blood glucose on admission Leave the evening meal dose unchanged | Stop until eating and drinking normally |
| | Avice daily separate injections of short acting (Actrapid, Humulin S, Insuman Rapid, Apidra, Humalog, Novorapid, animal neutral) and intermediate acting (Humulin I, Insulatard, Insuman Basal, animal isophane) | No dose change | Calculate the total dose of both morning insulins and give half as intermediate acting only in the morning Check blood glucose on admission Leave the evening meal dose unchanged | Calculate the total dose of both morning insulins and give half as intermediate acting only in the morning Check blood glucose on admission Leave the evening meal dose unchanged | Stop until eating and drinking normally |

Insulins

| | Day | Day of Surgery/whilst on a VRIII | | | |
|--|---------------------------------|--|--|--------------------------------------|--|
| Insulin | prior to surgery | Patient for a.m. surgery | Patient for p.m. surgery | If VRIII is being used* | |
| Once daily (evening) (Lantus, Levemir, | Give | Check blood glucose on admission | Check blood glucose on admission | | |
| Tresiba, Humulin I, Insulatard, Insuman Basal, Hypurin Bovine Lente or Protamine Zinc) | 80% of usual dose | Resume normal insulin d eating and drinking | ose in the evening if | Continue at 80% of the usual dose | |
| Once daily (morning) (Lantus, Levemir, Tresiba, Humulin I, Insulatard, Insuman Basal, Hypurin Bovine Lente or Protamine Zinc) | Give 80% of usual dose | Give 80% of usual dose Check blood glucose on admission | Give 80% of usual dose Check blood glucose on admission | Continue at 80% of the usual dose | |

*If the patient requires on going VRIII, then the long acting background insulin should be continued but at 80% of the dose the patient usually takes when they are well. Normal insulin doses to recommence when patients is eating and drinking.

International Approved Drug Name(s) (approved brands):

Isocarboxazid

 $Phenelzine \ (Nardil^{\circledast})$

Tranylcypromine

| Indication(s) | Depressive Illness |
|-------------------------------------|---|
| Risks associated with surgery | Irreversible monoamine-oxidase inhibitors act by inhibition of the metabolic breakdown of norepinephrine and serotonin by the MAO enzyme. Therefore, the level of both of these agents is increased at the receptor site ^{1,2} . |
| | This leads to the following potential problems that increase the risks associated with surgery:- |
| | Serotonin syndrome (SS) – a drug-induced condition that results from the effects of toxic levels of serotonin³. |
| | • Hypertensive crisis – from the resultant increase of norepinephrine ^{1,2} . |
| | Monoamine-oxidase inhibition (MAOI) with the irreversible MAOIs lasts for up to 2 weeks after cessation of MAOI therapy. $^{\rm 4}$ |
| | Hypertensive Crisis: |
| | Anaesthesia |
| | With proper monitoring, certain general and local anaesthesia can be given safely with MAOIs, although occasional reactions have been reported. ⁵ |
| | Pancuronium and MAOIs use should be avoided due to the release of stored noradrenaline ^{1,6} . Alcuronium, atracurium or vecuronium would appear to be suitable alternatives. ⁶ |
| | Inhalational anaesthetics (enflurane, halothane, isoflurane and nitrous oxide) are all safe in the presence of MAOIs (although there is a theoretical risk of hepatic damage with halothane) ^{1,6} . |
| | Spinal Anaesthesia |
| | Hypotension may result following spinal anaesthesia in patients receiving phenelzine or tranylcypromine ^{7,8} . |
| | Local Anaesthesia |
| | There is no clinical evidence of dangerous interactions between local anaesthetic preparations containing adrenaline and MAOIs although they could occur if the preparation was accidentally given into a vein ⁶ . Therefore, they should be used with caution ¹ . Caution is advised for use of local anaesthetics with isocarboxazid ⁹ . The manufacturers of Nardil [®] (phenelzine) and tranylcypromine advised against the |

concomitant use of local anaesthesia containing sympathomimetic vasoconstrictors^{7,8}.

Cocaine

MAOIs probably augment the pressor effect of cocaine.⁵The manufacturers of Nardil[®]and tranylcypromine advised against the concomitant use of cocaine^{7.8}.

Vasopressors

Use of sympathomimetic agents in conjunction with MAOIs may result in hypertensive crisis due to the enhancement of pressor activitiy^{3,6,7,8,9}.

Indirect-acting sympathomimetics pose the risk of serious and possibly lethal hypertensive interaction^{5,6}.Indirect-acting sympathomimetics are usually absolutely contra-indicated with MAOIs^{1,9}.

Direct-acting sympathomimetics, such as epinephrine, norepinephrine, isoprenaline and phenylephrine are reliable vasopressors in the presence of MAOIs although great care should be taken with their use because of enhanced receptor sensitivity which poses the risk of hypertensive crisis^{4,5,6}.Dosages should be carefully titrated¹.

The manufacturers of dopamine recommend that it can be used if the initial dose is reduced to one tenth of the normal dose and great care is taken^{5,10}.

Ketamine

The use of ketamine in patients receiving MAOIs should be avoided due to it causing sympathetic stimulation, although no interactions have been reported^{1,6}.

Serotonin Syndrome:

Opioid Analgesics

Several opioids are serotonin reuptake inhibitors and there is a risk of serotonin syndrome due to increased serotonin levels¹. Opioids, which do not trigger serotonin syndrome, include morphine, oxycodone and buprenorphine. Whereas fentanyl, pethidine and tramadol are all weak SRIs and can precipitate serotonin syndrome in conjunction with MAOIs³.

Pethidine

Concurrent use of pethidine and an MAOI has resulted in serious and potentially fatal reactions, including central excitation, muscle rigidity, hyperpyrexia, circulatory collapse, respiratory depression and coma. Concurrent use is generally contra-indicated.^{3,4,5,6,7,8,9,11}

Fentanyl

Possibly increased risk of serotonergic effects when MAOIs given with fentanyl⁴.Some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs^{4,12}. However, there are a number of views that consider fentanyl to be safe^{1,2}.

Alfentanil & Remifentanil

Alfentanil and Remifentanil are considered safe when used with MAOIs^{1,2}.

Morphine

Central nervous system excitation is possible when MAOIs given with opioid analgesics.^{4,7,8,9} However, there is limited evidence for an interaction between

morphine and MAOIs, and caution should be used if administering morphine to patients on MAOIs⁹. If the decision is taken to use morphine, start with a low dose (a third to a half) and titrate to clinical response. Monitor the patient carefully for any signs of adverse effects¹³, particularly blood pressure and levels of consciousness⁵.

Tramadol

Possible increased serotonergic effects and increased risk of convulsions when MAOIs given with tramadol⁴.Some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs^{1,4,6}. If combination is used, the patient should be monitored closely for signs of serotonin syndrome¹⁵.

Other Opioids

Evidence regarding the use of a number of other opioids with MAOIs is limited, and the advice given by manufacturers regarding concurrent use differs. Some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs. Concurrent use should be undertaken with extreme caution¹³.

Nefopam

Avoidance of MAOIs advised by manufacturer of Nefopam due to possible CNS excitation^{4.}

Central Nervous System (CNS) Depression:

CNS depression is thought to be due to MAOI inhibition of hepatic enzymes resulting in enhanced effects of opioids, which can be reversed by naloxone.^{1,4,9} For use of opioids with MAOIs please see above under serotonin syndrome.

Nefopam

Avoidance of MAOIs advised by manufacturer of Nefopam due to possible CNS depression⁴.

Seizures:

Tramadol can cause seizures (rarely) and MAOIs reduce the seizure threshold, therefore, there is an increased risk of convulsions when MAOIs are given with tramadol⁴. Some manufacturers advise avoid concomitant use and for 2 weeks after stopping MAOIs.^{4,6,14}

Other Risks:

Phenelzine prolongs the effects of suxamethonium by decreasing plasma cholinesterase concentrations.^{1,4,6}

Advice in the peri-operative period When a patient on an MAOI is to undergo elective surgery they must be considered on a case by case basis and discussion with the anaesthetist should always take place at the earliest opportunity.

Risks associated with drug continuation during surgery:

The anaesthetist must be informed if a patient is being treated with an MAOI in the event of emergency surgery.

MAOI-safe anaesthesia should be used.

The manufacturers of Isocarboxazid, Nardil® (Phenelzine) and Tranylcypromine all recommend that these agents are discontinued 2 weeks prior to elective suergery^{7,8,9}.

Ensure the patient is adequately hydrated; hypotension (from CNS depression) should be treated with intravenous fluids initially and then with cautious doses of phenylephrine^{1,3}.

Avoid concomitant use of:

Suxamethonium Phenelzine Pethidine Cocaine Ketamine and indirect-acting sympathomimetics.

Avoid co-administration of pancuronium and nefopam.

Opiate of choice – morphine, a reduced dose must be used and the dosage carefully titrated according to clinical response.

Avoid tramadol and drugs that increase the risk of serotonin syndrome and increased risk of seizures.

Risks associated with stopping therapy:

Withdrawal of MAOI treatment requires a minimum of two weeks prior to elective surgery. **This must be done in liaison with the patient's psychiatrist and anaesthetist.** It must be balanced against the risk of relapse and withdrawal effects (see below). There is the potential to switch to the reversible MAOI (moclobemide) two weeks pre-operatively^{7.9}.

If stopped, there is the risk of the relapse of the patient's condition^{1,2}.

Withdrawal:

MAOIs are associated with withdrawal symptoms on cessation of therapy. Symptoms include agitation, irritability, ataxia, movement disorders, insomnia, drowsiness, vivid dreams, cognitive impairment, and slowed speech. Withdrawal symptoms occasionally experienced when discontinuing MAOIs include hallucinations and paranoid delusions. If possible MAOIs should be withdrawn slowly.^{2,4,7}

| Special Instructions | Interactions with anaesthetic agents: Pancuronium should be avoided due to the release of stored noradrenaline ^{1,6} . | | |
|-------------------------|--|--|--|
| References | Attri JP, Bala N, Chatrath V. Psychiatric patient and anaesthesia. Indian Journal of Anaesthesia 2012: 56 (1); 8 – 13 | | |
| | Psychotropic Drugs in the Perioperative Period: A Proposal for Guideline in Elective Surgery. Psychosomatics 2006: 47(1); 8 – 22. | | |
| | Shaikh ZS, Krueper S, Malins TJ. Serotonin syndrome: take a closer look at the unwell surgical patient. Ann R Coll Surg Engl 2011: 93; 569 – 572 | | |
| | BNF 69, 4.3.2 Monoamine-oxidase Inhibitors (MAOIs), <u>www.medicinescomplete.com</u>. Accessed 20th June 2015. | | |

- 5. Bazire S, Psychotropic Drug Directory 2012, Lloyd-Reinhold Communications LLP, 2012.
- Martindale. The Complete Drug Reference. <u>www.medicinescomplete.com</u>. Accessed 24th May 2016.
- Nardil[®] Tablets, Archimedes Pharma UK Ltd, Last updated 28th May 2015, <u>www.medicines.</u> org.uk. Accessed 20th June 2015.
- Tranyclcypromine 10mg Tablets Summary of Product Characteristics, Amdipharm Mercury Company Limited, Last updated 24/04/14, <u>www.medicines.org.uk</u>. Accessed 20th June 2015.
- Isocarboxazid 10mg Tablets Summary of Product Characteristics, Alliance Pharmaceuticals, Last updated 11/02/15, www.medicines.org.uk. Accessed 20th June 2015.
- Dopamine Sterile 40mg/ml Concentrate, Hospira UK Limited, updated 24/2/2016, <u>www.</u> medicines.org.uk. Accessed 2nd June 2016.
- Stockley's Drug Interactions. MAOIs or RIMAs + Opioids; Pethidine (Meperidine). Last Updated 22/6/10, www.medicinecomplete.com. Accessed on 17th December 2015.
- Stockley's Drug Interactions. MAOIs or RIMAs + Opioids; Fentanyl and related drugs. Last Updated 1/11/12, www.medicinescomplete.com. Accessed on 17th December 2015.
- Stockley's Drug Interactions. MAOIs or RIMAS + Opioids; Miscellaneous. Last updated 30/11/2010, www.medicinescomplete.com. Accessed on 17th December 2015.
- Micromedex[®]2.0, (electronic version). <u>www.micromedexsolutions.com</u>. Accessed 25th May 2016.
- Stockley's Drug Interactions. MAOIs or RIMAs + Opioids; Tramadol. Last Updated 2/11/12, www.medicinescomplete.com. Accessed on 17th December 2015.

