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Case Report

Use of Intermittent Hemodialysis in the Management of Valproic Acid Poisoning: A Case Report and Literature Review

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Abstract

Since valproic acid was first approved in Europe in 1967 for the treatment of epilepsy, several cases of intoxication have been described, some of them leading to coma and acute hepatic insufficiency. In 2015 a review article proposed the use of extrarenal depuration therapies in cases of serious valproate intoxication, but the summary of product characteristics of valproic acid has not established yet a clear indication of these therapies. We present a case of a young female patient who suffered from valproate overdose leading to coma and hyperammonemia that required orotracheal intubation and admission to the intensive care unit. After a sole hemodialysis session she had a rapid recovery of her conscious level and mechanical ventilation could be removed with no further complications. We could confirm an adequate elimination of valproic acid in the dialysate and the reduction in serum levels, estimating a reduction in half-life, from 8.3 hours in normal conditions to 2.5 hours during the dialysis session (more than 3 times faster). We searched the literature for articles published after the 2015 EXTRIP review article that agree on the efficacy of different dialysis techniques in cases of valproate overdose. With the current evidence we consider that regulatory agencies should establish a clear recommendation for dialysis therapy in cases of serious valproic acid intoxication.

Keywords: *Valproic Acid; Valproate; Toxicity; Poisoning; Hemodialysis; Hemodiafiltration; Extracorporeal Elimination*

Abbreviations

AEMPS: Spanish Agency of Medicines and Medical Devices; CNS: Central Nervous System; EMEA: European Medicines Agency; EKG: Electrocardiogram; ER: Emergency Room; FDA: Food and Drug Administration; HD: Hemodialysis; HDF: Hemodiafiltration; HP: Hemoperfusion; ICU: Intensive Care Unit; SmPC: Summary of Product Characteristics; SpO2: Pulse Oximetry Saturation; Vd: Volume of Distribution

Introduction

Valproic acid was first approved in Europe for the treatment of epilepsy in 1967, and now it is one of the most widely used antiepileptic drugs worldwide. It became the first-line choice for the treatment of generalized epilepsy and since 1990 it has also been approved for the treatment of partial seizures. More recently, it has been indicated in the treatment of manic episodes related to bipolar syndrome and for the prophylaxis of migraine [1,2].

Although valproate is one of the oldest commercially available antiepileptic drugs, it continues to show an increasing frequency in its use [3].

Valproic acid has been reported as responsible for 7763 cases of poisoning in 2016 according to the Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS) [4], out of which 27% needed in-hospital treatment. In 2015 a review article was reported giving rise to the current guidelines for the management of valproate intoxication and the use of extracorporeal techniques for its elimination [5]. However, the full prescribing information for valproate is not clear in the management of an

overdose. In the present article we describe a case of severe intoxication with valproate where extracorporeal treatment with intermittent hemodialysis (HD) was effective for its removal, and we review the most recent literature including new cases described after the review article by EXTRIP workgroup [5] and the current guidelines for the management of valproate overdose [1].

Materials and Methods

Valproic acid serum concentrations were measured at admittance, before onset of HD (16 hours after admittance), at the end of the HD (3-hour duration session), and at 1 and 24 hours post-HD. We measured valproic acid concentration in two dialysate samples; one after 10 minutes of HD onset and the other 10 minutes before the end of the session (after 2 hours and 50 minutes of dialysis). We obtained the approval from our Hospital Ethics Committee to use the clinical data of this case for subsequent publication.

To review the most recently reported cases where HD was used for the treatment of Valproate overdose, we conducted a systematic literature search using the same terms as those used in the EXTRIP workgroup review article: [(valpro*) AND (dialysis OR hemodialysis OR haemodialysis OR hemoperfusion OR haemoperfusion OR plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR extracorporeal therapy OR CRRT)] in the National Library of Medicine's PubMed database and Cochrane database of systematic reviews (accessed in August 2018). The review was performed from 2014 since that year was used as reference in the search conducted by Ghannoum [5].

