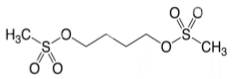
CASE REPORT NEWSLETTER

Issue 11

BUSULFAN	

AUTHORS: SANDRA GARCÍA CONTRERAS AND MARÍA REMEDIOS MARQUÉS MIÑANA

PHARMACOLOGICAL GROUP: Antineoplastic drugs - alkyl sulfonates.

MECHANISM OF ACTION: A potent cytotoxic bifunctional alkylating agent. In aqueous media, release of the methanesulphonate groups produces carbonium ions which can alkylate DNA. This leads to cross-linking of the twin strands resulting in interference of DNA replication and transcription.

PHARMACEUTICAL FORMS AVAILABLE:

- Concentrate for intravenous (IV) infusion: 6mg/ml, in vials of 10ml
- Film-coated tablets, oral administration (PO): 2mg (indications different from IV: polycythemia vera, essential thrombocythemia, myelofibrosis and palliative treatment of chronic granulocytic leukemia).

POSOLOGY AS ON DATA SHEET:

- **ADULTS:**
  - In combination with cyclophosphamide: 0.8 mg/kg as a 2-hour infusion every 6 hours over 4 consecutive days, followed by cyclophosphamide initiated at least 24 hours following the last dose of busulfan.
  - In combination with fludarabine: 3.2 mg/kg as a 3-hour infusion over 2/3 consecutive days, administered immediately after fludarabine .
- **PAEDIATRIC POPULATION (0 to 17 years):**
  - In combination with cyclophosphamide or melphalan:

Administered as a 2-hour infusion every 6 hours over 4 consecutive days, followed by cyclophosphamide or melphalan. Recommended dose:

Actual body weight (Kg)	Dose (mg/kg)
<9	1.0
9 to <16	1.2
16 to 23	1.1
>23 to 34	0.95
>34	0.8

- **OFF-LABEL POSOLOGY*:***

Recent protocols and expert consensus statements recommend 1 dose once daily. It can also be administered twice daily. In the two cases, the infusion lasts 3 hours. Recommended doses:

Actual body weight (Kg)	Dose (mg/kg)
Once daily (every 24h)	
3-15	5.1
15-20	4.9
25-50	4.1
50-75	3.3
75-100	2.7
Twice daily (every 12 h)	
3-15	2.5
15-20	2.4
25-50	2.1
50-75	1.6
75-100	1.3

In myeloablative conditioning, administer busulfan over 4 days, whereas reduced-intensity therapy, busulfan is administered over 3/4 days (same dose in the two cases).

THERAPEUTIC INDICATIONS:

- Indicated as a conditioning treatment prior to haematopoieitic progenitor cell transplantation (HPCT) in adult patients followed by cyclophosphamide when the combination is considered the best option available, or following fludarabine in candidates to a reduced-intensity conditioning regimen.
- Conditioning treatment prior to HPCT followed by cyclophosphamide or melphalan in paediatric patients.

The conditioning regimen can be myeloablative, when chemotherapy (CTX)/radiotherapy (RT) is administered at high doses and the desired effect is to destroy all stem cells in the bone marrow (more effective myelosuppression but higher non-haematological toxicity); and non-myeloablative or reduced-intensity, when CTX/RT is administered at lower doses to reduce toxicity and improve patient tolerance. In this case, having a lower myelosuppression effect, the treatment has sufficient intensity to inhibit the immune system of the patient and prevent rejection of donor stem cells (the desired effect is causing minimal cytopenia but significant lymphopenia).

ADVERSE REACTIONS:

- Very common (≥1/10) or common (≥1/100 to <1/10): Hematological (neutropenia, thrombocytopenia, anaemia); gastrointestinal (nausea, vomiting, stomatitis, mucositis); hepatic (increased transaminases and bilirubin, hepatic veno-occlusive disease (VOD)); neurological (headache, insomnia, anxiety); and cutaneous (alopecia, pigmentation disorders, rash) toxicity; tachycardia, oliguria, hemorrhagic cystitis, electrolyte disturbance, anorexia, myalgia.

