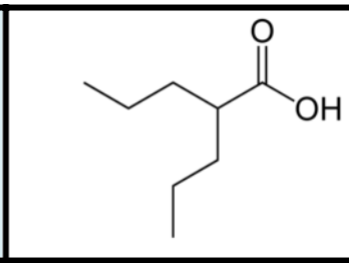
CASE REPORT NEWSLETTER

Issue 12

VALPROIC ACID

(PROPYL PENTANOIC ACID 2-ACID)



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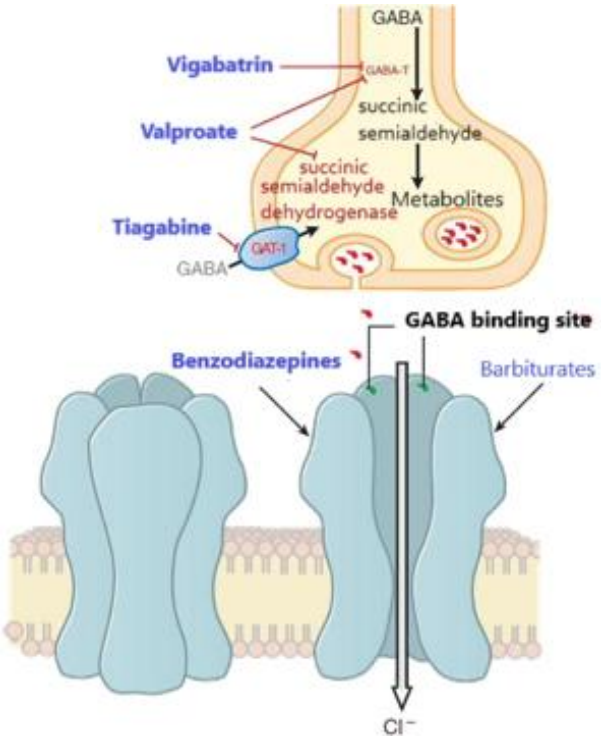
PHARMACOLOGICAL GROUP: Anticolvunsants

MECHANISM OF ACTION (1,2): The mechanism of action by which valproic acid (VPA) exerts its effects in the treatment of epilepsy is not fully understood. It seems to be related to an increased inhibitory activity of the neurotransmitter GABA (gamma-aminobutyric acid). Different hypotheses have been posited, namely:

- An inhibitor of the succinic semialdehyde dehydrogenase enzyme causing an elevation of succinic semialdehyde that is a GABA transaminase inhibitor and reduces GABA metabolism, thereby resulting in an increased bioavailability of this neurotransmitter.
- VPA activates the extracellular signal-regulated kinase (ERK) pathway causing an elevation of brain-derived neurotrophic factor (BDNF).
- Inhibition of voltage-gated sodium channels.
- Indirect, non-competitive inhibition of myoinositol-1-phosphate synthetase, ultimately inducing inositol depletion.
- Negative regulation of protein kinase C (PKC) proteins -α and -ε.
- Direct, non-competitive inhibitor of brain microsomal long-chain fatty acyl-CoA synthetases.
- Inhibition of histone deacetylases (HDAC).
- Modulation of calcium channels.



THERAPEUTIC INDICATIONS (3):

Generalized or partial epilepsy:

- Primary generalized epilepsy: convulsive, non-convulsive or absence seizures and myoclonic seizures.
- Partial: with elemental (including Bravais-Jacksonian forms) or complex symptoms (psychosensorial, psychomotor forms, among other).
- Partial seizures with secondary generalization.
- Mixed forms and generalized secondary epilepsy (West and Lennox-Gastaut).

Treatment of manic episodes in bipolar disorder, when lithium is contraindicated or poorly tolerated.

PHARMACEUTICAL FORMS:

- Intravenous infusion: valproic acid powder for injectable solution of 400 mg.
- Oral administration: extended-release tablets of 500 mg and 300 mg, gastroresistant tablets of 500 and 200 mg and oral solution of 200 mg/mL.