Valproate Summary of Product Characteristics (SmPC) and approved label in the FDA database [1] was reviewed from 2006 onwards, since it contains historical prescription and label data of the drug, to study the evolution and changes in the overdose section. In Spain this historical data is not available, but the authors had a printed full prescribing information sheet from 2013, and it was compared to its last update in 2018 [2].

Case Report

A 35 year old woman with a past history of bronchial asthma, irritable bowel syndrome and paranoid schizophrenia with several in-hospital admittances in the Psychiatry Ward due to episodes of psychotic decompensation and suicidal attempts, was admitted to the emergency room (ER) in a state of reduced conscious level and reported drug intoxication with approximately 140 mg of olanzapine, 2225 mg of venlafaxine, 700 mg of pregabalin, 4g of levetiracetam and 50g of valproic acid. On arrival to the ER, flumazenil and naloxone were administered with no improvement in her conscious level and was transferred to the Intensive Care Unit (ICU) due to a low conscious level (Glasgow Coma Scale 7), hypoxemia (SpO2 88% with 35% Oxygen mask flow) and a tendency for hypotension.

On admittance to the ICU, initial airway protection and respiratory stabilization was carried out by performing endotracheal intubation and mechanical ventilation, and noradrenaline perfusion was required for circulatory stabilization at a dose of 0.17 mcg/Kg/min.

Gastrointestinal decontamination was performed by gastric lavage and administration of activated charcoal obtaining scarce drug remains. Intravenous bicarbonate perfusion was started for urine alkalinization, maintaining a urine flow rate of 100 ml/hr. Given the suspicion of intoxication with large doses of valproic Acid, and its potential hepatotoxicity, L-carnitine was administered and Valproate serum levels were monitored; with a first determination of > 352 µg/ml and hyperammonemia of 234 µmol/l on admittance, with normal liver function tests (Table 1).

Chest X-ray was normal and EKG showed a corrected QT on the upper normal limit, not presenting any arrhythmias during the hospital stay. Toxicology tests were positive for benzodiazepines in urine, and negative for acetaminophen, opioids, cannabis, barbiturates and salicylic acid.

Given the high serum valproic acid levels and the patient's poor clinical situation, a 3-hour HD session was performed with high-flux membrane and without hemoperfusion (HP), achieving a significant improvement in the patient's conscious level and a rapid reduction in serum valproic acid and ammonium levels after a single HD session, being able to remove respiratory and circulatory supportive measures and discharged from the ICU after 72 hours of admittance. Valproic acid concentration levels in the dialysate (CpUF) were measured at the beginning and end of HD; CpUF was 60 µg/mL ten minutes after onset of HD and 9 µg/mL ten minutes before the end of the session.

	On Admittance	End-Dialysis	24 Hours Post-Dialysis	48 Hours Post-Dialysis
Hemoglobin (gr/dl)	13	13	12.8	10.9
Hematocrit (%)	43	42	39	34
Leukocytes (/µl)	7100	15900	6500	7700
Neutrophils (%)	67	78	65	78
Platelets (/µl)	295000	224000	175000	109000
INR/Prothrombin time (%)	1/88	1.1/ 85	1/99	0.9/106
Glucose (mg/dl)	122	84	97	84
Urea (mg/dl)	14	12	12	9
Creatinine (mg/dl)	0.78	0.46	0.58	0.5
Sodium (mmol/L)	149	140	141	138
Potassium (mmol/L)	3.9	3.6	2.9	3.4
ALT/AST (U/L)	7/12	11/17	8/13	6/15
Total bilirubin (mg/dl)	0.2	0.3	0.4	0.5
Ammonium (umoL/L)	234	48	30	39
Albumin (gr/dl)	-	3.3	-	2.9
pH	7.45	7.48	7.48	7.45
$PaCO_2$ (mmHg)	42	51	47	39
Bicarbonate (mmol/L)	29	30	35	34
Base excess	4.7	4	9.9	2.9
Lactate (mmol/L)	1.8	0.6	0.8	0.6
Serum Valproate (µg/mL)	352	126	62	60