References checked but no relevant information found:

- 1. www.nice.org.uk Accessed on 29th April 2015
- 2. www.rcoa.ac.uk. Accessed 19th May 2015

Leflunomide

Approved Brands:

| | Arava® | | | | |
|----------------------------|--|--|--|--|--|
| Indication(s) | Licensed: Active rheumatoid arthritis and active psoriatic arthritis ^{1,2} . Unlicensed: Crohn's disease ³ | | | | |
| Risks | There is limited and conflicting data relating to peri-operative risk of leflunomide ^{4,5,6} . | | | | |
| associated with surgery | Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections. Infections may be more severe in nature and may, therefore, require early and vigorous treatment ¹ . | | | | |
| | Some studies have found increased risk of infection and wound healing complications with continued therapy ^{4,7} . | | | | |
| | Treatment interruption may increase the risk of disease flare and the associated complications ⁶ . | | | | |
| | Limited evidence suggests that the failure rate of spinal anaesthesia with bupivacaine may be markedly increased in patients who are receiving antirheumatic drugs and/or who drink alcohol ⁸ . | | | | |
| Advice in the | Consider interruption of treatment for procedures carrying increased risk of infection6. | | | | |
| peri-operative period | Decisions to interrupt treatment should be made on an individual patient basis. Contact the prescriber or specialist team for advice. | | | | |
| Special Instructions | The decision to interrupt treatment requires balancing the risk of disease flare with the risk of infection ^{5,6} . | | | | |
| | Leflunomide has a long half-life (approximately 2 weeks) ^{1,9} . | | | | |
| | Short-term interruption in treatment may reduce drug levels without withdrawal ⁵ . | | | | |
| | In the event of acute infection or other indication to reverse treatment, seek specialist advice. Instruction for washout can be found in the product literature ¹ . | | | | |
| | Patients taking leflunomide may also be taking corticosteroids and/or biologics, which could influence overall peri-operative management plans. | | | | |
| References | Summary of product characteristics Arava 20mg tablets- (last updated 10th October 2014) Available from: <u>https://www.medicines.org.uk/emc/medicine/26344</u> [accessed 16.8.15]. | | | | |
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| | Martindale: The complete drug reference (June 2015) Available from: <u>https://www.medicinescomplete.com/mc/martindale/current/</u> [accessed 16.8.15]. | | | | |
| | Pieringer H et al. (2007) Patients with rheumatoid arthritis undergoing surgery: How should we deal with antirheumatic treatment? <i>Seminars in Arthritis and Rheumatism.</i> 36(5) p.278- 286. | | | | |
| | 5. Goodman SM (2015). Rheumatoid arthritis: Peri-operative management of biologics and DMARDs. <i>Seminars in Arthritis and Rheumatism</i> 44 p. 627-623. | | | | |

Leflunomide

- BSR/BHPR (The British Society for Rheumatology/British Health Professionals in Rheumatology) Non-biologic DMARD guidelines http://www.rheumatology.org.uk/includes/ documents/cm_docs/2016/f/full_dmards_guideline_and_the_executive_summary.pdf accessed 17/7/16
- Fuerst et al. (2006) Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. *Rheumatology international*. 26 p.1138-1142.
- Stockley's Drug Interactions (2015) Available from: <u>https://www.medicinescomplete.com/</u> <u>mc/stockley/current/</u> [accessed 16.8.15].
- Howe CR et al. (2006) Perioperative medication management for the patient with rheumatoid arthritis. Journal of the American Academy of Orthopaedic Surgeons. 14(9) p.544-551.

Levetiracetam

Approved Brands:

Keppra ®

Indication(s) Licensed indications:

Monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation.

Adjuvant therapy of myoclonic and tonic-clonic seizures.

Off label uses:

Levetiracetam has been tried in a variety of movement disorders and as treatment of anxiety disorders.

It has been used successfully in management of non-convulsive status epilepticus and refractory status epilepticus³.

Treatment of neuropathic pain under specialist advice only⁷.

Risks associated with drug continuation during surgery:

associated with surgery Some patients can experience somnolence or other CNS adverse effects (head ache, dizziness), particularly at the beginning of therapy. This could theoretically lead to cumulative effects if used with other CNS depressing drugs during the perioperative period. The specialist literature does not suggest this to be of clinical significance.^{24,6}

> In case reports, levetiracetam was associated with loss of, or changes in motorevoked potential monitoring during craniotomy.^{8,9} However, levetiracetam has been used successfully as seizure prophylaxis in certain neurosurgical procedures^{10,11}. Neurosurgery is a highly specialist area, if in doubt, expert clinicians and specialist literature should be consulted.

Risks associated with stopping therapy:

As with other antiepileptic medicines, therapy with levetiracetam should not be suddenly stopped but withdrawn gradually to avoid precipitating an increase in the frequency of seizures.³

Advice in the peri-operative period

Risks

An oral solution of levetiracetam is available from a variety of manufacturers as are granules, which can be used for administration via feeding tubes. Oral bioavailability is close to $100\%^{1,2,5}$.

If levetiracetam has to be discontinued or changed to another antiepileptic agent, a suggested reduction regimen can be found in the product information².

Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained^{1,2}.

| Special | Drug interactions with anaesthesia: | | | | | |
|--------------|---|---|--|--|--|--|
| Instructions | Antipsychotics (including haloperidol or droperidol) which may be used in the perioperative period, e.g. premedication, may antagonise effect of levetiracetam and thereby lower the seizure threshold ¹ . | | | | | |
| | The standard literature does not list any interactions between levetiracetam and anaesthetic drugs ^{2,4,6} . | | | | | |
| References | 1. | BNF 70. 6.1. Epilepsy | | | | |
| | 2. | UCB Pharma Limited. Summary of Product Characteristic for Keppra 250,500,750 and 1000 mg film-coated Tablets, 100 mg/ml oral solution and 100 mg/ml concentrate for solution for infusion. Last updated on 03/09/2015. Accessed on <u>www.medicines.org.uk</u> on 07/10/2015. | | | | |
| | 3. | Martindale. The complete drug reference. Monograph for Levetiracetam. Latest modification 30th September 2015. Accessed on <u>www.medicinescomplete.com</u> on 15th January 2016 | | | | |
| | 4. | Stockley's Drug Interactions. Levetiracetam. Last updated February 2016. Accessed on <u>www. medicinescomplete.com</u> on 26/02/2016 | | | | |
| | 5. | White R and Bradnam V. Drug administration via enteral feeding tubes. Last updated October 2014. Accessed on <u>www. medicinescomplete.com</u> on 26/02/2016 | | | | |
| | 6. | Micromedex Solutions. Monograph for levetiracetam. Last modified 23/02/2016. Accessed on <u>www.micromedexsolutions.com</u> on 26/02/2016 | | | | |
| | 7. | NICE guideline CG 173 (2013). Neuropathic pain in adults: pharmacological management in non-specialist settings. Section 1.1.12. Accessed on www.nice.org.uk on 26/02/2016 | | | | |
| | 8. | Simpao AF, Janik LS, HSU G et al (2015). Transient and reproducible loss of motor-evoked potential signals after intravenous levetiracetam in a child undergoing craniotomy for resection of astrocytoma. A&A case reports. 4(2):26-28 | | | | |
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| | 10. | Weston J, Greenhalgh J and Marston AG (2015): Antiepileptic drugs as prophylaxis for post- craniotomy seizures. The Cochrane database of Systematic Reviews. 3 (CD007286) | | | | |
| | 11. | Klimek M and Dammers R (2010). Antiepileptic drug therapy in the perioperative course of neurosurgical patients. Current opinion in Anaesthesiology. 23 (5): 564-567. | | | | |

Levodopa

International Approved Drug Name:

| | Levodopa; existing as levodopa + benserazide (co-beneldopa), levodopa + carbidopa (co-careldopa) and levodopa + carbidopa + entacapone) | | | | |
|---|--|--|--|--|--|
| | Brands: | | | | |
| | Co-beneldopa (Madopar®) (Madopar CR®) | | | | |
| | Co-careldopa (Apodespan PR®) (Duodopa intestinal gel®) (Lecado®) (Sinemet®) (Sinemet CR and Half Sinemet CR®) | | | | |
| | Levodopa + carbidopa + entacapone (Sastravi®) (Stalevo®) (Tremapecil®) $^{\rm 1.9}$ | | | | |
| Indication(s) | Levodopa is used for the treatment of Parkinson's disease. | | | | |
| | It is usually formulated alongside an extracerebral dopa-decarboxylase inhibitor, benserazide or carbidopa. Dopa-decarboxylase inhibitors help to reduce the incidence of side effects such as nausea and cardiovascular effects, by preventing extracerebral conversion of levodopa to dopamine. ¹⁻⁷ | | | | |
| Risks | Risks associated with stopping therapy ^{2-3,5-6,8-10,12-14} | | | | |
| associated with surgery | Stopping anti-Parkinson combination products containing levodopa abruptly may precipitate neuroleptic malignant-like syndrome. This can present with symptoms such as hyperpyrexia, rigidity, psychological abnormalities, confusion, rhabdomyolysis and can be fatal. Levodopa has a relatively short half life (1.5 hours) and administration delays can precipitate worsening symptoms. Patients taking large doses of levodopa are most at risk of development of neuroleptic malignant-like syndrome. | | | | |
| | Risks associated with continuing therapy ²⁻¹⁰ | | | | |
| | There is a risk of blood pressure fluctuations and arrhythmias. Additionally, the following side effects are possible; agitation, anxiety, hallucination, confusion, dyskinesia, nausea, vomiting, diarrhoea, restless legs syndrome. | | | | |
| | Usually, the strategy is to maintain the levodopa regimen as closely as possible to the patient's normal treatment. Often, the risk of exacerbation of Parkinsonian symptoms through withholding medication outweighs the risk of medication side effects due to continuation. ^{9-10,12-14} | | | | |
| Advice in the peri-operative period | Ideally, surgery should be planned and the patient's movements disorder team should be consulted prior to the operation. This will facilitate specialist advice regarding an appropriate medication regimen around the operation ⁸⁻¹⁰ . | | | | |
| | It is advisable to place Parkinson patients, including those taking levodopa, first on the scheduled operating list. This allows greater predictability towards operation time thus allowing the nil by mouth (NBM) period to be minimised. Levodopa therapy should be continued as close to the operation as possible, up to the point of anaesthetic induction. Furthermore, a dose of levodopa may be administered on the morning of surgery with a minimal amount of water ⁸⁻¹⁰ . | | | | |

Levodopa

| | | ferred as it enables close monitoring of Parkinson n can be given intra-operatively in rare circumstances, arkinson control. | |
|-------------------------|---|--|--|
| | | d during anaesthesia. If halothane is required during Id be discontinued 12 hours prior to surgery ^{2-7,8-10} . | |
| | Antiemetics that antagonise prochlorperazine and metod | e central dopamine receptors should be avoided, such as clopramide ¹⁰ . | |
| | appropriate. Consideration s Absorption can be impaired | ed as soon as possible post surgery, once clinically should be given to the ability to absorb oral levodopa. I be vomiting or post-operative ileus. In such circumstance, rrom a Parkinson's disease specialist ¹⁰ . | |
| Special Instructions | administered via a naso gas | e upper bowel via active transport. Levodopa can be stric tube if swallowing is impaired, however this is limited M. Dispersible formulations of levodopa should be used for be10-15. | |
| | If the total duration of surgery and NBM period will be > 6 hours consider the use of a rotigotine patch or other alternative medication regimens 8,10. | | |
| | Surgery requiring a strict NBM period: e.g abdominal surgery Refer to dopamine agonist section | | |
| | Surgery requiring a period of NBM for a few hours: e.g non-abdominal surgery Refer to dopamine agonist section | | |
| | Surgery requiring subsequent admission to an intensive care unit: Refer to dopamine agonist section | | |
| | Refer to information in dopamine agonist monograph for information on conversion between levodopa preparations and rotigotine. | | |
| | Management of patients with swallowing difficulties or enteral tubes ¹¹ | | |
| | Current levodopa regime | Equivalent dispersible form | |
| | Madopar Hard Capsules | Use equivalent dose Madopar dispersible tablets | |
| | Sinemet 62.5mg | Madopar dispersible 62.5mg | |
| | | | |