- Uncommon adverse reactions include convulsions (associated with high doses), which are prevented by prophylactic administration of antiepileptic drugs). Other side effects of unknown frequency include interstitial pulmonary fibrosis, ovarian failure or cataract.

PHARMACOKINETICS:

- **ABSORPTION:** adequate despite its poor solubility. High intra- and inter-subject variability in terms of absorption half-life and area under the curve (AUC). Absorption was lower in the paediatric population, as compared to adults. Intravenous infusion allows for the immediate and complete availability of the dose and reduces variability.
- **DISTRIBUTION:**
    - Terminal volume of distribution: 0.62 and 0.85 l/kg (higher in the paediatric population)
    - Irreversible binding to plasma proteins (primarily to albumin) was 32%, while reversible binding was variable (around 7%).
    - Binding to blood cells: 47%. .
    - At high doses, it enters the cerebrospinal fluid (CSF) at concentrations comparable to plasma concentrations (CSF:plasma ratio 1, 3:1).
- **METABOLISM:** Busulfan is metabolised to inactive compounds both, spontaneously through conjugation with glutathione in the liver by mediation of glutathione-S-trasferase (GST), and by subsequent oxidation.
- **ELIMINATION:**
    - The metabolites, and a minimal amount of unchanged busulfan (1%) are excreted into the urine. Approximately 30% of the dose is excreted over 48 hours. Elimination in faeces is negligible.
    - Clearance: 2.25-2.74 ml/minute/kg. Paediatric population: 2.52-3.97 ml/minute/kg.
    - Half-life: 2.8-3.9 hours. Paediatric population: 2.24-2.5 hours.
- **POPULATION PHARMACOKYNETIC MODEL:** different models available: Two models including adults and paediatric population: Shukla 2020 (one-compartmentalmodel), McCune 2013 (two-compartmentalmodel).
- **NON-COMPARTMENTAL AUC ESTIMATION:** non-linear regression or trapezoidal method.

TARGETED THERAPEUTIC WINDOW:

- Cumulative AUC = $AUC_{0\text{-}24}$ x (No. of days on treatment)

	MYELOABLATIVE	REDUCED-INTENSITY
Cumulative AUC (ng/ml*h)	85,000 – 95,000	60,000 – 70,000

REASON FOR THERAPEUTIC DRUG MONITORING

- **High intra- and inter-individual variability in plasma concentrations, primarily in paediatric patients (<9kg and newborns).**
- **Narrow therapeutic margin.**
- **Presence of genetic polymorphisms** (GSTA1, GSTM1, GSTP and GSTT1).
- **Good correlation of plasma concentration and therapeutic response/toxicity.**
- **Availability of an analytical technique.**
- Cumulative evidence of its clinical utility.

ANALYTICAL TECHNIQUE:

- Liquid chromatography coupled to high-resolution mass spectrometry (LC–HRMS)
- Homogeneous immunoassay based on the aggregation of nanoparticles.

CASE REPORT: MONITORING OF BUSULFAN PHARMACOKINETICS IN A PATIENT WITH SEVERE COMBINED IMMUNODEFICIENCY

SEVERE COMBINED IMMUNODEFICIENCY

Severe Combined Immunodeficiency (SCID) is one of the most severe forms of primary immunodeficiency (PIs), a group of genetic diseases disrupting the normal function of the immune system.

SCID is a rare disease than can be caused by mutations in different genes. This disease can be inherited in an X-linked (the most common form) or autosomal recessive pattern. Incidence ranges from 1:50.000 – 1:100.000 live births, depending on the country and screening methods used.

SCID is characterized by an impaired humoral and cellular response due to the absence or severe deficiency of functional T and B lymphocytes. Patients with SCID are extremely vulnerable to recurrent severe infections from birth, including respiratory infections, ear infections or gastrointestinal infections with frequent or persistent diarrhea. Recurrent infections negatively affect growth and weight gain in these children.

Diagnosis is established by flow cytometry and genetic testing.

Treatment involves continuous antimicrobial prophylaxis and intravenous immunoglobulin replacement therapy. However, this treatment does not restore the normal function of T and B cells. The most effective curative treatment for SCID is HPCT.