POSOLOGY AS PER DATA SHEET for the autorized therapeutic indications (3):

The total daily dose is adjusted in each patient as a function of clinical response. Therefore, up-titration according to patient needs every 4 to 7 days from initiation of treatment is recommended.

If the patient is receiving other antiepileptic drug, introduce VPA progressively over 2 to 8 weeks and reduce in parallel the concomitant antiepileptic drug by 1/3 or 1/4, especially in the case of phenobarbital or phenytoin.

The recommended average daily dose is:

- Infants and children (28 days to 11 years): 30 mg/kg.
- Adolescents (≥12 years) and adults (≥18 years): 20-30 mg/kg.
- Patients of advanced age (≥65 years): 15-20 mg/kg.

POSOLOGY FOR off-label indications (4,5):

- Prophylaxis of migraine: 500 mg once daily
- Epileptic status: Loading dose, 20 to 30 mg/kg IV in infusion at 6 mg/kg/min, followed by continuous infusion of 1 to 3 mg/kg/h.

ADVERSE REACTIONS (3):

- The most frequently reported adverse reactions (≥ 1/100 to < 1/10)) include: anaemia; thrombocytopenia; extrapyramidal disorders; stupor somnolence; convulsions; memory gaps; headache; nystagmus; dizziness (some minutes after intravenous injection; the patient may feel lightheaded; although it disappears spontaneously in a few minutes); deafness; vomiting; gingival disorder (primarily; gingival hyperplasia); stomatitis; upper abdominal pain; diarrhea (common at initiation of treatment; but disappears after some days without treatment withdrawal); urine incontinence; ungual and subungual diseases; hypersensitivity; transient alopecia; hyponatremia; weight gain; hemorrhage; liver damage; dysmenorrhea; confusional state; hallucinations; aggression; agitation; and attention disorders.

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- The safety profile in the pediatric population is comparable to that for adults. However, some adverse reactions are more severe or common in the pediatric population. There is a specific risk of severe liver damage in infants and young children, especially in children < 3 years. Children also have a higher risk of pancreatitis. These risks decrease with age. Mental disorders such as aggression, agitation, attention disturbance, abnormal behavior, psychomotor hyperactivity, and learning disorders are most commonly observed in the pediatric population.

PHARMACOKINETICS (3,4):

- BIOAVAILABILITY (F) 70-90%, depending on the pharmaceutical form. Extended-release VPA F=70%
- DISTRIBUTION: Volume of distribution 0.13-0.19 L/Kg. Strong affinity for plasma proteins: 71-93%
- METABOLISM: The main biotransformation pathway is glucuronidation (~40%) mainly via UGT1A6, UGT1A9 and UGT2B7 and beta-oxidation.
- ELIMINATION: Clearance mainly by the kidneys. Plasma half-life (t1/2) 12-16 h in adults and 8-13 h in children. Newborns and infants < 2 months: 1-67 h (high variability).

It is a potent inhibitor of UGT2B7glucuronidation and interacts with lamotrigine in a clinically significant way (6).

Population pharmacokinetic model:

One-compartmental model

- Ka: 1.2 h^{-1}
- Vd: 0.2 L/kg
- Cl = 0.004 × TBW × VPA dose$^{0.304}$ × 1.363 CBZ × 1.541 PHT × 1.397
  PB ○ TBW: total body weight (kg)
  ○ CBZ: concomitant treatment with carbamazepin (yes: 1; no: 0)
  ○ PHT: concomitant treatment with phenytoin (yes: 1; no: 0)
  ○ PB: concomitant treatment with phenobarbital (yes: 1; no: 0)

REASONS FOR THERAPEUTIC MONITORING (TDM)

- Availability of an analytical technique.
- Good correlation between serum concentration and therapeutic response/toxicity.
- Evidence of an association between concentration cut-offs and response/toxicity.

CANDIDATES TO TDM

Due to the high intra- and inter-individual variability in VPA pharmacokinetics, VPA dose adjustments should be guided by serum concentration monitoring in all patients.