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| losage reduction |
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| losage reduction |
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Levodopa

| References | 1. | Joint formulary committee (2016) British National formulary, 71st edition. London. Pharmaceutical Press. |
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| | 3. | Madopar CR 100mg/25mg Prolonged Release Hard Capsules , Summary of Product Characteristics, Roche products Limited. Last updated March 2016. <u>www.medicines.org.uk</u> Accessed on 1st September 2016. |
| | 4. | Sastravi 100mg/25mg/200mg film coated tablets , Summary of Product Characteristics, Actavis UK Ltd. products Limited. Last updated November 2014. <u>www.medicines.org.uk.</u> Accessed on 1st September 2016. |
| | 5. | Sinemet CR and Half Sinemet , Summary of Product Characteristics, Merck Ltd. Last updated October 2015. www.medicines.org.uk . Accessed on 1st September 2016. |
| | 6. | Stavelo 125/21.25/200mg. Summary of Product Characteristics, Orion Pharma. Last updated February 2015. www.medicines.org.uk . Accessed on 1st September 2016. |
| | 7. | Tremapecil 50mg/12.5mg/200mg tablets. Summary of Product Characteristics, Accord Healthcare Limited. Last updated June 2016. <u>www.medicines.org.uk.</u> Accessed on 1st September 2016. |
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Low Molecular Weight Heparin (LMWH)

| | International Approved Drug Name(s) (approved brands): |
|-------------------------------------|---|
| | Enoxaparin (Clexane®), |
| | Dalteparin (Fragmin®), |
| | Tinzaparin (Innohep®) |
| Indication(s) | Prevention, and Treatment (often until adequate oral anticoagulation established) of venous thromboembolism (VTE) in surgical, medical and pregnant patients (latter unlicensed use) ^{1,2,3,4} . |
| | Short-term Management of acute myocardial infarction (STEMI) and unstable angina (including NSTEMI) ^{1,2,3} . |
| | Prevention of clotting during haemodialysis and other extracorporeal circulatory procedures ^{1,2,3} . |
| | Extended treatment and prophylaxis of VTE in patients with solid tumours (dalteparin, tinzaparin licensed) ^{1,2,3} . |
| | Bridging anticoagulation in high risk patients during the perioperative stopping of warfarin (unlicensed indication) ^{8,9,10} . |
| Risks associated with surgery | Interrupting anticoagulation for a surgical procedure transiently increases the risk of thromboembolism. However, surgery has associated bleeding risks that are increased by the anticoagulant administered. A balance between reducing the risk of VTE and preventing excessive bleeding is required ^{4,10} . |
| | Bleeding risk is determined by the type of surgery, patient comorbidities and medications that affect haemostasis. A higher bleeding risk confers a need for a longer period of anticoagulant interruption ¹⁰ . |
| | The higher the thromboembolic risk, the greater the importance of minimizing the interval without anticoagulation. Factors that increase perioperative VTE risk include but are not limited to. ^{8,9,10} |
| | Atrial fibrillation (AF). Risk is based on age, and coexisting vascular disease affecting CHADS VASc score. |
| | Prosthetic heart valves. |
| | Recent VTE or stroke (within the last 12 weeks), or history of VTE associated with inherited thrombophilia such as antiphospholipid syndrome. |
| | In high thrombotic risk patients, to minimize the time without anticoagulation, administration of heparin or a short acting LMWH is used to bridge. Bridging is normally started 3 days before surgery (2 days after stopping warfarin), when the PT/ INR drops below the therapeutic range. Clinical judgment is required to determine the appropriate dose for each patient dependent upon their risk factors and the procedure ^{8,10} . |
| | If thromboembolic risk is transiently increased (eg, recent stroke or PE), individuals should preferably delay surgery until the risk returns to baseline. VTE risk is greater in the immediate period following a thromboembolic event and declines over time, with events > 12 months ago having a low risk of complications ^{9,10} . |

Low Molecular Weight Heparin (LMWH)

Neuraxial (spinal or epidural) anaesthesia should be used with caution in anticoagulated individuals, due to the risk of haematoma resulting in prolonged or permanent paralysis. The risk applies both to catheter placement and removal, and increases with the use of therapeutic dose LMWH^{1.5,6,10}.

| Advice in the | Prophylactic LMWH dose options for DVT prevention in Surgical patients: |
|----------------|---|
| peri-operative | Dalteparin ^{1,2,3} |
| period | 2500 units: can be given 1-2 hours pre-op. |

Enoxaparin^{1,2,3}

20mg: can be given 2 hours pre op. 40 mg: stop 12 hours before surgery.

5000 units: stop evening before surgery.

Tinzaparin^{1,2,3}

3500 units or 50 units/kg: can be given 2 hours pre op. 4500 units: stop 12 hours before surgery.

Therapeutic dose LMWH/ Bridging of Warfarin:

Once daily regimes*: stop 24 hours before surgery^{8,9,10}.

Twice daily regimes: omit the evening dose the night before surgery^{8,10}.

*An alternative for once daily regimes is to give one half of the total daily dose on the morning of the day before.^{8,10}

Epidural or Spinal Catheter:

LMWH Prophylactic dose: Stop 10-12 hours before insertion or removal of catheter^{1,5,6,10}.

LMWH Therapeutic dose: Stop 24 hours before insertion or removal of catheter^{1,5,6,10}.

For twice daily regimes, omit the evening dose the night before surgery¹.

Manufacturer of Enoxaparin recommends doubling the timings for patients with renal impairment (Cr Cl < 30ml/min) before catheter removal.¹

Special Post-Surgical VTE prevention:

. Instructions

Prophylactic dose LMWH can be started once haemostasis is secure. Continue once every 24 hours, for as long as guidelines recommend and until patient mobile⁴.

Post-surgical Bridging of Warfarin:

Clinical judgement is required to determine the appropriate dose of LMWH for each patient dependent upon their risk factors and the procedure. Continue until INR is in range^{7,8,9,10,11}.

Restarting Post removal of Catheter/ after Cather insertion:

Restart Prophylactic and Therapeutic dose LMWH after a minimum of 4 hours. The use of therapeutic doses LMWH whilst catheter in place is not recommended ^{1,5}.

Low Molecular Weight Heparin (LMWH)

| References | 1. | SPC Fragmin, Clexane, Innohep [Accessed 3rd August 2015] |
|------------|-----|--|
| | 2. | BNF online [Accessed 4th August 2015] |
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| | 4. | NICE Clinical Guideline 92: Venous thromboembolism in adults admitted to hospital: reducing the risk Issued. January 2010 last modified. [Accessed June 2015] |
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| | 7. | Waldemar E. Wysokinski; Robert D. McBane II, Periprocedural Bridging Management of Anticoagulation <i>Circulation.</i> 2012;126:486-490 |
| | 8. | Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence based and practical approach. Blood 2011; 117:5044 |
| | 9. | Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence Based Clinical Practice Guidelines. Chest 2012; 141:e326S. |
| | 10. | Up to date online accessed 3/8/15. Gregory YH Lip, James D Douketis: Perioperative management of patients receiving anticoagulants |
| | 11. | Consensus |
| | | |

Meglitinides

| | International Approved Drug Name (approved brands): Repaglinide (Enyglid®) (Prandin®) Nateglinide (Starlix®) | |
|-------------------------------------|--|--|
| Indication(s) | Type 2 diabetes mellitus, alone (repaglinide) or in combination with metformin ^{1,2,3} | |
| Risks associated with surgery | Loss of glycaemic control ^{2,3} | |
| Advice in the | Morning Surgery | |
| peri-operative period | Omit morning dose if nil by mouth ⁴ , restart when next dose is due once eating and drinking. | |
| | Afternoon Surgery | |
| | Take as normal prior to surgery (if breakfast is eaten ⁴), restart once patient is eating and drinking ⁴ . | |
| | Omit if patient is receiving variable rate insulin infusion ⁴ | |
| Special Instructions | Patients taking meglitinides in addition to metformin are at greater risk of hypoglycaemia ^{2,3} | |
| | Be aware that an unconscious or sedated patient may not exhibit all the signs of hypoglycaemia. | |
| References | 1. British National Formulary Available at: <u>www.bnf.org</u> [Accessed: 23 June 2016]. | |
| | Novartis Pharmaceuticals UK Ltd. (2015). Starlix tablets–Summary of Product Characteristics (SPC)–(eMC). Available at: <u>http://www.medicines.org.uk/emc/</u> medicine/25216 [Accessed 23 June 2016] | |
| | Novo Nordisk Ltd. (2016). Prandin tablets–Summary of Product Characteristics (SPC)– (eMC). Available at: <u>http://www.medicines.org.uk/emc/medicine/18980</u> [Accessed 23 June 2016] | |
| | Management of adults with diabetes undergoing surgery and elective procedures: improving standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: <u>http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm</u> [Accessed 16th February 2016] | |

Mercaptopurine

Approved brands:

Xaluprine®

| Indication(s) | Acute Leukaemia; | |
|---|---|--|
| | Lymphoblastic leukaemia (ALL) and | |
| | Myelogenous leukaemia (AML) ¹ | |
| | Chronic granulocytic leukaemia 1 | |
| | Unlicensed uses: | |
| | Severe Ulcerative Colitis | |
| | Chrons Disease ² | |
| Risks | Risks associated with drug continuation during surgery: | |
| associated | Hepatotoxicity | |
| with surgery | Bone Marrow Suppression | |
| | Pancreatitis | |
| | Hyperuricemia 1 | |
| | Risks associated with stopping therapy: | |
| | Risk of flare of Ulcerative Colitis or Chrons Disease | |
| Advice in the peri-operative period | Each patient should be individually assessed for continued prescribing in the peri- operative period as postoperative infections and healing rates are affected by patients comorbidities ⁴ . | |
| | Pre-operatively : | |
| | Withdraw thiopurines on day of surgery and resume post-operatively if renal function remain is stable ^{3,4} . Check renal function and white cell count pre- and post-operatively. | |
| | Mercaptopurine has not been shown to increase early post-operative complications ^{5,6} . However, consider stopping immunosuppressive therapy if a patient develops a significant systemic infection. | |
| | Consult the specialist team (responsible for the medication) if further advice is required. | |
| | | |

| Special | Dose reduction is required in patients who develop renal and hepatic impairment ¹ . | |
|--------------|---|--|
| Instructions | Monitor for signs of bone marrow suppression and hepatotoxicity. Withdraw immediately if jaundice occurs. (See SPC for monitoring advice) ¹ . | |
| | Haematological monitoring is advised if switching between mercaptopurine tablets and Xaluprine $\ensuremath{\mathbb{B}}$ oral suspension, as they are not bioequivalent ² . | |
| | Mercaptopurine should be administered 1 hour before, or 3 hours after, food or milk ¹ . | |
| References | Aspen. (2015) Mercaptopurine 50mg tablets – Summary of Product Charecteristics (SPC) - (eMC). Available from: <u>https://www.medicines.org.uk/emc/medicine/24688</u> [Accessed 22^{mc} March 2016] | |
| | 2. British National Formulary Available at: www.bnf.org [Accessed: 22 nd March 2016] | |
| | Kumar, A. Auron, M. Aneja, A. et al. (2011). Inflammatory Bowel Disease: Perioperative Pharmacological Considerations. <i>Mayo Clinic Proceedings</i>. 86 (8), 748-757. | |
| | Scanzello, CR. Figgie, MP. Nestor, BJ. et al. (2006). Perioperative Management of Medications Used in the Treatment of Rheumatoid Arthritis. HSS Journal. 2 (1), 141-147. | |
| | Colombel, JF. Loftus, EV. Tremaine, WJ. et al. (2004). Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. <i>American Journal of Gastroenterology</i>. 99 (5), 878-883. | |
| | Tay, GS. Binion, DG. Eastwood, D. et al. (2003). Multivariate analysis suggests improved perioperative outcome in Crohn's disease patients receiving immunomodulator therapy after segmental resection and/or strictureplasty <i>Surgery</i>. 134 (4), 565-572. | |

Metformin

| Approved Brands: | |
|---|--|
| Glucophage® | Glucient SR® |
| Glucophage SR® | Diagemet XL® |
| | |
| Combination Products: | |
| Competact ${\ensuremath{\mathbb B}}$ (with pioglitazone) | Synjardy ${}^{\mbox{\scriptsize \ensuremath{\mathbb R}}}$ (with empagliflozin) |
| Eucreas® (with vildagliptin) | $Vipdomet \ensuremath{\mathbb{B}}$ (with alogliptin) |
| Janumet® (with sitagliptin) | Vokanamet ${\ensuremath{\mathbb R}}$ (with canagliflozin) |
| Jentadueto® (with linagliptin) | Xigduo® (with dapagliflozin) |
| Komboglyze® (with saxagliptin) | |

For combination products, also see advice for individual agents

| Indication(s) | Treatment of type 2 diabetes mellitus alone, or in combination with other oral antihyperglcaemic agents or insulin ^{1,2} . Polycystic ovary syndrome (unlicensed) ^{1,2} |
|---|---|
| Risks associated with surgery | Lactic acidosis ^{2,3} For combination products, also see individual agents |
| Advice in the peri-operative period | Metformin and surgery: Confliction exists between the manufacturers and specialists groups as to how to manage metformin therapy in the peri-operative period. Here is a summary of the advice, from which the UKCPA has formed a consensus. Manufacturer's advice: Omit for 48hours before surgery and restart no sooner than 48hours after surgery or oral diet resumes^{2,3}. Joint British Diabetes Societies (JBDS) for Inpatient Care Group recommendations: There is no need to omit metformin in the peri-operative period unless the patient takes a lunchtime dose, in which case this dose should be omitted. Patients should only resume metformin therapy with oral diet, if eGFR is >60⁴. UKCPA consensus guidance: There is no need to omit metformin prior to the day of surgery in patients with an eGFR >60. |

Metformin

Metformin and iodinated contrast dyes:

Confliction exists between the manufacturers and specialists groups as to how to manage metformin therapy in patients receiving contrast dyes. Here is a summary of the advice, from which the UKCPA has formed a consensus.

UKCPA consensus guidance:

There is no need to omit metformin prior to use of contrast medium in patients with an eGFR > 60.

Manufacturer's advice:

Omit metformin for 48hours post contrast agent in patients with eGFR>60. If the patient has an eGFR between 45-60 to omit 48hours pre and post-contrast ^{2,3}.

Specialist group recommendations:

The Royal College of Radiologists and Joint British Diabetes Societies state to discontinue metformin for 48hours post contrast in patients with eGFR<60mL/min and there is no need to discontinue therapy in patients with eGFR >60^{4,5}.

UKCPA consensus guidance:

Metformin and surgery

Patients with an eGFR >60: Continue metformin.

Patients taking a lunchtime dose, should omit this on the day of surgery.