Patients not receiving an adequate treatment usually die within two years after birth due to severe infections. Conversely, in patients receiving an HPCT within 4 months of life, 5-year survival is 95%. Prognosis is determined by the presence of active or latent infections and the age of the patient at HPCT.

Therefore, early diagnosis and management of the disease are essential to prevent associated complications.

CASE REPORT

We present the case of an infant with severe combined immunodeficiency who is receiving treatment with allogenic HPCT with a previous conditioning regimen including busulfan.

THE PATIENT:

- 5-month old infant
- Full-term newborn, normal pregnancy. Birth weight: 3250g
- Vaccine Schedule: 1st dose of hexavalent vaccine + pneumococcus + meningococcus C. Nirsevimab administered.
- No known adverse drug reactions.

History:

- No family history of interest.
- Diagnosed of atopic dermatitis in the presence of cutaneous eczemas with face and trunk rash from the first weeks of life. On treatment with topic beclomethasone.
- Recurrent infections.

A patient admitted to our Centre to undergo screening for immunodeficiencies. From birth, the patient had recurrent infections:

- At 5 weeks of life, the patient developed an upper airway infection with suspicion of superinfection based on radiographic findings. The infection was treated with a 10-day amoxicillin-clavulanic treatment.

- At 2 months, the patient developed bronchitis with associated fever, treated with azithromycin.

- At 3 months, the patient had a 15-day course of fever with apparent acute otitis media, treated with oral cefixime for 5 days. After the event, the patient developed hand and feet onychomadesis, with suspicion of herpangina.

All infections were solved without complications.

At 5 months, the patient was admitted with fever, cough and nasal congestion. Sputum culture was positive for haemophilus. Treatment with ceftazidime was administered.

Although the patient did not suffer from vomiting or diarrhea, he had lost appetite the previous weeks, which resulted in his failing to gain weight and his weight dropping in percentile (p50 at birth to p16).

Serial laboratory tests revealed lymphopenia. Immunological testing including cytometry and lymphocyte population count demonstrated global lymphopenia with the distinctive profile of severe combined immunodeficiency (T and B lymphopenia and elevated levels of NK cells). Diagnosis of Artemis-deficient SCID was confirmed genetically.

Antibiotic treatment with ceftazidime was maintained and prophylaxis with cotrimoxazol, fluconazol and aciclovir was initiated. Intravenous administration of immunoglobulins was initiated.

Two months later, the patient received an allogenic HPCT from a 10/10 matched unrelated donor.

The conditioning and prophylaxis regimen involved:

ANTIEPILEPTIC PROPHYLAXIS
Levetiracetam IV
NAUSEA/VOMITING PROPHYLAXIS
Granisetron IV
ANTIMICROBIAL PROPHYLAXIS
Cotrimoxazol PO (prior to HPCT)
Amoxicillin PO (+16 - present)
Caspofungin IV (pre- post-HPCT 2 weeks)
Fluconazol PO (post-HPCT 2 weeks – post 3 weeks)
Amphotericin B IV (post 3 weeks - present)
Aciclovir PO (pre-HPCT – present)
CONDITIONING REGIMEN
Busulfán 5.1mg/kg IV x 3 days (-6 to -4)
Fludarabine 30mg/m² IV x 6 days (-8 to -3)

VOD PROPHYLAXIS
Ursodeoxycholic acid PO (Pre-HPCT -present)
GvHD PROPHYLAXIS
Rabbit anti human T lymphocyte immunoglobulin IV (-7,-6,-5)
Methotrexate IV (+1, +3, +6)
Ciclosporin Vo (-1 - +8)
Tacrolimus PO (+8 - present)

SOAP METHOD: Monitoring Busulfan pharmacokinetics and dosage optimization

Clinical event	Therapeutic goal
Patient with SCID receiving a conditioning regimen with busulfan prior to allogenic HPCT	Optimizing busulfan treatment by monitoring changes in concentrations and estimating their AUCs

Subjective

- Recurrent infections from birth with cough and nasal congestion, loss of appetite and failure to gain weight.