Table 1: *Course of laboratory values on admittance, immediately after the hemodialysis session and at 24 and 48 hours after dialysis.*

The course of valproic acid serum concentration levels before and after HD is shown in figure 1. On admittance to the ICU, valproic acid serum levels were > 352 µg/ml (undiluted). After 16 hours of gastrointestinal decontamination valproic acid levels decreased to 286 µg/ml (just before HD) and to 126 µg/ml after 3 hours of dialysis. Knowing the course of valproic acid serum concentrations and the time between determinations, a measurement of valproic acid half-life can be performed by using the following formulae:

K_{el} = ln (initial concentration/final concentration)/time

$T_{½} = \ln 2/K_{el}$

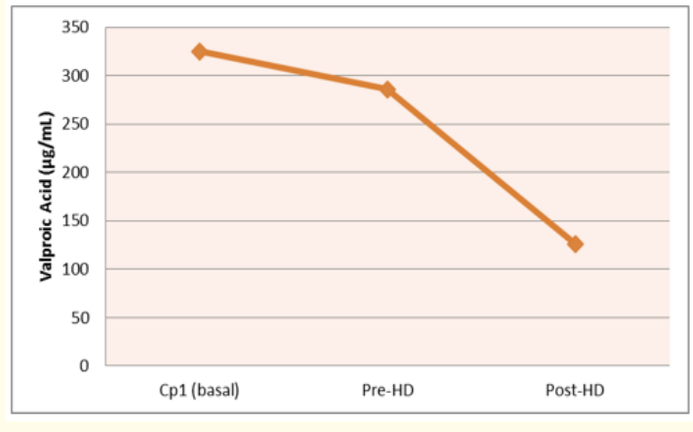

Figure 1: *Valproic acid serum concentration levels (µg/mL)before and after hemodialysis. Prehemodialysis (Pre-HD). Posthemodialysis (Post-HD).*

In the first sample a proper dilution could not be performed so the exact value was unknown. However, with the aforementioned formulae and based on the literature that describes that in valproate poisoning its half-life is above 30 hours [6,7] we could calculate an approximated initial concentration by accepting a 30-hour half-life. The result was of an approximated concentration of 414 µg/ml. Since the exact pre and post-dialysis concentration levels were known, a precise elimination half-life could be calculated after dialysis. The half-life for valproate during dialysis was reduced to 2.5 hours. After dialysis the half-life was similar to that of valproate in usual conditions (8.3 hours) (See table 2).

Time (h)	Valproic acid (µg/ml)	Kel	Half-life (hr)
0	> 352 (approximately 414)		
16h (onset of HD)	286	0.023/h	30
19h (end of HD)	126	0.27/h	2.5
20h (1h post-HD)	116	0.082/h	8.3

Table 2: *Course of concentrations and kinetic parameters.*

Valproic acid serum levels were similar after 24 and 48 hours of dialysis (Table 1) without having administered valproate again. This could be explained by the rebound phenomenon and drug redistribution described in other cases of valproate intoxication in which renal replacement therapies were used [8].

Discussion

We identified seven new articles in our literature search of recent reports concerning valproate poisoning and extracorporeal elimination techniques published after the EXTRIP workgroup review article [5]. On reviewing these articles, we found that HD was used in valproate poisoning in three case reports [9-11], HP in one case report [12], one article that described two episodes in the same patient separated by 8 months [13] and two case series articles. The first one registered three cases of valproate poisoning treated with HD [14] and the other one registered another three cases [15]. In summary, 11 new cases have been described after the EXTRIP workgroup review. In all of them, HD resulted as an effective treatment for the reduction of valproate concentration levels and clinical improvement of the patients.