Patients with an eGFR between 45 and 60: Omit metformin on day of surgery and for 48hours after surgery.

Metformin and iodinated contrast dyes

Patients with an eGFR >60: Continue metformin.

Patients with an eGFR between 45-60: Discontinue metformin for 48hours post contrast.

The information above applies to both modified release and standard release preparations – modified-release preparations of metformin do not have an extended elimination half-life⁶.

Special If patient is likely to miss more than one meal, consider starting a variable rate intravenous insulin infusion (do not give metformin alongside insulin infusion).

Be aware that an unconscious or sedated patient may not exhibit all the signs of hypoglycaemia.

Metformin

| References | 1. | British National Formulary Available at: www.bnf.org [Accessed: 21st March 2016]. |
|------------|----|---|
| | 2. | Merck-Serono UK Ltd. (2015). Glucophage <i>tablets – Summary of Product Characteristics</i> (<i>SPC) – (eMC)</i> . Available from <u>http://www.medicines.org.uk/emc/medicine/4236</u> [Accessed: 21st March 2016] |
| | 3. | Merck-Serono UK Ltd. (2015). Glucophage SR <i>tablets – Summary of Product Characteristics</i> (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/4236</u> [Accessed: 21st March 2016] |
| | 4. | Management of adults with diabetes undergoing surgery and elective procedures: improving standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm [Accessed 16th February 2016] |
| | 5. | Royal College of Radiologists. Standards for intravascular contrast administration to adult patients, third edition. London: Royal College of Radiologists; 2015. |
| | 6. | Personal communication with Merck-Serono UK Ltd regarding Glucophage SR® (21st March 2016) |

Methotrexate

Approved Brands:

Maxtrex®

Zlatal®

Indication(s) Licensed indications¹:

- Severe, active, classical or definite rheumatoid arthritis that is unresponsive or intolerant to conventional therapy.
- Severe, uncontrolled psoriasis, not responsive to other therapy.
- A wide range of neoplastic conditions including acute leukaemias, non-Hodgkin's lymphoma, soft-tissue and osteogenic sarcomas, and solid tumours particularly breast, lung, head and neck, bladder, cervical, ovarian, and testicular carcinoma.

Unlicensed indications^{2,3}:

Moderate active Rheumatoid arthritis (RA).

- Severe Crohn's disease and the maintenance of remission of severe Crohn's disease.
- Prevention of graft vs. host disease after bone marrow transplantation.
- Ectopic pregnancy and the early termination of pregnancy.

| Risks associated with surgery | Several studies relating to patients with RA undergoing elective orthopaedic surgery have found no increase in the risk of post-operative infection or complications with continued methotrexate therapy ^{4,5,6,7} . |
|---|---|
| | One large study found that risk of post-operative infection following orthopaedic surgery was not increased when any of the conventional disease-modifying antirheumatic drugs (DMARDs) (including methotrexate) were being taken as monotherapy for RA. However, the risk of infection was significantly increased when more than one disease modifying drug (any other conventional DMARD, biologic agent or steroids) was being taken ⁸ . |
| | Evidence for the safety of peri-operative use of methotrexate for other indications is very limited: one small study found no increased risk of early complications after elective abdominal surgery for Crohn's disease with pre-operative methotrexate use ⁹ . |
| | Methotrexate-induced stomatitis and other toxic effects may be increased by the use of nitrous oxide 3 . |
| | Very limited evidence suggests that the failure rate of spinal anaesthesia with bupivacaine may be markedly increased in patients who are receiving antirheumatic drugs and/or who drink alcohol ¹⁰ . |
| Advice in the peri-operative period | Methotrexate for the treatment of rheumatoid arthritis should not be routinely interrupted. However, decisions should be made on an individual basis taking into consideration other risk factors, including concomitant disease modifying drugs and the procedure being undertaken ^{7,8,11} . |
| | Avoid nitrous oxide in patients taking methotrexate and other DMARDs ³ . |
| | Refer to prescriber or seek specialist advice for patients taking methotrexate for other indications. |
| | |

Methotrexate

| Special Instructions | The decision to interrupt treatment requires balancing the risk of disease flare with the risk of infection ^{7, 11} . | | | |
|-------------------------|---|---|--|--|
| | Consider impact of any concomitant DMARD and/or corticosteroid treatment for RA ⁸ and the risk associated with disease flare if treatment interrupted. | | | |
| | pati | se attention should be paid to peri-operative renal function, particularly in older ients as dehydration and renal impairment increase the risk of methotrexate toxicity subsequent infection ^{7,11} . | | |
| References | 1. | Summary of product characteristics Maxtrex 2.5mg tablets- (last updated 2th October 2014) Available from: https://www.medicines.org.uk/emc/medicine/6003 [accessed 31.7.16]. | | |
| | 2. | BNF (July 2016) [mobile app] Available from: Apple store [accessed 31.7.16]. | | |
| | 3. | Martindale: The complete drug reference (June 2016) Available from: <u>https://www.</u> medicinescomplete.com/mc/martindale/current/ [accessed 31.7.16]. | | |
| | 4. | Grennan et al. (2001). Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Annals of the Rheumatic Diseases. 60(3) p. 214-217. | | |
| | 5. | Murata et al. (2006) Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Modern Rheumatology 16(1) p.14-19. | | |
| | 6. | Abou Zahr et al. (2014) Perioperative use of anti-rheumatic agents does not increase early postoperative infection risks: a Veteran Affairs' administrative database study. <i>Rheumatology international.</i> 35(2) p.265-272. | | |
| | 7. | BSR/BHPR (The British Society for Rheumatology/British Health Professionals in Rheumatology) Non-biologic DMARD guidelines http://www.rheumatology.org.uk/includes/documents/cm_docs/2016/f/full_dmards_guideline_and_the_executive_summary.pdf . Accessed 17/7/16 | | |
| | 8. | Scherrer et al. (2013) Infection Risk After Orthopedic Surgery in Patients With Inflammatory Rheumatic Diseases Treated With Immunosuppressive Drugs. Arthritis care and research. 65(12) p.2032-2040. | | |
| | 9. | Colombel et al (2004) Early Postoperative Complications are not increased in Patients with Crohn's Disease treated Perioperatively with Infliximab or Immunosuppressive Therapy. <i>American Journal of Gastroenterology</i> 99(5) p.878-883 | | |
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| | 11. | Goodman SM (2015). Optimizing perioperative outcomes for older patients with Rheumatoid Arthritis undergoing arthroplasty: emphasis on Medication Management. <i>Drugs Aging 32</i> p.627-623. | | |

Minoxidil

Approved Brands:

Loniten®

| Indication(s) | Severe hypertension ¹ . | |
|---|--|--|
| Risks associated with surgery | Hypernatraemia, water retention, tachycardia ⁴ . | |
| Advice in the peri-operative period | ne available evidence ^{2,3} supports the continuation of treatment with vasodilators, such s minoxidil. As a result the dose should be taken on the morning of surgery. | |
| Special Instructions | Minoxidil can cause marked sodium and water retention which is important to consider perioperatively ⁴ . Ensure electrolytes and fluid balance are monitored closely and action taken as appropriate ⁴ . | |
| References | Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. | |
| | Noble, D; Webster, J. Interrupting Drug Therapy in the Perioperative Period, 2002. Drug Safety, 25 (7): 489-495. | |
| | Drugs and Therapeutics Bulletin (DTB). Drugs in the Perioperative Period 1: Stopping or continuing drugs around surgery, 1999. <i>DTB</i>; 37:862-64. | |
| | Pfizer Ltd. Summary of Product Characteristics (SPC): Loniten ®, 2016. Available from: URL: <u>www.medicines.org.uk</u> [Cited 2016 July 11]. | |

Morphine

| | Approved Brands | Modified Release preparations | | |
|--------------------------|--|---|--|--|
| | Oramorph®(solution) | MST® (tablets and sachets) | | |
| | Sevredol® (immediate release tablet) | Morphgesic® | | |
| | | Zomorph® (12 hourly) | | |
| | | MXL® (24 hourly) | | |
| Indication(s) | For the prolonged relief of severe and interpret operative pain ^{1a} . | ractable pain, and for the relief of post- | | |
| | For the relief of severe pain in adults, adolescents (aged 13-18 years) and children (aged 1-12 years) ^{1b} . | | | |
| Risks | **As per strong opioids monograph | | | |
| associated | Minimise missed doses to avoid withdrav | val if a patient is on chronic opioid therapy. | | |
| with surgery | Interaction with postoperative analgesia regimes – take regular opioid use into consideration. | | | |
| | Regular observations for signs of toxicity i.e, sedation scores, respiratory rates, blood pressure will ensure opioid toxicity is detected early. | | | |
| | Sustained/modified release preparations of morphine are not recommended for preoperative use, in the first 24 hours post-operation or until bowel function has returned to normal ^{1a} . This is due to the unpredictability of the bowel function and hence the morphine absorption. | | | |
| | Interactions ⁴ | | | |
| | Morphine can increase the bioavailability of gabapentin. Gabapentin has been reported to enhance the analgesic effects of morphine and other opioids. | | | |
| | Metoclopramide increases the rate of absorption of oral morphine and increases its rate of onset and sedative effects. | | | |
| | Rifampicin increases the metabolism of morphine. | | | |
| | A case of respiratory depression has bee given to a patient who had been receiving | n reported when intravenous lidocaine was g fentanyl and morphine. | | |
| Advice in the | **As per strong opioids monograph | | | |
| peri-operative period | Morphine can be given by a range of routes. The bioavailability of each route differs; consult local guidelines for dose/route conversions. | | | |
| | Should paralytic ileus be suspected or occur during use, modified release morphine preparations should be discontinued immediately ^{1a} . | | | |
| | For those patients nil by mouth, consider via another route. | the parenteral route or an alternative opioid | | |
| | | | | |

Morphine

| | For patients with swallowing difficulties and enteral tubes: | | |
|--------------|--|--|--|
| | Use the oral solution if immediate pain relief is required. | | |
| | For intrajejunal administration, dilute the oral liquid with an equal volume of water immediately prior to administration⁶. | | |
| | Consider using MST sachets® flushing the tube well to ensure that the total dose is delivered. Any granules left in the tube will break down over a period of time and a bolus of morphine will be delivered when the tube is next flushed; this has resulted in a reported fatality. Ensure that dose prescribed can be administered using whole sachets⁶. | | |
| | • For high maintenance doses or for patient with very fine-bore tubes, consider changing to a fentanyl transdermal patch. | | |
| Special | **As per strong opioids monograph | | |
| Instructions | Modified release preparations should not be crushed or chewed ^{1a} . | | |
| | A preservative free preparation of morphine must be used if administered epidurally or intrathecally. | | |
| References | MST tablets. Napp Pharmaceuticals, September 2014. Summary of Product Characteristics Accessed via <u>www.medicines.org.uk</u> on 15.05.2016 | | |
| | Oramorph oral solution. Boehringer Ingelheim, October 2015. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 15.05.2016 | | |
| | 2. British National Formulary. Accessed via www.medicinescomplete.com on 15.8.15 | | |
| | 3. Martindale. Accessed via www.medicinescomplete.com on 17.05.16 | | |
| | 4. Stockley's Drug Interactions. Accessed via www.medicinescomplete.com on 17.05.16 | | |
| | 5. Micromedex. Accessed via www.micromedexsolutions.com on 21.05.2016 | | |
| | 6. Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.medicinescomplete.com</u> on 21.05.2016 | | |
| | 7. Medline search via www.evidence.nhs.uk on 21.05.16 | | |
| | | | |

Oxcarbazepine

Approved Brands:

| | Trileptal® |
|---|--|
| Indication(s) | Monotherapy or adjunctive therapy of partial seizures with or without secondarily generalised tonic-clonic seizures ¹ . |
| Risks associated with surgery | Abrupt withdrawal of any anticonvulsant drug in a responsive epileptic patient may precipitate seizures or status epilepticus. Do not discontinue abruptly due to risk of increased seizure frequency ² . |
| Advice in the peri-operative period | In patients with a history of well-controlled epilepsy, it is vital that efforts are made to avoid disruption of antiepileptic medication peri-operatively. |
| | Patients should be advised to take their regular medications on the morning of surgery and regular dosing should be re-established as early as practicable after surgery ³ . |
| | For patients where swallowing is compromised, oxcarbazepine suspension can be used and is suitable for enteral tube administration ⁴ . The manufacturer of Trileptal® states that oral bioavailability of oxcarbazepine tablets appear to be similar to that of suspension, therefore, these preparations can be used interchangeably on a mg-formg basis ⁵ . The oral suspension should be shaken well before administration ⁴ . |
| | For intragastric administration: |
| | Stop enteral feed. |
| | • Flush enteral feeding tube with the recommended volume of water. |
| | Shake the medication bottle thoroughly to ensure adequate mixing. |
| | Draw required dose into the appropriate size and type of syringe. |
| | Dilute with recommended amount of water. |
| | Flush medication dose down feeding tube. |
| | Draw another 10 mL of water into the syringe and also flush this via feeding tube (this will rinse syringe and ensure total dose is administered). |
| | Finally, flush with the recommended volume of water. |
| | Re-start the feed, unless a prolonged break is required.⁴ |
| | The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultations with the patient, taking into account factors such as seizure frequency and treatment history. ¹ |
| Special Instructions | Different formulations of oral preparations may vary in bioavailability. Patients being treated for epilepsy should be maintained on a specific manufacturer's product ¹ . |

| References | 1. | British National Formulary. Oxcarbazepine: <u>http://dx.doi.org/10.18578/BNF.827714740</u> accessed 25/05/2016 |
|------------|----|---|
| | 2. | AHFS Drug Information. Carbamazepine: <u>https://www.medicinescomplete.com/mc/</u> ahfs/2010/a382237.htm |
| | a. | Accessed 24/05/2016 |
| | 3. | Anaesthesia and Epilepsy. A. Perks, S. Cheema and R. Mohanraj. British Journal of Anaesthesia 108 (4): 562 – 71 (2012) |
| | 4. | Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.</u> medicinescomplete.com on 25/05/2016 |
| | 5. | AHFS Drug Information. Oxcarbazepine: <u>https://www.medicinescomplete.com/mc/ahfs/</u> current/a301030.htm?q=oxcarbazepine&t=search&ss=text&tot=33&p=1#_hit |