Objective

- Fever CRP of 81mg/L, lymphopenia of 990/µL. Microbiological tests: Sputum culture positive for *Haemophilus infuenzae*.
- Lymphopenia in serial testing and T and B lymphopenia and elevated levels of NK in immunology tests.

Analysis

Upon diagnosis of SCID, first-line treatment with allogenic HPCT was administered preceded by a conditioning regimen including busulfan and fludarabine.

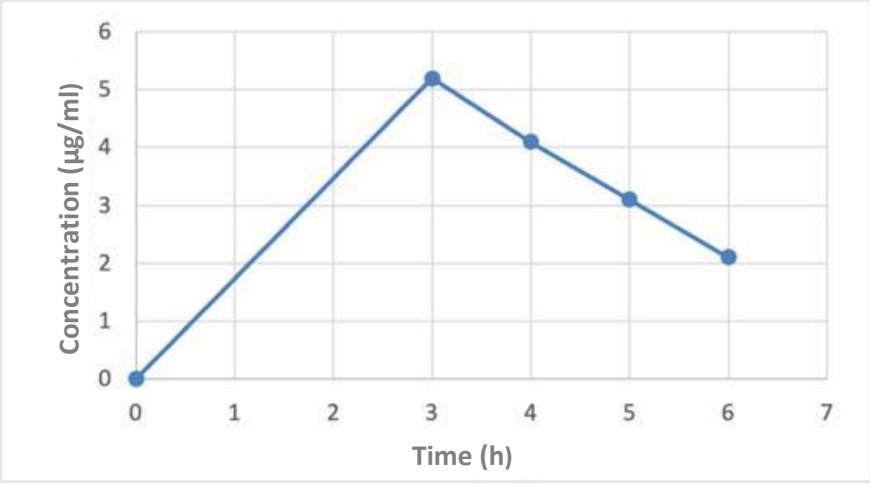
A weight-based busulfan dose of 5.1mg/kg (40mg, weight 7.9kg) in 3-h intravenous infusion over 3 consecutive days (-6 to -4). It is a non-myeloablative regimen with a target cumulative AUC of 65,000 ng/ml*h.

Plan

To optimize the efficacy of busulfan and reduce toxicity, plasma concentrations were determined at 3 (fn of infusion), 4, 5 and 6 hours from infusion.

Post-dose time (hours)	Concentration (ng/ml)
3	5,217.60
4	4,107.76
5	3,123.62
6	2,163.28

Plasma concentration curve - time:



Later, the AUC_{0-24} was estimated by non-linear regression, along with individual pharmacokinetic parameters:

AUC_{0-24}	25,050 ng/ml*h
Kel	0.29 h^{-1}
Vd	5.47 L
t1/2	2.31 h

Considering that the total target cumulative AUC was 65,000 ng/ml*h for 3-day a non-myeloablative regimen of busulfan, the AUC_{0-24h} of the second and third day must be 19,975 ng/ml*h approximately, and being the AUC proportional to the dose, it is recommended to reduce the dose of busulfan to 32 mg the second day of treatment with busulfan.

Follow-up

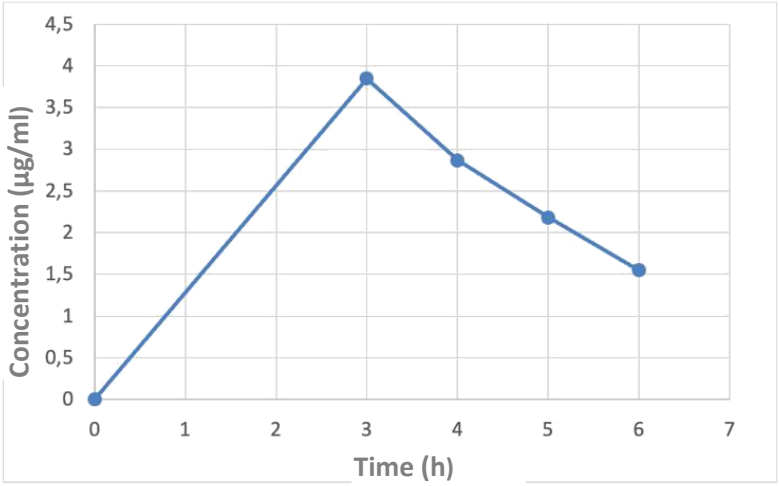
The second day of treatment with busulfan, concentrations were determined again. This time, predose testing was carried out (prior to infusion) for the residual drug concentration in the body to be considered.