Determination of total VPA and free VPA is recommended in patients with:

- Hypoalbuminemia (alb<3.5 g/dL)
- Patients receiving concomitant treatment with drugs with strong affinity for plasma proteins.

Monitoring **conditions** include:

- After 2-3 treatment days.
- Pre-dose **concentration** (Cmin) or steady state concentration (Css) when administered in continuous IV infusion.

The therapeutic range is: (8)

- For total valproic acid: 50-100 g/mL
- For free valproic acid: 5-10 g/mL.

ANALYTICAL TECHNIQUE (9):

- Turbidimetric immunoassay
- Matrix for total VPA: serum
- Matrix for free VPA: serum ultrafiltration fluid

CASE REPORT:

THERAPEUTIC MONITORING OF VALPROIC ACID IN A CRITICALLY-ILL PATIENT WITH HYPOALBUMINEMIA

We present the case of a patient with hypoalbunimenia and focal myoclonic seizures in his left arm that initiated VPA therapy in continuous infusion. Therapeutic monitoring of total and free VPA concentrations was performed for dose adjustment.

THE PATIENT

A 60-year old man.
Weight 120 kg
Height 170 CM
History:
- No ADR.
- Drinker of 1-4 beers a day.
- Dilated cardiomyopathy with reduced LV-EF.
- Chronic stage III kidney disease
- Ulcus Bulbar surgery

Regular medication:
- Olmesartan 10 mg OD
- Bisoprolol 5 mg OD
- Atorvastatin 30 mg OD
- Torasemide 10 mg OD

CASE REPORT

A 60 year-old patient without known adverse drug reactions, drinker of 1-4 beers a day. Medical history of interest: dilated cardiomyopathy with reduced ventricular function and stage-3 chronic kidney disease (CKD) controlled by Nephrology until 2014. Surgical history: ulcus bulbar treated surgically in 2003. After surgery, the patient had a hemorrhagic shock, acute respiratory distress syndrome and septic shock with multiorgan failure, which required continuous renal replacement therapy.

On 10/05/2024, the patient was admitted to our ED after a fall with loss of consciousness and symptoms of disorientation and fever.

On examination, the patient was in poor general condition, with normal cardiac and pulmonary auscultation, left upper abdomen painful to palpation, without edemas in the lower limbs, BP 169/88 mmHg, tympanic temperature 39.1ºC; O2 Sat 96%; HR 95 bpm (beats per minute); creatinine 1.77 mg/dL; GF CKD-EPI 40.58 mL/min/1.73m^2; urea 54 mg/dL; GGT 104 IU/L; NT-proBNP 1.526 pg/ml; procalcitonin 0.97 ng/ml; C-reactive protein 259 mg/L; D-dimer 1.501 ng/ml; neutrophilia of 9;400/mcL; lymphopenia 600 /mcL and hematuria.

Acute abdominal disease was confirmed by contrast-enhanced abdominopelvic CT scan. Pulmonary thromboembolism was confirmed by CT angiography of the pulmonary arteries.

At neurologic level, the patient did not exhibit neck rigidity or apparent sensorimotor deficit, although he was disoriented.

Lumbar puncture demonstrated lactic acid elevation. PCR was positive for *Listeria monocytogenes*, which was subsequently demonstrated to be sensitive to ampicillin. CSF had a slightly cloudy appearance with glucose: 138 mg/dL; proteins: 333 mg/dL; leokocytes: 903/mcL and erythrocytes < 2000/mcL.

Antibiotic treatment with ceftriaxone and ampicillin was initiated plus antiepileptic treatment with VPA, levetiracetam and lacosamide.

DESCRIPTION OF THE ANALYTICAL TECHNIQUE USED TO DETERMINE FREE VPA:

The analytical technique used to measure VPA concentration involved a particle-enhanced turbidimetric inhibition immunoassay on an Alinity® (Abbott®) autoanalyzer. The analytical technique has a limit of detection of 12.5 g/mL to 150 g/mL. As free VPA concentrations are presumably < 12.5 g/mL, our Unit of Clinical Pharmacokinetics performed precision, linearity and accuracy testing for concentrations < 12.5 g/mL (tables 1,2, 3 and 4).