Oxycodone

Approved Brands:

| | Immediate release preparations: Lynlor® OxyNorm® Shortec® | Modified Release preparations: Abtard® Carexil® OxyContin® Longtec® Oxeltra® Reltebon® Zomestine® | Combination products: Targinact® (oxycodone modified release and naloxone) |
|---|--|--|--|
| Indication(s) | Moderate to severe postoperative and cancer pain ^{1a-b} . For the treatment of severe pain requiring the use of a strong opioid ^{1a-b} . | | |
| Risks associated with surgery | **As per strong opioids monograph, additionally: Minimise missed doses to avoid withdrawal if a patient is on chronic opioid ther Interaction with postoperative analgesia regimens – take regular opioid use into consideration. Regular observations for signs of toxicity i.e. sedation scores, respiratory rates, pressure will ensure opioid toxicity is detected early. Contraindicated in severe renal impairment (creatinine clearance <10ml/min) a moderate to severe hepatic impairment^{1a-b}. Interactions⁴ Clarithromycin and telithromycin decrease the metabolism of oxycodone. Rifampicin increases the metabolism of oxycodone. Itraconazole, ketoconazole and voriconazole moderately increase the exposure to oxycodone, and miconazole slightly increases the exposure to oxycodone. Carbamazepine appears to reduce oxycodone concentrations. The impairment of cognitive and gross motor function caused by oxycodone app to be additive with pregabalin, but there was no pharmacokinetic interaction. | | regular opioid use into res, respiratory rates, blood arance <10ml/min) and n of oxycodone. crease the exposure to e to oxycodone. ons. used by oxycodone appears |
| Advice in the peri-operative period | for the first 24 hours post-op utilised across a number of e | tablets are not recommended beratively1a. However, this for enhanced recovery programm olorectal surgery where the al | mulation has been widely es. |

Oxycodone

Modified release formulations should not be used in patients with paralytic ileus.

For those patients nil by mouth, consider the parenteral route or an alternative opioid via another route.

The modified release formulations must be swallowed whole. They cannot be chewed or crushed for administration via an enteral feeding tube or in swallowing difficulties6. The liquid preparation can be used, up to the total daily dose of the modified release preparation but given at more frequent intervals throughout the day. The liquid formulation can be administration via the feeding tube.

If a sustained opiate effect is required and 4-hourly dosing is not practical, consider using fentanyl or buprenorphine patches; seek advice from pharmacy for dose conversion⁶.

| Special Instructions | **As per strong opioids monograph When a patient no longer requires therapy with oxycodone, it is advisable to taper the dose gradually to prevent symptoms of withdrawal ^{1a} . | |
|-------------------------|---|---|
| References | 1.a | Napp Pharmaceuticals. OxyContin Summary of Product Characteristics. Accessed via <u>www.</u> <u>medicines.org.uk</u> on 10.08.2015 |
| | 1.b | Napp Pharmaceuticals. OxyNorm Summary of Product Characteristics. Accessed via www. medicines.org.uk on 10.08.2015 |
| | 2. | British National Formulary. Accessed via www.medicinescomplete.com on 10.8.15 |
| | 3. | Martindale. Accessed via www.medicinescomplete.com on 17.05.2016 |
| | 4. | Stockley's Drug Interactions. Accessed via www.medicinescomplete.com on 17.05.16 |
| | 5. | Micromedex. Accessed via www.micromedexsolutions.com on 21.05.2016 |
| | 6. | Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.</u> medicinescomplete.com on 21.05.2016 |
| | 7. | Medline search via www.evidence.nhs.uk on 21.05.16 |
| | 8. | Embase search via www.evidence.nhs.uk on 22.05.16 |

Pethidine

| Indication(s) | Relief of moderate to severe pain ^{1a,1b} |
|---------------|---|
| | Premedication ^{1a,1b} |
| | Obstetric analgesia ^{1a,1b} |
| | Enhancement of analgesia ^{1b} |
| Risks | **As per strong opioids monograph |
| associated | Minimise missed doses to avoid withdrawal if a patient is on chronic opioid therapy. |
| with surgery | Interaction with postoperative analgesia regimes – take regular opioid use into consideration. |
| | Regular observations for signs of toxicity i.e. sedation scores, respiratory rates, blood pressure will ensure opioid toxicity is detected early. |
| | Contraindications ^{1a,1b} |
| | Pethidine should not be administered to patients with severe renal impairment or severe hepatic impairment. |
| | Avoid in patients with acute alcoholism, delirium tremens, raised intracranial pressure or in those with convulsive states such as status epilepticus. |
| | Not to be administered to patients receiving monoamine oxidase inhibitors or moclobemide, or within two weeks of their withdrawal. |
| | Pethidine should not be administered to patients receiving ritonavir or selegiline. |
| | Avoid in patients with supraventricular tachycardia. |
| | Use of pethidine in patients with phaechromocytoma may result in hypertensive crisis. |
| | Avoid in patients with diabetic acidosis where there is danger of coma. |
| | Pethidine may precipitate spasm of the ureter or Sphincter of Oddi. Subsequently it should be used with caution in patients with prostatic hypertrophy and biliary tract disorders including those with pain secondary to gallbladder pathology^{1b}. |
| | Interactions ⁴ |
| | SSRIs–Increased risk of serotonin syndrome. |
| | Monoamine oxidase inhibitors and moclobemide—do not administer pethidine to patients receiving within two weeks of their withdrawal. |
| | Isoniazid–An isolated case report describes hypotension and lethargy. |
| | Linezolid–Risk of serotonin syndrome. |
| | Rasagiline or selegiline (MAOBIs)—have serotonergic effects that might result in serotonin syndrome. |
| | Phenytoin–Increased production of the toxic metabolite of pethidine. |
| | Hudrowzina Raapiratary depression has been seen when given with pathiding |

• Hydroxyzine–Respiratory depression has been seen when given with pethidine.

| | Phenobarbital–Increased sedation with severe CNS. The analgesic effects of pethidine can be reduced by barbiturates. | | |
|--------------------------|--|--|--|
| | • Ritonavir–Moderately decreases pethidine exposure and slightly increases that of its active metabolite, norpethidine. | | |
| | Chlorpromazine–Reported to increase the analgesic effect of pethidine; increased respiratory depression, sedation, CNS toxicity, and hypotension can also occur. Other phenothiazines such as levomepromazine, promethazine, prochlorperazine, propiomazine, and thioridazine might also interact with pethidine to cause some of these effects. | | |
| | Aciclovir–An isolated report describes pethidine toxicity associated with high doses. Cimetidine potentiates the effect of pethidine^{1a}. | | |
| | | | |
| | The urinary clearance of pethidine might be increased by acidification of the urine. | | |
| Advice in the | **As per strong opioids monograph | | |
| peri-operative period | For those patients nil by mouth, consider the parenteral route or an alternative opioid via another route. | | |
| | There is no information on administering pethidine tablets via an enteral feeding tube ⁶ . Seek advice from pharmacy and consider an alternative opioid or route. | | |
| Special | **As per strong opioids monograph | | |
| Instructions | Pethidine has a weaker action on smooth muscle than morphine and its lower potential to increase biliary pressure may make it a more suitable opioid analgesic for pain associated with biliary colic and pancreatitis ² . | | |
| | Pethidine has also been used in the management of shivering associated with anaesthesia ² . | | |
| References | Pethidine tablets. Martindale Pharmaceuticals Ltd, October 2014. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 21.05.2016 | | |
| | Pethidine Injection. Martindale Pharmaceuticals Ltd, January 2015. Summary of Product Characteristics. Accessed via <u>www.medicines.org.uk</u> on 21.05.2016 | | |
| | 2. British National Formulary. Accessed via www.medicinescomplete.com on 21.5.16 | | |
| | 3. Martindale. Accessed via www.medicinescomplete.com on 17.05.16 | | |
| | 4. Stockley's Drug Interactions. Accessed via www.medicinescomplete.com on 17.05.16 | | |
| | 5. Micromedex. Accessed via www.micromedexsolutions.com on 21.05.2016 | | |
| | Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.</u> <u>medicinescomplete.com</u> on 21.05.2016 | | |
| | 7. Medline search via www.evidence.nhs.uk on 21.05.16 | | |
| | 8. Embase search via <u>www.evidence.nhs.uk</u> on 22.05.16 | | |
| | | | |

Pioglitazone (Thiazolidinedione)

| | International Approved Drug Name (approved brand): Pioglitazone (Actos®) | | | |
|----------------------------|---|--|--|--|
| | Combination product (approved brand): Metformin and pioglitazone (Competact®) | | | |
| Indication(s) | Treatment of type 2 diabetes mellitus – either alone or in combination with metformin and/or sulfonylurea ¹ . | | | |
| Risks | Risks associated with drug continuation during surgery: | | | |
| associated with surgery | Hypoglycaemia may occur particularly in patients who are also receiving metformin and /or a sulfonylurea or insulin ² . Hypoglycaemia will be masked by the anaesthetic ³ . | | | |
| | Risks associated with stopping therapy: | | | |
| | Nil associated. | | | |
| Advice in the | Pre-operatively: | | | |
| peri-operative | Continue ⁴ | | | |
| period | If the patient is likely to miss more than one meal consider starting a variable rate intravenous insulin infusion. | | | |
| | *Please note some sources advise omitting pioglitazone or pioglitazone containing combination products on the morning of surgery ^{1,3} , however the rationale for this is not clear and national guidelines ⁴ advise to continue. | | | |
| | Post-operatively: | | | |
| | If variable rate insulin infusion has been commenced, withhold pioglitazone doses until the insulin infusion has been discontinued and the patient is eating and drinking normally ³ . | | | |
| | Combination product: | | | |
| | Continue unless metformin monograph advises otherwise. | | | |
| Special Instructions | Patients having surgery for bladder cancer should have their pioglitazone reviewed as it is contraindicated in patients with previous or active bladder cancer ^{1,2} . | | | |
| | Be aware that an unconscious or sedated patient may not exhibit all the signs of hypoglycaemia. | | | |
| References | 1. British National Formulary Available at: <u>www.bnf.org</u> [Accessed: 2 July 2015]. | | | |
| | Takeda UK. (2010). Actos tablets – Summary of Product Characteristics (SPC) – (eMC). Available from <u>http://www.medicines.org.uk/emc/medicine/4236</u> [Accessed: 2 July 2015] | | | |
| | Joshi, GP. Chung, F. Vann, M. <i>et al.</i> (2010). Society for Ambulatory Anesthesia Consensus Statement on Perioperative Blood Glucose Management in Diabetic Patients Undergoing Ambulatory Surgery. <i>Anaesth Analg</i> 111: 1378-1387. | | | |
| | Management of adults with diabetes undergoing surgery and elective procedures: improving standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm [Accessed 12 November 2015] | | | |

Prazosin

Approved Brands:

Hypovase ®

| Indication(s) ¹ | Hypertension | | |
|-------------------------------------|---|--|--|
| | Benign Prostatic Hyperplasia (BPH) | | |
| | Congestive Heart Failure (CHF) | | |
| | Raynaud's Syndrome | | |
| Risks associated with surgery | IFIS (Intraoperative Floppy Iris Syndrome) – In a small study (n=31) ⁵ , the incidence of IFIS in a population of patients having undergone cataract surgery were examined. Prazosin demonstrated a significant incidence of IFIS. | | |
| Advice in the peri-operative | It is reasonable to withhold prazosin prior to cataract surgery to decrease the risk of IFIS ^{2,4,5} . | | |
| period | No specific recommendations surrounding timescales are available however it is reasonable to advise temporary withdrawal of prazosin for two weeks prior to surgery ³ . | | |
| Special Instructions | If prazosin is withheld peri-operatively, blood pressure should be closely monitored upon restarting treatment, owing to the risk of severe hypotension ⁶ . | | |
| | If indicated for the treatment of BPH (Benign Prostatic Hyperplasia), prazosin may be stopped following an effectual TURP (Transurethral Resection of Prostate), subject to a successful TWOC (Trial Without Catheter). | | |
| References | Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. | | |
| | Haridas, A., Syrimi, M., Al-Ahman, B., et al. Intraoperative floppy iris syndrome (IFIS) in patients receiving tamsulosin or doxazosin-a UK-based comparison of incidence and complication rates, 2013. Graefes Arch Clin Exp Ophthalmol, 251(6): 1541-5. | | |
| | Chang, D.F., Campbell, J.R. Intraoperative floppy iris syndrome associated with tamsulosin (Flomax), 2005. J Cataract Refract Surg; 31: 664 – 73. | | |
| | Schwinn, D.A., Afshari, N.A. Alpha (1)-adrenergic receptor antagonists and the iris: new mechanistic insights into Floppy Iris Syndrome, 2006. <i>Surv Ophthalmol</i>; 51: 501 – 12. | | |
| | Issa, S. A., Hadid, O. H., Baylis, O., <i>et al.</i> Alpha antagonists and intraoperative floppy iris syndrome: A spectrum, 2008. <i>Clin Ophthalmol</i>, 2(4): 735-41. | | |
| | Pfizer Ltd. Summary of Product Characteristics (SPC): Hypovase [®], 2009 [Online]. Available from: URL: www.medicines.org.uk | | |

| | Progesterone-Only Contraceptives | | |
|---|---|--|--|
| | International Approved Drug Name(s) (approved brands): | | |
| | Desogestrel (Aizea®)(Cerazette®)(Cerelle®)(Desomono®)(Desorex®)(Feanolla®) (Nacrez®)(Zelleta®) | | |
| | Levonorgestrel (Emerres®)(Emerres Una®)(Isteranda®)(Levonelle®) | | |
| | (Levonelle One Step®)(Upostelle®)(Norgeston®)(Jaydess® intra-uterine device) | | |
| | (Levosert® intra-uterine device)(Mirena® intra-uterine device) | | |
| | Etonogestrel (Nexplanon®) | | |
| | Medroxyprogesterone (Provera®)(Climanor®)(Depo-Provera®)(Sayana Press®) | | |
| | Ulipristal Acetate (EllaOne®)(Esmya®) | | |
| Indication(s) | Contraception | | |
| | Endometriosis | | |
| | Uterine fibroids | | |
| | Menorrhagia | | |
| Risks associated with surgery | There is no evidence to suggest an increased risk of VTE is associated with the use of oral or injectable progesterone-only methods (progesterone-only pill and hormone releasing intra-uterine devices), including the emergency progesterone-only contraception ¹⁻⁵ . | | |
| Advice in the peri-operative period | Progesterone-only oral contraceptives are recommended as an alternative to combined oral contraceptives in the peri-operative period, and thus are safe to continue ^{1,4.} | | |
| Special Instructions | The progesterone-only pill can be initiated immediately if a combined oral contraceptive has been used consistently and correctly. Or if the healthcare professional is resaonably certain that the women is not pregnant and that there has been no risk of conception ^{4.} | | |
| References | The British National Formulary. Edition 70 – September 2015 – March 2016. BMJ Group and Pharmaceutical Press. | | |
| | Scottish Intercollegiate Guidelines Network (SIGN). Prevention and management of venous thromboembolism. A national clinical guideline 122. December 2010. Available at <u>http://</u> www.sign.ac.uk/pdf/sign122.pdf | | |
| | Faculty of Sexual & Reproductive Healthcare. Statement on Venous Thromboembolism and hormonal contraception. November 2014. Available at: <u>http://www.fsrh.org/pdfs/</u> FSRHStatementVTEandHormonalContraception.pdf | | |
| | Faculty of Sexual & Reproductive Healthcare. Clinical Guidance. Progesterone-only pills. Clinical Effectiveness Unit. November 2008 – updated June 2009. Available at: <u>http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyPill09.pdf</u> | | |
| | Lidgaard AU, Lokkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: nation follow-up study. BMJ. 2009; 339:b2890. | | |

| | Proton Pump Inhibitor | rs (PPIs) | | | |
|-------------------------|---|--|--|--|--|
| | International Approved Drug Name(s): Esomeprazole (Emozul ®)(Nexium®) | Combination Products: Vimovo® (Esomeprazole & Naproxen) | | | |
| | | Axorid® (Ketoprofen & Omeprazole) | | | |
| | Lansoprazole (Zoton®) | | | | |
| | Omeprazole (Losec®) (Mepradec®) (Mezzopram®) | | | | |
| | Pantoprazole (Pantoloc®) (Protium®) | | | | |
| | Rabeprazole (Pariet®) | | | | |
| Indication(s) | Treatment for short term treatment of gas | stric and duodenal ulcers. | | | |
| | Used in combination with antibacterial therapy for eradication of <i>Helicobacter Pylori</i> ¹ (H. pylori). | | | | |
| | Treatment and prophylaxis of dyspepsia, oesophagitis, gastro-oesophageal reflux disease (GORD) and non-steroidal anti-inflammatory drugs (NSAID) associated ulcers ^{1,2} . | | | | |
| | Control of excessive gastric secretions in Zollinger-Ellison Syndrome ¹ . | | | | |
| Risks | Risks associated with drug continuation during surgery: | | | | |
| associated | Masks symptoms of gastric cancer and alarm symptoms ¹ | | | | |
| with surgery | Gastro-intestinal disturbances and headaches 1 | | | | |
| | Risk of osteoporosis 1 | | | | |
| | Increased risk of <i>Clostridium Difficile</i> 1,3,13 | | | | |
| | Risks associated with stopping therapy: | | | | |
| | Potential for duodenal and gastric ulceral | tion, and symptomatic GORD ^{2,4,5} . | | | |
| Advice in the | Pre-operatively : | | | | |
| perioperative period | The manufacturers of proton pump inhibitors were unable to provide advice on their use in the perioperative period including use of combination drugs ^{6.7} . | | | | |
| | Avoid for 2 weeks prior to investigations for gastric cancers and <i>H.Pylori</i> or in patients who are undergoing endoscopic procedures ¹ . | | | | |
| | PPI's prior to surgery reduces acid aspiration, reduces the risk of GI bleeding and prevents stress ulcer bleeding, with the oral preparation being more effective in preventing GI complications ^{8,11,12,13} . | | | | |
| | Oral proton pump inhibitors are more effective and economic compared to IV PPI in prophylaxis of GI complications ¹¹ . | | | | |
| | Post-operatively: | | | | |
| | PPI's reduce heartburn frequency in baria marginal ulcers in gastric bypass surgery | | | | |

| | Proton Pump Inhibitors (PPIs) High dose IV PPI is effective in reducing gastric acid secretions due to post-operative stress ¹⁵ . Patients should be made aware that long term PPI may be necessary after surgery for reflux ¹⁶ . Measure serum magnesium concentrations before and during long term treatment with proton pump inhibitors ¹ . | | |
|-------------------------|---|---|--|
| | | | |
| | | | |
| Special Instructions | | | |
| References | 1. | British National Formulary Available at: www.bnf.org [Accessed: 11th May 2016] | |
| | 2. | AstraZeneca UK. (2016) <i>Losec Capsules 10mg – Summary of Product Charecteristics (SPC)</i> – (eMC). Available from: <u>https://www.medicines.org.uk/emc/medicine/7275</u> [Accessed 11 th May 2016] | |
| | 3. | Mcdonald et al (2015) Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent Clostridium difficile Infection. | |
| | 4. | Pfizer Ltd. (2016) <i>Zoton Fas Tab 30mg – Summary of Product Charecteristics (SPC) –</i> (eMC). Available from: <u>https://www.medicines.org.uk/emc/medicine/31461</u> [Accessed 11 th May 2016] | |
| | 5. | Eisai Ltd. (2015) <i>Pariet 10mg & 20mg – Summary of Product Charecteristics (SPC) –</i> (eMC). Available from: <u>https://www.medicines.org.uk/emc/medicine/2577</u> [Accessed 11 th May 2016] | |
| | 6. | Personal correspondence with Astrazeneca UK Ltd regarding Losec ${}^{\ensuremath{\mathbb{R}}}$ (6th April 2016) | |
| | 7. | Personal Correspondence with Dexcel Pharma Ltd regarding Mepradec ${\ensuremath{\mathbb R}}$ (21st April 2016) | |
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Selective Serotonin Reuptake Inhibitors (SSRIs)

International Approved Drug Name (approved brand): Citalopram (Cipramil®) Fluvoxamine (Faverin®) Escitalopram (Cipralex®) Paroxetine (Seroxat[®]) Fluoxetine (Prozac[®]) Sertraline (Lustral®) Indication(s) All SSRIs are indicated for the treatment of depressive illness, the exact licensed indications vary between agents (please refer to the current BNF and product literature). In general, SSRIs are licensed for the following: Depressive illness Panic disorder with or without agoraphobia Social anxiety disorder/Social phobia · Generalised anxiety disorder Obsessive compulsive disorder (OCD) Post-traumatic stress disorder (PTSD) Bulimia nervosa (Fluoxetine only) **Risks Bleeding Risk:** associated There have been reports of prolonged bleeding time and/or bleeding abnormalities with surgery with SSRIs (gastrointestinal bleeding, gynaecological haemorrhage, and other

There have been reports of prolonged bleeding time and/or bleeding abnormalities with SSRIs (gastrointestinal bleeding, gynaecological haemorrhage, and other cutaneous or mucous bleeding). Caution is advised in patients taking SSRIs, particularly with concomitant use of active substances known to affect platelet function (e.g. NSAIDs) or other active substances that can increase haemorrhage (e.g. Warfarin/Novel Oral Anticoagulants [NOACs]). Gastroprotection should be considered when SSRIs and NSAIDs are used together^{1,2,3,4,5,6,7,8,9,10}.

Serotonin Syndrome:

Serotonin syndrome is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity. Co-administration of serotonergic drugs with SSRIs may increase the risk of serotonergic syndrome^{1,2,3,4,5,6,7,11,12,13,14}.

Symptoms of serotonin syndrome have been reported in patients taking the following medicines when in conjunction with an SSRI;

- Fentanyl
- Oxycodone
- Pentazocine
- Pethidine
- Tramadol

It should be noted that the summary of product characteristics for Cipramil[®] states that Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as tramadol².

Selective Serotonin Reuptake Inhibitors (SSRIs)

In practice, there is little evidence to suggest that the above medicines, (including Cipramil[®]) cannot be used safely and effectively with SSRIs and so there is little reason for totally avoiding concurrent use. The patient should be monitored closely and the possibility of serotonin toxicity should be considered in patients experiencing altered mental state, autonomic dysfunction and neuromuscular adverse effects^{1,11,12,13}.

Methylthioninium Chloride (Methylene Blue)

There have been case reports that describe serotonergic symptoms in patients given methylthioninium chloride (methylene blue) who are also taking a serotonergic antidepressant (such as an SSRI)^{14,15,16,17}. The MHRA advise that concomitant use of methylthioninium and drugs that enhance serotonergic transmission should be avoided. However, if administration is necessary, the lowest possible dose should be used and the patient monitored for signs of CNS toxicity for up to 4 hours after administration^{1,17}.

Seizures:

period

Tramadol can cause seizures (rarely) and SSRIs can reduce seizure threshold, therefore, there is an increased risk of seizures in patients taking these cocomittantly^{12,14}.

Advice in the Continue treatment throughout the peri-operative period; abrupt withdrawal should be avoided (see below).

Caution with the use of NSAIDs (increased bleeding risk); consider co-prescription of a proton pump inhibitor if use of an NSAID is indicated.

Caution with co-administration of serotonergic drugs (e.g. Fentanyl, Tramadol); monitor the patient for symptoms of serotonin syndrome.

Avoid co-administration of methylthioninium chloride (methylene blue); if avoidance is not possible, use the lowest dose of methylthioninium and monitor the patient for 4 hours after administration.

Caution with co-administration of Tramadol (increased seizure risk) – avoid combination in patients who have an underlying condition that pre-disposes them to seizures.

Withdrawal:

Discontinuation, especially if abrupt, commonly leads to withdrawal symptoms including dizziness, sensory disturbances (including paraesthesia), sleep disturbances, agitation/anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, palpitations, emotional instability, irritability and visual disturbances. Generally, these are mild to moderate and self-limiting (resolve within 2 weeks). However, in some patients they may be severe and/or prolonged (2 – 3 months)^{1,2,3,4,5,6,7,8,14}.

Withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy^{2,3,4,5,6,7}. Risk of withdrawal is increased if the SSRI is stopped suddenly after regular administration of 8 weeks or more¹.

The risk of withdrawal is higher with paroxetine due to its short half-life¹.