Time (hours)	Concentration (ng/ml)
0 (predose)	0
3	3,846.94
4	2,865.60
5	2,183.72
6	1,564.42

AUC_{0-24h} and individual parameters:

AUC_{0-24}	18,809.5 ng/ml*h
Kel	0.30 h^{-1}
Vd	5.67 L
t1/2	2.33 h

Plasma concentration curve - time:



Considering the $AUC_{0\text{-}24h}$ of 18,729.3ng/ml*h, it is recommended to maintain the same dose of 32 mg the third day of conditioning since if we presume that a similar $AUC_{0\text{-}24h}$ will be obtained, the AUC_{total}will be = 25,050+18,809.5 + 18,809.5 = 62,669.0ng/ml*h, which falls within the non-myeloablative targeted therapeutic window (60.000-70.000ng/ml*h).

Following the conditioning therapy, hematopoietic progenitor cell transplantation is performed on Day 0. Leukocyte engraftment on Day +13.

The most significant complications associated with transplantation include:

Hematological toxicity

During admission, the patient needed transfusions of erythrocytes (x1) and platelets (x3). Treatment with filgrastim IV from Day +7 to Day +11.

Digestive system toxicity/ grade IV mucositis

First-step analgesia and IV morphine infusion are administered to control pain. The patient refuses to eat and receives parenteral nutrition for 21 days.

Febrile neutropenia

Fever peaked on Day +7, and triple antibiotic therapy was initiated with piperacillin-tazobactam IV, teicoplanin IV and amikacin IV. After that, the patient remained afebrile with negative blood cultures and antibiotic therapy was discontinued.

Upper airway infection

On Day +11, symptoms of a cold appeared with associated cough and severe nasal congestion. Saline nebulization was initiated. Positive for Rhinovirus/Enterovirus. Good clinical course. The patient remained asymptomatic since Day +16.

Engraftment syndrome

On Day +13, the patient developed tachypnea, hepatomegaly, low-grade fever and weight gain. Chest X-ray demonstrated a bilateral diffuse interstitial pattern. Treated with furosemide PO and methylprednisolone IV.

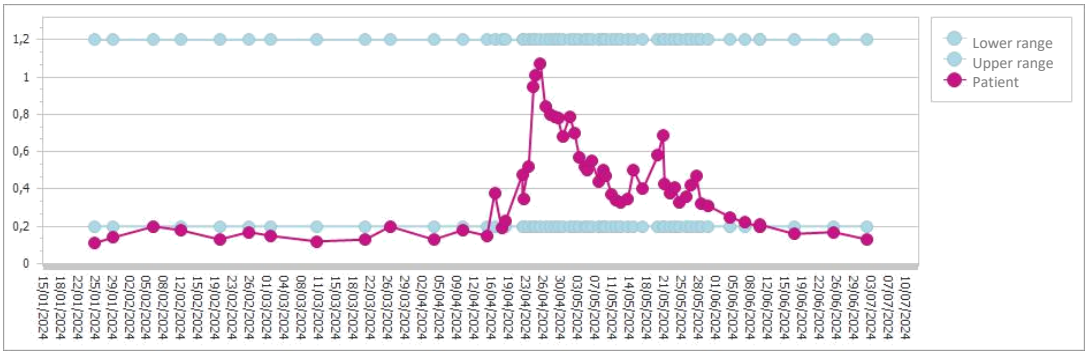
HTN

High blood pressure persisted for 6 days. Treatment with hydralazine PO and amlodipine PO was administered and later down titrated to amlodipine monotherapy. On suspicion of Ciclosporin toxicity, the therapy was discontinued and treatment with tacrolimus was initiated.