Serum total VPA concentration was determined from blood samples collected in a no-additive red tube centrifuged at 5300 rpm for 7 minutes to separate serum. To determine free fraction, serum ultrafiltration was performed using Millipore® filters for 25 minutes at 3700 rpm at room temperature.

***Table 1**. Intra-day precision Coefficient of variation (CV) of each concentration after determination in triplicate. CV values ≤ 10% were considered valid. Different dilutions are prepared each day to assess the precision of a given value throughout the same day.*

CONCENTRATION (g/mL)	CV (%) Solution A Day 1:	CV (%) Solution B Day 2:	CV (%) Solution C Day 3:
12.5	4.64	2.58	0.82
10.0	0.00	3.00	3.45
5.0	2.04	3.40	2.33
2.5	3.03	6.06	2.37

***Table 2.** Inter-day precision. Coefficient of variation after determination of the same solution for 3 consecutive days. CV values ≤ 10% were considered valid.*

Determinations were performed in the same dilution to assess the precision of a given value in different days.

CONCENTRATION (g/mL)	CV (%) at days 1, 2 and 3 Solution D
12.5	4.75
10.0	5.17
5.0	1.14
2.5	4.53

Linearity was assessed using regression lines based on the concentrations obtained from the intra-day precision study. A straight line was obtained (y= mx+b) from the average concentrations obtained for each of the four dilutions performed in the intra-day study. This way, the level of linearity was examined in determinations within the concentration range of 12.5 mg/L to 2.5 mg/L. Straight lines with a regression coefficient (R^2) ≥ 0.98 are considered valid

***Table 3.** Evaluation of linearity. The correlation coefficient of the average obtained from the four concentrations obtained for each of the four dilutions performed each day.*

	Solution A Day 1:	Solution B Day 2:	Solution C Day 3:
R^2	0.9986	0.9913	0.9915

Accuracy is expressed as the percent difference between the concentration obtained and the labeled concentration. An acceptance criterion ≤15% is adopted. The average of the three determinations was calculated for each known concentration. As valproic acid undergoes volume displacement after reconstitution and biased concentrations can be

obtained when calculating accuracy, dilutions were not performed using vials but Alinity® valproic acid calibrators.

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***Table 4**. Evaluation of accuracy.*

Labeled concentration (Ct) (g/mL)	Experimental concentration (Cexp) (g/mL)	Accuracy (Cexp-Ct)/Ct)
11.5	10.0	-13.0
5.75	6.4	11.3
3.83	3.9	1.82
2.30	2.6	13.0

SOAP METHOD: therapeutic monitoring of VPA.

Clinical event	Therapeutic goal
Patient with meningitis for *Listeria monocytogenes* *With myoclonies refractory to treatment with 3 anticonvulsants*	Optimizing VPA dosage by therapeutic monitoring of Css

Subjective

The patient was somnolent, disoriented and instable.

Objective

The presence of *Lysteria monocytogenesb* in CSF and blood culture was confirmed microbiologically on 10/05/24.

Patient instability led to admission to the Intensive Care Unit (ICU) of our center, where he developed neurological deterioration from 14 to 8 on the Glasglow scale, requiring orotracheal intubation, mechanical ventilation and sedoanalgesia with propofol and fentanyl.

Analysis

On 13/05/2024, the patient had focal epileptic seizures in his left arm that required initiation of treatment with levetiracetam 1500 mg twice daily plus VPA (intravenous infusion of a bolus of 1600 mg followed by continuous infusion of 2400 mg).

On 14/05/2024, treatment was initiated with levetiracetam and lacosamide at a loading dose of 200 mg, followed by 100 mg twice daily.