Selective Serotonin Reuptake Inhibitors (SSRIs)

| Special | Paroxetine suspension: | | |
|--------------|--|--|--|
| Instructions | Plasma concentration may be influenced by gastric pH. <i>In vitro</i> data has shown that an acidic environment is required for release of the active drug from the suspension. Absorption may be reduced in patients with a high gastric pH, such as after the use of certain drugs (PPIs), in certain disease states (atrophic gastritis) and after surgery (vagotomy, gastrectomy) ⁶ . | | |
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| | Seroxat[®] Summary of Product Characteristics, GlaxoSmithKline UK, updated 23/02/15, www.medicines.org.uk. Accessed 29th April 2015 | | |
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| | Stockley's Drug Interactions. SSRIs, Tricyclics and related antidepressant. Antidepressants - Methylioninium Chloride (Methylene Blue) Last updated 6/11/12, <u>www.medicinescomplete</u> <u>com</u>. Accessed on 19th May 2015 | | |
| | Vradley KW, Cameron AJD. The Role of Methylene Blue in Serotonin Syndrome: A Systemat Review. Psychomatics 2010; 51(3); 194-200. | | |
| | References checked but no relevant information found: | | |
| | 1. www.nice.org.uk Accessed on 29th April 2015 | | |

2. www.rcoa.ac.uk. Accessed 19th May 2015

SGLT2 inhibitors (Sodium-glucose co-transporter-2 inhibitors) International Approved Drug Name **Combination products:** (approved brands): Vokanamet® (metformin and canadliflozin) - see metformin Canagliflozin (Invokana®) monograph for additional information Dapagliflozin (Forgixa®) Xigduo® (metformin and dapagliflozin) Empagliflozin (Jardiance®) Indication(s) Treatment of type 2 diabetes mellitus – either alone or in combination with insulin or other antidiabetic drugs¹. **Risks** Risks if continued during the peri-operative period: associated Potential for hypoglycaemia, especially if also taking insulin or sulfonylureas^{2,3,4}. with surgery Potential to increase serum creatinine^{2,3,4}. Can exacerbate volume depletion^{2,3,4}. Potential for diabetic ketoacidosis secondary to dehydration, restricted food intake and stress of surgerv⁵. Risks if discontinued during the peri-operative period: Potential for hyperglycaemia^{2,3,4} **Pre-operatively** Advice in the peri-operative Do not take on day of surgery⁹. period If a patient is likely to miss more than one meal consider starting a variable rate intravenous insulin infusion. The manufacturers of the SGLT2 inhibitors are unable to provide any advice about their use in the perioperative period.^{6,7,8}. However, they do advise temporary interruption of treatment in patients with volume depletion^{2,3,4}. The EMA recommend temporarily stopping SGLT2 inhibitors in patients undergoing major surgery⁵. Post-operatively Recommence postoperatively when the next dose is due if the patient is eating and drinking normally, is not receiving variable rate intravenous insulin infusion⁹ and is not dehvdrated. **Combination products** Omit on day of surgery, restart as above unless metformin monograph advises

otherwise.

| Special Instructions | | nitor renal function as there is potential for SGLT2 inhibitors to increase serum atinine ^{2,3,4} . | | |
|-------------------------|-----|---|--|--|
| | | Consider possibility of diabetic ketoacidosis in patients taking SGLT2 inhibitors who have symptoms consistent with condition even if blood sugar levels are not high ⁵ . | | |
| | | aware that an unconscious or sedated patient may not exhibit all the signs of oglycaemia. | | |
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| | 4. | Boehringer Ingelheim Ltd. (2015). <i>Jardiance tablets – Summary of Product Characteristics (SPC) – (eMC)</i> . Available at: <u>http://www.medicines.org.uk/emc/medicine/28973</u> [Accessed 2 July 2015] | | |
| | 5. | European Medicines Agency. (2016). <i>SGLT2 inhibitors: PRAC makes recommendations to minimise risk of diabetic ketoacidosis.</i> Available at: <u>http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document</u> | | |
| | 6. | /SGLT2_inhibitors20/Recommendation_provided_by_ Pharmacovigilance_Risk_ Assessment_ Committee/WC500201886.pdf | | |
| | 7. | Personal correspondence with AstraZeneca UK Ltd regarding Forgixa® (7th August 2015) | | |
| | 8. | Personal correspondence with Boehringer Ingelheim Ltd, regarding Jardiance $\ensuremath{\mathbb{R}}$ (12th Augus 2015) | | |
| | 9. | Personal correspondence with Janssen Cilag Ltd, regarding Invokana ${\ensuremath{\mathbb R}}$ (7th August 2015) | | |
| | 10. | Management of adults with diabetes undergoing surgery and elective procedures: improving standards (September 2015). Joint British Diabetes Societies for inpatient care. Available at: http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm [Accessed 12 November 2015] | | |
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| | | | | |

Statins

| | International Approved Drug Name (approved brand): | | |
|---|---|--|--|
| | Simvastatin (Zocor®) | Rosuvastatin (Crestor®) | |
| | Atorvastatin (Lipitor®) | Fluvastatin (Lescol®)(Lescol XL®) | |
| | Pravastatin (Lipostat®) | | |
| Indication(s) | Hypercholesterolaemia ^{1,2} | | |
| | Prevention of cardiovascular events in patients at high risk of a first cardiovascular event ^{1,2} | | |
| | | rents in patients with previous myocardial infarction, c disease or diabetes mellitus ^{1,2} | |
| Risks associated with surgery | Studies have demonstrated that perioperative statin use is not associated with an increased risk of myopathy after major vascular surgery ³ . However, the following points must be considered: | | |
| | Statins can increase concent | tration of creatinine kinase ^{1,2} | |
| | • Elimination may be longer in | patients with renal insufficiency ^{1,2} | |
| | No liquid formulation availab patient has swallowing difficult | le may make the administration of statins difficult if the ulties | |
| Advice in the peri-operative period | | t be caused by coronary plaque rupture, thrombus . Statins stabilise plaques and therefore may be prative myocardial infarcts ⁴ . | |
| | There is some evidence that indicates that statin discontinuation is associated with an increased risk for post-operative troponin release, myocardial infarction and cardiovascular death, compared with statin continuation in long term users ^{3,5,6,7} . | | |
| | which can add additional benef | sterol biosynthesis, statins block mevalonate production fits. These pleiotropic effects include vasodilatation, on, antioxidant, anti-inflammatory function and | |
| | Recommendation: | | |
| | Continue statin therapy during after surgery ^{3,5,6,7} | the perioperative period and restart as soon as possible | |
| | Monitor the renal and hepati | c function. | |
| Special Instructions | or for those who have a history | ients with risk factors for myopathy or rhabdomyaloysis of liver disease. Risk factors for myopathy include a igh alcohol intake, renal impairment, hypothyroidism | |
| | Monitor the liver function enzyr Discontinue statin if: | nes and creatinine kinase in the peri-operative period. | |
| | Serum transaminases of more | re than 3 times the upper limit of the reference range. | |

Statins

 If myopathy occurs and the creatinine kinsase is more than 5 times the upper limit of normal, or the muscular symptoms are severe ¹

If the patient has swallowing difficulties or an Enteral Feeding Tube:

Simvastatin, atorvastatin, pravastatin and rosuvastatin may be dispersed in water

Caution:

- Care should be taken with some of the higher strengths as these tablets may not crush easily and hence may block the tubes.
- Some brands are film coated and hence will not crush or disperse easily. Consult the Handbook of Drug Administration via Enteral Feeding Tubes for further information (available on medicines complete)
- Modified release tablets (Lescol XL) are not suitable for administration via an enteral feeding tube ^{9,10}

Counselling Points:

- · Take the medicine at night
- · Report any unexplained muscle pains to the general practitioner

References 1. British National Formulary. September 2015. 2. Summary of Product Characteristics. 3. Schouten O, et al. Effect of statin withdrawal on frequency of cardiac events after vascular surgery. Am J Cardiol. 2007; 100: 316 - 320 Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial 4. infarction: implications regarding pathophysiology and prevention. Int J Cardiol. 1996; 57:37-44. 5. Blanco M. Nombela F. Castellanos M. Rodriguez-Yáñez M. García-Gil M. Leira R. Lizasoain I. Serena J, Vivancos J, Moro MA, et al. (2007) Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology 69:904-910 Risselada R, Straatman H, van Kooten F, Dippel DW, van der Lugt A, Niessen WJ, Firouzian 6. A, Herings RM, Sturkenboom MC. (2009) Withdrawal of statins and risk of subarachnoid hemorrhage. Stroke 40: 2887-2892 7. Le Manach Y, Godet G, Coriat P, et al. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. Anesth Anala 2007: 104(6):1326-33: 8. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005; 45:89-118 Handbook of Drug Administration via Enteral Feeding Tubes. White, R & Bradnam, V. 9. Accessed via medicinescomplete.com 10. The NEWT Guidelines for administration of medication to patients with enteral feeding tubes or swallowing difficulties. Second edition. May 2010. Pp. 470

Strong Opioids

| | International Approved Drug Name(s) (approved brands): |
|-------------------------------------|---|
| | Morphine (Severedol®) (MST Continus®) (Morphgesic®) (Zomorph®) (MXL®) (Oramorph®) |
| | Oxycodone (Abtard®) (Carexil®) (Longtec®) (Oxeltra®) (OxyContin®) (Oxylan®) (Reltebon®) (Zomestine®) (Lynlor®) (Oxynorm®) (Shortec®) |
| | Fentanyl (Abstral®) (Recivit®) (Effentora®) (Actiq®) (Durogesic DTrans®) (Fencino®) (Matrifen®) (Mezolar®) (Mylafent®) (Opiodur®) (Osmanil®) (Victanyl®) (Yemex®) (Rentalis Resevoir®) (Tilofyl®) (Fentalis Resevoir®) (Ionsys®) (Instanyl®) (PecFent®) |
| | Pethidine |
| | (For Buprenorphine & Methadone see separate monographs) |
| Indication(s) | Acute moderate to severe pain e.g. trauma, supplementation of anaesthesia and postoperative pain. |
| | Breakthrough pain for patients on chronic opioid therapy. |
| | Chronic cancer pain. |
| | Chronic non-malignant pain. |
| | Recreational use. |
| Risks associated with surgery | Long term opioids can produce physical dependence and withdrawal symptoms if suddenly stopped. If stopped too early preoperatively, the patient may experience withdrawal signs and symptoms. |
| with surgery | If a patient has been taking chronic opioids, tolerance to opioids will need to be considered. For opioid tolerant patients, exploiting suitable regional anesthesia or regional analgesia procedures, and prevention of a physical opioid withdrawal syndrome have utmost priority. Discharge planning should commence at an early stage and may involve limiting duration of additional opioid use. At all stages, there should be appropriate and regular consultation and liaison with the patient, other treating teams and specialist services. |
| | In opioid-naive patients, surgical procedures are associated with varying risks of chronic opioid use in the postoperative period ^{12,13} . |
| | It is difficult to define the dose of opioid if bought off the street and taken recreationally. When there is a clinical need for analgesia in this patient group, advice from local pain teams should be sought. |
| | Regular observations for signs of toxicity i.e. sedation scores, respiratory rates, blood pressure will ensure opioid toxicity is detected early. The reversal agent for opioids is naloxone. |
| | Opioids will reduce bowel motility postoperatively. This is significant in colorectal surgery and can increase the risks of ileus. Opioids should be reviewed in patients with paralytic ileus. |
| | Liver function and renal function should be monitored while a patient is prescribed regular opioids. If renal or hepatic function deteriorates or is impaired, a switch to an alternative opioid and/or formulation may be recommended to reduce the risks |

Strong Opioids

of toxicity – contact your pharmacy department for advice. An extensive resection of the liver may reduce the patients' capacity to metabolise opioid medicines. In these patients opioid doses should be kept to a minimum and patients should be monitored closely. In those patients with renal impairment the effects of opioids will be increased and prolonged.

Interactions with opioids³

- Central Nervous System Depressants: adverse effects of opioids will be potentiated
 when given concurrently
- Smoking: smokers require more opioid analgesics for postoperative pain control than non-smokers.
- Inhaled anaesthetics: enhanced effect of inhalational anaesthetics may be enhanced by opioid analgesics, the dose requirements of desflurane, etomidate, propofol and thiopental may be lower after opioid use.
- Monoamine Oxidase Inhibitors (MAOIs): hypotension (profound in one case) has been seen in a few patients given morphine and MAOI. Serious adverse effects are predicted to occur with the concurrent use of other opioids (oxycodone) and MAOIs or moclobemide, although there do not appear to be any published reports of an interaction.
- Metoclopramide: opioids may antagonise the effects on gastric emptying.
- Selective Serotonin Reuptake Inhibitors (SSRIs): symptoms of serotonin syndrome have been reported with opioids including fentanyl, hydromorphone, oxycodone, and possibly also morphine, when given with SSRIs.
- Benzodiazepines: concurrent use of opioids and benzodiazepines generally
 results in enhanced sedation and respiratory depression; however, in one case
 benzodiazepines have antagonised the respiratory depressant effects of opioids.
 An additive effect on pain control has been seen, conversely, diazepam has been
 shown to antagonise the analgesic effect of morphine. Opioids delay the oral
 absorption of diazepam.
- Opioids with mixed agonist/antagonist properties (e.g. buprenorphine, butorphanol, nalbuphine, pentazocine) might precipitate opioid withdrawal symptoms in patients taking pure opioid agonists (e.g. fentanyl, methadone, morphine).

Advice in the peri-operative period

The patients chronic analgesia should be considered when prescribing postoperative analgesia, tolerance to opioids may mean a patient is prescribed increased doses or higher potency of opioid in comparison to an opioid-naïve patient. For patients admitted taking long term opioids, consideration of the postoperative analgesia technique should be taken in conjunction with the chronic analgesia regimen and communicated clearly in the medical notes i.e. should the modified release morphine be administered alongside the IV PCA. Clear communication and documentation of these intentions will reduce risk of inadvertent co-administration or missed doses.