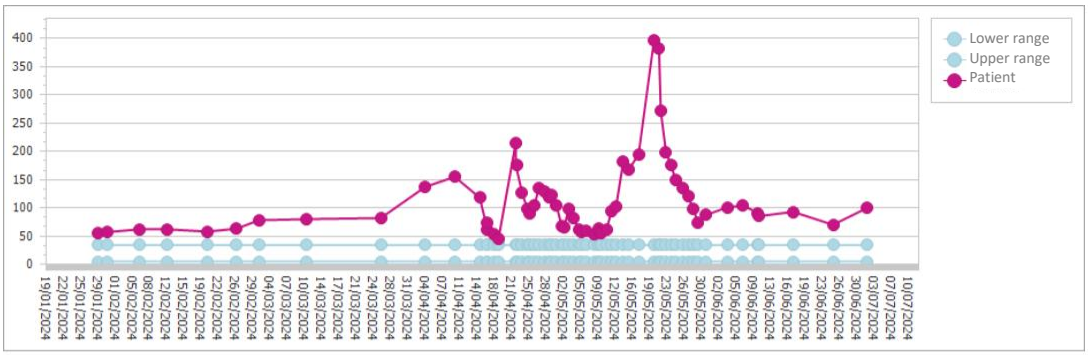
Hepatic toxicity

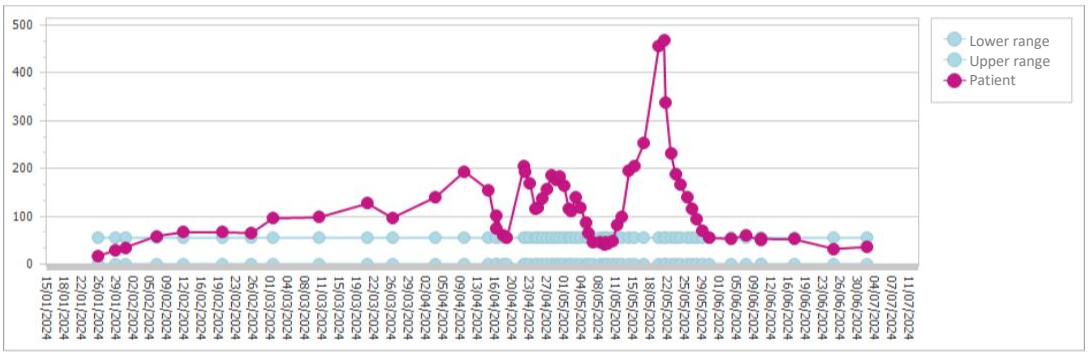
During the hospital stay, high levels of transaminases were noted (maximum GOT 215U/L, GPT 205U/L and GGT 129U/L). The patient remained asymptomatic, with the rest of biochemical parameters within normal limits, including bilirubin (it increased but without exceeding normal limits). Hepatomegaly or ascites were excluded by abdominal ultrasound.

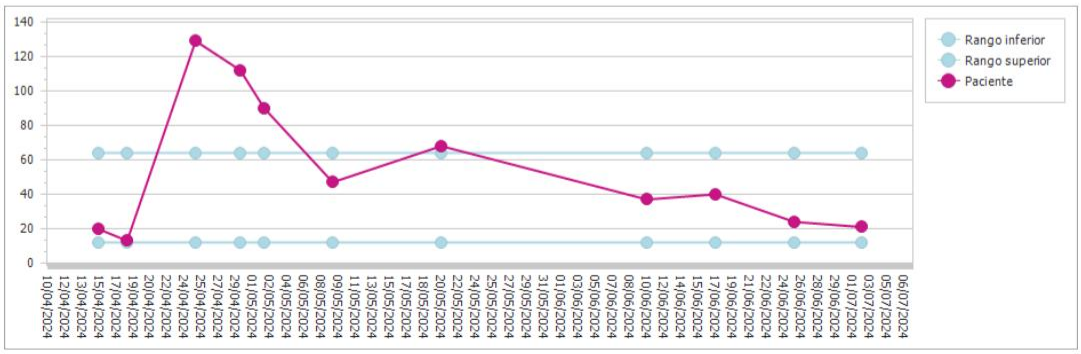
The graph below displays changes in bilirubin values over time, at diagnosis, during transplantation (April 2024) and during follow-up.