Plan

To reach an optimal antiepileptic effect and prevent adverse drug reactions secondary to VPA overexposure, therapeutic monitoring of Css of total VPA (Css_T) and free VPA (Css_L) was performed. Clinical outcomes, analytical status of the patient (albumin, kidney function, thrombocytopenia…) and concomitant administration of drugs with strong affinity for plasma proteins were jointly considered.

Follow-up

In the light of the findings at the Emergency Department, the patient was admitted to the ICU on 13/05. Valproic acid therapy was initiated (bolus of 1,600 mg followed by continuous infusion of 2,400 mg once daily) plus levetiracetam 1,500 mg twice daily.

On 14/05, (day +1), in the presence of focal epileptic seizures in his left arm, lacosamide was added (bolus of 200 mg followed by 100 mg twice daily). As patient status did not improve, coma was induced using barbiturates. The three previous anti-epileptic drugs were maintained. Analgesic treatment with fentanyl was maintained.

On 15/05 (day +2), therapeutic monitoring of VPA revealed a Css_T of 41.6 g/mL. The patient had hypoalbuminemia (albumin=2.67 g/dL). The Unit of Pharmacokinetics determined free VPA and obtained a Css_L=14 g/mL. At this time point, the binding percent of VPA was 66.3%. Hence, down-titration of the dose to 2000 mg (16.5 mg/kg) in continuous infusion once daily was recommended. Therapeutic monitoring was performed at 24 h.

Given that VPA is a dangerous Class 3 drug, all doses were prepared by the Service of Pharmacy in a vertical laminar flow cabinet, with quality control performed by UV/Vis spectroscopy (Druglog®).

Second monitoring (day +3) revealed a Css_T=37.3 g/mL, Css_L=13.5 g/mL and a binding percentage of VPA to albumin of 64.0%. Albumin remained stable with respect to the previous day. Thus, down-titration of the dose to 1,500 (12.5 mg/kg) mg in continuous infusion once daily was recommended. Monitoring was repeated the following day

The third monitoring (day +4), demonstrated a Css_T=18.2 g/mL and Css_L=8.5 g/mL, with a binding percentage of VPA to albumin of 53.3% (serum albumin= 2.91 g/dL). As free serum concentration fell within therapeutic range, it was recommended to maintain the dose and repeat therapeutic monitoring in 3 days. In the absence of seizures, barbiturate sedation was discontinued. Fentanyl analgesia was maintained.

Serum concentration on Day+7 of treatment was Css_T=10 g/mL and Css_L=5.8 g/mL, with a binding percentage of VPA to albumin of 42.0% and an albumin concentration of 2.67 g/dL. It was recommended to maintain the dose and repeat therapeutic monitoring at 2 days to verify that drug exposure remained within therapeutic range.

Finally, the fifth monitoring (day +9) demonstrated a Css_T=2.2 g/mL and Css_L=undetectable and an albumin value of 2.43 g/dL. This sudden drop of Css was due to the initiation of treatment with meropenem on 21/05/24. In view of the clinically relevant interaction of VPA with Meropenem (9, 10), VPA was discontinued. Treatment with levetiracetam and lacosamide was maintained.

Additionally, on 16/05, monitoring of levetiracetam 1,500 mg PO twice daily demonstrated a therapeutic Cmin of 22.49 g/mL (therapeutic interval 50-100 g/mL). The same dose was maintained during his ICU stay.

It is worth mentioning that concomitantly to VPA, the patient received other drugs with strong affinity for plasma proteins (PPB), primarily albumin. These drugs could have interfered with VPA binding to albumin and result in the elevation of free valproic acid fraction in blood. The drugs with strong PPB administered to the patient are detailed in Table 5.