Surgery may negate the need to continue chronic analgesia postoperatively and in this case an appropriate opioid reduction regimen should be prescribed.

Doses of 'as required' opioids should be proportionate to the dose of regular opioids prescribed.

Use laxatives to reduce constipating effects of opioids where appropriate.

| | Courses of modified release opioids should be clearly defined on the discharge prescriptions to avoid inadvertent continuation of opioids in primary care. Patient should be informed of the short term intention of the prescription and need to be informed of the drug driving law ⁷ . For patients addicted to opioids, the perioperative period is not a suitable time to initiate weaning ⁸ . | • |
|-------------------------|--|---------|
| Special Instructions | Formulation changes may be required, this can be the same drug in a different formulation e.g. morphine modified release tablets to sachets. In some cases this indicate a change in opioid e.g. morphine modified release to a fentanyl patch du persistent vomiting or a patient having an ileostomy. | |
| | Use opioid switching tables with care and consider the indication for the switch, a straight dose switch applicable? A significant number of errors are reported to NRLS regarding inappropriately prescribed opioid doses ⁹ . | |
| References | 1. British National Formulary. Accessed via <u>www.medicinescomplete.com</u> on 10.8.15 | |
| | 2. Martindale. Accessed via www.medicinescomplete.com on 17.05.16 | |
| | 3. Stockley's Drug Interactions. Accessed via <u>www.medicinescomplete.com</u> on 17.05.16 | 3 |
| | 4. Micromedex. Accessed via www.micromedexsolutions.com on 21.05.2016 | |
| | 5. Medline search via www.evidence.nhs.uk on 21.05.16 | |
| | 6. Embase search via www.evidence.nhs.uk on 22.05.16 | |
| | Department of Transport. Guidance for Health Professionals on Drug Driving. July 201 Available at https://www.gov.uk/government/uploads/system/uploads/attachment_da file/325275/healthcare-profs-drug-driving.pdf | |
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| | Soneji N, Clarke HA, Ko DT, Wijeysundera DN. Risks of developing persistent opioid us major surgery. JAMA Surg. Published online August 10, 2016. | e after |
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Sulfonylureas

| | International Approved Drug Name(s) (approved brands): | | |
|----------------------------|--|--|--|
| | Glil | benclamide, | Glimepiride (Amaryl®) |
| | | clazide (immediate and modified | Glipizide (Minodiab®) |
| | | ease preparations available) amicron®) | Tolbutamide |
| Indication(s) | Treatment of type 2 diabetes mellitus – either alone or in combination with other antidiabetic medications ¹ . | | |
| Risks | Ris | sks associated with drug continuati | on during surgery: |
| associated with surgery | Pot | tential for hypoglycaemia ^{2,3} which will be | e masked by anaesthetic ⁴ |
| | Ris | sks associated with stopping therap | by: |
| | Ris | sk of hyperglycaemia | |
| Advice in the | Pro | e-operatively: | |
| peri-operative | Do not take sulfonylurea on morning of surgery ^{1,5} . | | |
| period | If the patient is likely to miss more than one meal consider starting a variable rate intravenous insulin infusion. | | |
| | Post-operatively: | | |
| | Morning surgery patients: Recommence postoperatively when next dose is due if eating and drinking normally ¹ and not receiving variable rate intravenous insulin infusion. | | |
| | Afternoon surgery patients: Recommence on morning after surgery if eating and drinking normally ⁵ and not receiving variable rate intravenous insulin infusion | | |
| | , | e. if the patient takes twice a day, both de rgery). | oses should be withheld on the day of |
| Special Instructions | Be aware that an unconscious or sedated patient may not exhibit all the signs of hypoglycaemia. | | |
| References | 1. | British National Formulary Available at: www | w.bnf.org [Accessed: 22 July 2015]. |
| | 2. | Personal correspondence with Servier Laba August 2015). | arotories Ltd, manufacturers of Diamicron MR (6^{th} |
| | 3. | Personal correspondence with Sanofi, man | ufacturers of Amaryl (6th August 2015). |
| | 4. | | Society for Ambulatory Anesthesia Consensus Management in Diabetic Patients Undergoing 378-1387. |
| | 5. | standards (September 2015). Joint British | going surgery and elective procedures: improving Diabetes Societies for inpatient care. Available at: <u>DS/JBDS.htm</u> [Accessed 12 November 2015] |

Tamsulosin

Approved Brands:

Flowmaxtra ® XL

| | Ponian Drostatia Hypornlagia (DDH) | |
|---|---|--|
| Indication(s) ¹ | Benign Prostatic Hyperplasia (BPH) | |
| Risks | IFIS (Intraoperative Floppy Iris Syndrome) – | |
| associated with surgery | Meta-analysis ³ examined the comparative incidence of IFIS was examined across a range of alpha-blockers, in patients having undergone cataract surgery. | |
| | The incidence of IFIS was significantly higher in tamsulosin patients (48 %; $p < 0.0001$) than control groups, with a higher complication rate ³ . Patients maintained preoperatively on tamsulosin have the highest incidence of IFIS ^{2.3} . | |
| Advice in the peri-operative period | Tamulosin should be withheld prior to cataract surgery to decrease the risk of IFIS ³ . As tamsulosin is considered to be an irreversible antagonist of alpha1-adrenoceptors, discontinuation of tamsulosin shortly before surgery may not completely prevent the incidence of IFIS4. Temporary withdrawal of tamsulosin is advised two weeks prior to cataract surgery ⁴ . | |
| Special Instructions | If tamsulosin is withheld peri-operatively, blood pressure should be closely monitored upon restarting treatment, owing to the risk of severe hypotension ⁵ . Prolonged release formulations should not be crushed for administration via enteral feeding tube post-operatively ⁶ . | |
| | If indicated for the treatment of BPH (Benign Prostatic Hyperplasia) tamsulosin may be stopped following an effectual TURP (Transurethral Resection of Prostate), subject to a successful TWOC (Trial Without Catheter). | |
| References | Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. | |
| | Chatziralli, I.P., Sergentanis, T.N. Risk factors for intraoperative floppy iris syndrome: a meta- analysis, 2011. <i>Opthalmol</i>; 118(4): 730-5. | |
| | Haridas, A., Syrimi, M., Al-Ahman, B., et al. Intraoperative floppy iris syndrome (IFIS) in patients receiving tamsulosin or doxazosin-a UK-based comparison of incidence and complication rates, 2013. Graefes Arch Clin Exp Ophthalmol; 251(6): 1541-5. | |
| | Chang, D.F., Campbell, J.R. Intraoperative floppy iris syndrome associated with tamsulosin (Flomax), 2005. J Cataract Refract Surg; 31: 664 – 73. | |
| | Bird, S.T., Delaney, J.A.C, Brophy, J.M., <i>et al.</i> Tamsulosin treatment for benign prostatic hyperplasia and risk of severe hypotension in men aged 40-85 years in the United States: risk window analyses using between and within patient methodology, 2013. <i>BMJ</i>; 5: 347. | |
| | Boehringer Ingelheim Limited. Summary of Product Characteristics (SPC): Flowmax [®] Relief MR, 2009 [Online]. Available from: URL: <u>www.medicines.org.uk</u> | |

Terazosin

Approved Brands:

| | Hytrin ® | | |
|------------------------------|---|--|--|
| Indication(s) ¹ | Hypertension | | |
| | Benign Prostatic Hyperplasia (BPH) | | |
| Risks | with surgery | | |
| associated | IFIS (Intraoperative Floppy Iris Syndrome) – In a small study (n=31) ⁵ , the incidence of IFIS in a population of patients having undergone cataract surgery were examined. Terazosin demonstrated a significant incidence of IFIS in the small study population ⁵ . | | |
| Advice in the peri-operative | It is reasonable to withhold terazosin prior to cataract surgery to decrease the risk of IFIS ^{2,4} . | | |
| period | No specific recommendations surrounding timescales are available however it is reasonable to advise temporary withdrawal of terazosin for two weeks prior to cataract surgery ³ . | | |
| Special Instructions | If terazosin is withheld peri-operatively, blood pressure should be closely monitored upon restarting treatment, owing to the risk of hypotension ⁶ . | | |
| | If indicated for the treatment of BPH (Benign Prostatic Hyperplasia), terazosin may be stopped following an effectual TURP (Transurethral Resection of Prostate), subject to a successful TWOC (Trial Without Catheter). | | |
| References | Joint Formulary Committee. British National Formulary, 68th Ed, 2015. London: BMJ Group and Pharmaceutical Press. | | |
| | Haridas, A., Syrimi, M., Al-Ahman, B., et al. Intraoperative floppy iris syndrome (IFIS) in patients receiving tamsulosin or doxazosin-a UK-based comparison of incidence and complication rates, 2013. Graefes Arch Clin Exp Ophthalmol; 251(6): 1541-5. | | |
| | Chang, D.F., Campbell, J.R. Intraoperative floppy iris syndrome associated with tamsulosin (Flomax), 2005. J Cataract Refract Surg; 31: 664 – 73. | | |
| | Schwinn, D.A., Afshari, N.A. Alpha (1)-adrenergic receptor antagonists and the iris: new mechanistic insights into Floppy Iris Syndrome, 2006. <i>Surv Ophthalmol</i>, 51: 501 – 12. | | |
| | Issa, S. A., Hadid, O. H., Baylis, O., <i>et al.</i> Alpha antagonists and intraoperative floppy iris syndrome: A spectrum, 2008. <i>Clin Ophthalmol</i>, 2(4): 735-41. | | |
| | Amdipharm UK Ltd. Summary of Product Characteristics (SPC): Hytrin ® tablets, 2016 [Online]. Available from: URL: <u>www.medicines.org.uk</u> | | |

Valproate (Sodium valproate, Valproic Acid as Semisodium Valproate)

| | Approved Brands: Epilim® (sodium valproate) Episenta® (sodium valproate MR) | Convulex® (valproic acid) Depakote® (valproic acid) | |
|-------------------------------------|--|---|--|
| | Epival® (sodium valproate) All forms of epilepsy | Orlept® (sodium valproate) | |
| Indication(s) | Migraine prophylaxis (unlicensed) Mania | | |
| | Treatment of manic episodes associated with bipolar disorder when lithium contraindicated or not tolerated ^{1,2} | | |
| Risks associated with surgery | Risks associated with stopping therapy: Risk of seizure recurrence if doses omitted. | | |
| | Do not discontinue anticonvulsant drugs abruptly in patients receiving valproate to prevent major seizures; strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life ⁴ . | | |
| | Risks associated with drug continuation during surgery: | | |
| | aggregation, and abnormal coagulation | a, inhibition of the secondary phase of platelet parameters, it is recommended that patients telet count and coagulation parameters prior | |
| Advice in the | Dose should be continued as normal du | ring peri-operative period ⁸ . | |
| peri-operative period | Valproate is rapidly and completely absorbed from the gastrointestinal tract ⁵ . For the treatment of epilepsy, consider IV route if oral route is not an option. The IV dose should be the same as the established oral dose, given by intravenous injection or infusion in 2-4 divided doses or as a continuous intravenous infusion ¹ . | | |
| | Where swallowing is compromised, liquid or crushable tablets can be considered and is suitable for administration via some enteral feeding tubes ⁷ . | | |
| | The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultations with the patient, taking into account factors such as seizure frequency and treatment history ¹ . | | |
| Special Instructions | | latelet count, bleeding time and coagulation because of the reported side effects on the | |

Valproate (Sodium valproate, Valproic Acid as Semisodium Valproate)

| References | 1. | British National Formulary 69, accessed at www.medicinescomplete.com 17/4/15 |
|------------|----|--|
| | 2. | Summary of product characteristics for: |
| | | -Epilim 200 Gastro resistant tablets, Sanofi, last updated on eMC 23/3/15, accessed at www.medicines.org.uk on 17/4/15 |
| | | -Orlept 200mg Gastro resistant tablets, Wockhardt Ltd, last updated on eMC 03/03/15, accessed at <u>www.medicines.org.uk</u> on 17/4/15 |
| | | -Depakote 250mg tablets, Sanofi, last updated on eMC 23/3/15, accessed at <u>www.</u> medicines.org.uk on 17/4/15 |
| | 3. | Valproate Professional Monograph-FDA prescribing information, side effects and uses, updated 9/2014, accessed at <u>www.drugs.com</u> on 1/5/15 |
| | 4. | Valproate Sodium AHFS Monograph, last updated 12/2013, accessed at $\underline{\sf www.drugs.com}$ on 1/5/15 |
| | 5. | Martindale: The complete drug reference, accessed at www.medicinescomplete.com 1/5/15 |
| | 6. | NICE Clinical Guideline 137 The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Updated January 2015, accessed at guidance.nice.org.uk/cg137 on 17/4/15 |
| | 7. | Handbook of Drug Administration via Enteral Feeding Tubes, accessed at <u>www.</u> medicinescomplete.com on 1/5/15 |
| | 8. | SIGN Guideline 70 Diagnosis and Management of Epilepsy in Adults, accessed at $\underline{\rm www.sign.}$ $\underline{\rm ac.uk}$ on 1/5/15 |
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