The following graphs display changes in transaminases, GOT, GPT and GGT, respectively.







On Day +23 (after discharge), GOT and GPT were elevated, possibly as a side effect of fluconazol, which was discontinued and shifted to amphotericin B IV twice weekly.

VOD associated with busulfan. VOD results from toxic injury to the hepatic sinusoidal capillaries that leads to obstruction of the small hepatic veins and sinusoids. It is manifested as painful hepatomegaly, jaundice and fluid retention (weight gain, edemas, ascites). It is more common in the paediatric population.

If VOD occurs, it is treated with a 2-hour defibrotide IV infusion at a dose of 6.25 mg/kg every 6 hours (25 mg/kg/day) for at least 21 days, maintained until symptoms and signs of severe VOD disappear.

Toxicity to rabbit anti-human T lymphocyte immunoglobulin

Grade 3 cutaneous toxicity and fever. The episode was solved without complications with IV antihistamines and by reducing the infusion rate.

Tear duct stenosis

At discharge, the patient had acute conjunctivitis in his right eye. Topic treatment with dexamethasone eye drops + tobramycin was initiated.

After discharge, his clinical course was uneventful. On Day +23, the patient developed an generalized pruritic maculopapular rash and erythematous palms (soles free). Skin rash in the neck, axillas and groins, possibly secondary to busulfan toxicity. Treatment with topic methylprednisolone, oral hydroxyzine and zinc ointment alternated with mupirocin was initiated.

48 hours after the initiation of treatment, the exanthema disappeared and skin rash improved significantly.

Then, the patient had an episode of acute gastroenteritis that required a long hospital stay due to hypoglycemia secondary to gastrointestinal bleeding, deficient supply and adrenal insufficiency associated with previous corticosteroid therapy. Treatment with hydrocortisone PO was initiated, gastroenteritis was solved and hypoglycemias improved.

At present, the patient is in very good condition on Day +62. Analytical values are: Glucose 98 mg/dl, GOT 100U/L, GPT 36U/L, GGT 21U/L, PCR 3,9mg/L, hemoglobin 9,1g/dL, leukocytes 4760/µL, platelets 299,000/µL. The patient is adequately nourished. No further events.

Discussion

Monitoring the pharmacokinetics of busulfan has demonstrated to be useful for treatment optimization, as this agent has a narrow therapeutic window. Busulfan can cause toxicity to different organs at high doses (i.e. VOD, convulsions) and is associated with a higher incidence of relapse and graft rejection at low doses. Busulfan also shows a high inter-subject variability, which increased when administered orally, as compared to intravenously, especially in paediatric patients, and in the presence of genetic polymorphisms.

Plasma busulfan concentrations over time and their AUCs correlate to patient response. These parameters can be useful in assessing patient exposure to busulfan, performing an individualized dose adjustment and achieving concentrations within the therapeutic range. As a result, the efficacy of busulfan is optimized and its toxicity reduced.

In the case reported, the $AUCo_{0\text{-}24h}$for the dose administered exceeded the daily therapeutic target. Thus reducing the dose is recommended to obtain an $AUCo_{total}$ within the recommended therapeutic range and prevent severe toxicity.

This demonstrates the relevance of monitoring the pharmacokinetics of busulfan in routine clinical practice, especially in the paediatric population.

CONCLUSIONS

- Therapeutic monitoring of busulfan facilitates an individualized dose adjustment, thereby increase its efficacy and reducing toxicity, with a cumulative evidence available on its utility in clinical practice.
- Patient exposure to busulfan can be easily assessed by estimating the AUC by non-compartmental methods (non-linear regression or trapezoidal method) and by compartmental methods using Bayesian methods.
- In agents with a narrow therapeutic margin and high variability such as busulfan, therapeutic monitoring becomes crucial for treatment optimization.

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Editado por: Grupo de Farmacocinética de la Sociedad Española de Farmacia Hospitalaria
C/ Serrano, 40. 28001 Madrid
Tel: +34 91 571 44 87 Fax: +34 91 571 45 86
Email: sefh@sefh.es
Web: http://www.sefh.es
ISSN: 2697-083X