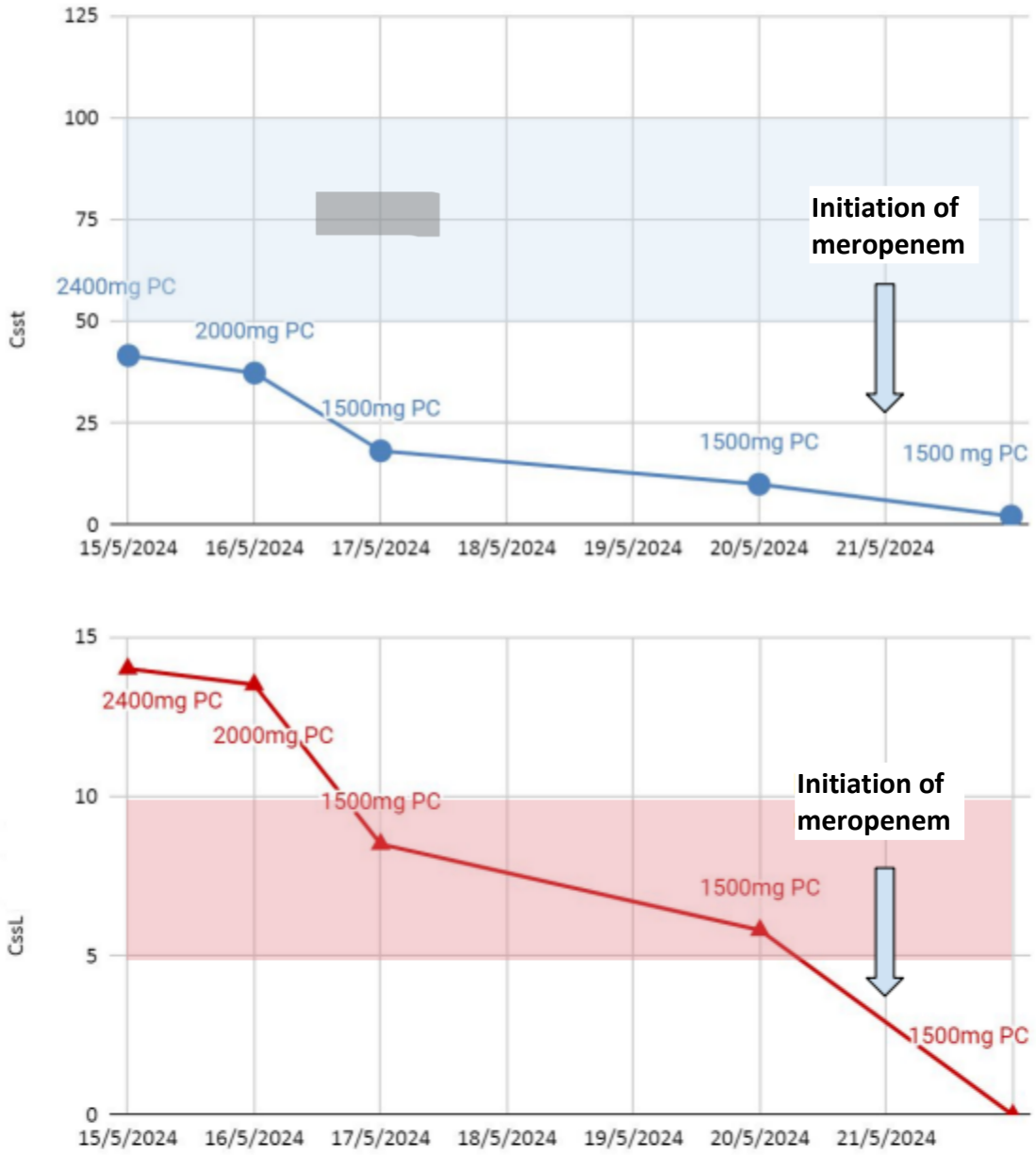
***Table 5**. Drugs with strong PPB administered concomitantly (11)*

Drug	PPB
Propofol	95-99
Penthotal	80
Amiodarone	96
Omeprazol	95
Fentanyl	< 7.0 %*

The table below describes other analytical aspects of interest on which recommendations for therapeutic monitoring were based:

***Table 6**. Analytical aspects of interest and therapeutic monitoring. UD: Undetectable.*

Date	Dose daily (mg)	Css_T (g/mL)	Css_L (g/mL)	Binding % to Albumin	Cr (mg/L)	GF (mL/min/sup)	Albumin (g/dL)	Platelets (/ L)
15/05	2,400	41.60	14.00	66.3	1.67	43.53	2.67	246,000
16/06	2,000	37.30	13.50	64.0	1.63	44.80	2.67	277,000
17/05	1,500	18.20	8.50	53.3	1.54	48.00	2.91	327,000
20/05	1,500	10.00	5.80	42.0	1.37	55.00	2.67	362,000
22/05	1,500	2.20	ID	----	1.54	48.00	2.53	364,000



***Graph 1**. Changes in Css$_T$ (* g/mL*, in blue) and Css$_L$ (* g/mL*, in red) throughout the therapeutic monitoring plan. The shaded areas correspond to the therapeutic range recommended for the treatment of epilepsy.*

DISCUSSION

Therapeutic monitoring of VPA is essential for an individualized dose adjustment. This is especially relevant to critical patients, who receive multiple concomitant therapies and often have hypoalbuminemia.

The clinical case reported demonstrates the relevance of monitoring free VPA in critical patients with hypoalbuminemia for an optimal dose adjustment. If total Css alone would have been considered, the recommendation after monitoring would have been up-titration. The first monitoring already revealed a non-linear distribution of VPA, with saturation in binding to plasma proteins. The free fraction of VPA accounted for over 30% of the total Css.

When examining drug exposure, the difference between determining free serum concentration and total serum concentration has been extensively described in the literature. Some authors have developed formulas for calculating experimental free fractions in Department of Pharmacokinetics where this technique is not available. In Table 7, differences are observed between the experimental Css_L and the one obtained using the formulas developed by Conde, Doré, Parent and Hermida (12). As shown in the Table, these formulas provide an approximate value, although it may be inaccurate.

In this case, the different empirical formulas underestimate the actual free VAP concentrations obtained. This underestimation becomes more significant as concentrations decrease. The patient was receiving multiple concomitant drugs with strong affinity for proteins that may have caused a displacement of VAP to the already reduced concentration of albumin in blood, thereby increasing Css_L elevation in blood.

Table 7. *Comparison between the free Cp obtained experimentally and the one calculated from albumin concentration using the formulas developed by Conde, Doré, Parent and Hermida.*

				Experimental		Conde	Doré	Parent	Hermida
Date	Cr (mg/dL)	FG (ml/min /sup)	Alb (g/dL)	Total Cp (g/mL)	Free Cp (g/mL)	Free Cp experimental (g/mL)	Free Cp experimental (g/mL)	Free Cp experimental (g/mL)	Free Cp experimental (g/mL)
15/05	1.67	43.5	2.67	41.6	14.0	11.35	12.53	7.41	8.36
16/06	1.63	44.8	2.67	37.3	13.5	9.98	10.90	6.64	7.49
17/05	1.54	48.0	2.91	18.2	8.5	2.78	2.49	2.71	2.94
20/05	1.37	55.0	2.67	10.0	5.8	1.38	1.09	1.78	2.01
22/05	1.54	48.0	2.53	2.2	0.0	--	--	--	--

A significant interaction of VPA with carbapenem antibiotics is observed. This interaction is clinically relevant, as it causes a rapid, sudden drop of serum VPA concentrations, which was observed in our patient. In this setting, one of the therapies involved in interaction should be discontinued and therapeutic monitoring would not be necessary (9,10).

CONCLUSIONS

- Therapeutic monitoring of serum VPA concentrations is essential to optimize treatment effectively and safely.
- Determining VPA free fraction is essential for adjusting dose in patients with abnormal analytical results (especially in the presence of hypoalbuminemia) who are receiving concomitant drugs with strong affinity for plasma proteins. In this setting, VPA pharmacokinetics follows a non-linear distribution.
- Although the formulas developed for the determination of free VPA are not useful, in cases of severe hypoalbuminemia and albumin saturation secondary to a concomitant therapy may lead to the underestimation of free VAP. In this context, experimental determination, whenever possible, of free fraction is necessary.

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