In regards to valproate SmPC, each valproate formulation and each country in the European Union has a different information sheet. Thus, the description and management of valproate dose in each of them is different. The only case in which we could trace the course of the SmPC was that of the FDA, and since 2006 till now the overdose section has not varied. The FDA states a brief reference to the rationale of HD and HP as useful tools for the elimination of valproate, without specifying whether it should be used in all cases or in massive intoxications only [1]. The SmPC in Spain has not suffered modifications in the overdose section from 2013 till now [2]. It states that there is not a known specific antidote for valproate overdose, and that in-hospital treatment should be symptomatic and monitoring of cardio-respiratory functions. It mentions that forced diuresis or HD could be useful and that in cases of massive intoxications (without specifying a definition for massive intoxication) treatment with HD and HP has been successful.

Valproate overdose is a common reason for emergency consultation, with some cases of severe intoxication that require in-hospital admittance for monitoring and treatment. Clinical manifestations include an altered mental state that can vary from somnolence to coma or cerebral edema, tremors, agitation, myoclonic jerks, respiratory depression, hypotension, tachycardia and hyperthermia. Measuring valproate serum concentration levels can be useful to establish the severity of the intoxication. Concentrations exceeding 450 µg/ml can be associated to moderate or severe adverse events, and concentrations exceeding 850 µg/ml are more likely to develop coma, respiratory depression or metabolic acidosis [16], therefore current recommendations support the early initiation of HD in these cases. On the other hand, it has been established that in cases with concentrations exceeding 300 mg/L, protein-binding of valproate becomes saturated and only 35% are bound to plasma proteins in these cases [7], compared to 94% protein-binding when concentrations are within therapeutic range, which increases the amount of free plasma valproate. Valproate has a low molecular weight and a low Vd that is conductive for extracorporeal elimination. Therefore, although HD has little effect on the elimination of valproate at therapeutic range concentrations because of its extensive protein binding, significant clearance can be obtained at supratherapeutic drug levels when plasma proteins become saturated [17].

In 1983 the first case of valproic acid overdose successfully treated with HD was described [18]. From then on several other cases have been reported in which intermittent HD, HP or continuous hemodiafiltration (HDF) have been used. Charcoal HP has been successfully used but is limited by early column saturation [19]. Tandem HD-HP may be the most effective technique but probably offers limited advantage over HD to justify the added cost of the technique [6]. There is insufficient evidence to determine whether intermittent HDF has an additional benefit over hemodialysis alone, although some cases have been reported [20]. Continuous renal replacement therapies appear to be considerably less effective than intermittent hemodialysis [21]. Albumin dialysis, slow low-efficiency dialysis with filtration, plasmapheresis and peritoneal dialysis have been described to be inferior to high-flux intermittent HD and are not recommended [22,23]. The review conducted by EXTRIP workgroup [5] has led to a series of indications for extracorporeal treatment in valproic acid overdose: when valproic acid serum concentration exceeds 1300 mg/L or in presence of cerebral edema or shock that could be attributed to valproate toxicity. On the other hand, they suggest its use when valproate serum concentration exceeds 900 mg/L or in presence of coma, respiratory depression that requires mechanical ventilation, acute hyperammonemia or severe metabolic acidosis with pH ≤ 7.10. Our patient presented a case of multidrug intoxication. Thus, CNS and respiratory depression could be due to other causes and not exclusive to valproate toxicity. In principle, pregabalin could be excluded as the possible ingested dose (700 mg) was near the maximum daily dose (600 mg) and in healthy volunteers doses up to 900 mg/day have been tolerated [24]. The same goes for levetiracetam (possible ingested dose 4g), since the maximum daily dose is 3 g/day and during its clinical development for commercialization doses up to 4 g/day were used [25]. Concerning venlafaxine, the possible ingested dose of 2.2g was far superior to the maximum recommended daily dose (375 mg/day). The most frequently notified events in venlafaxine overdose [26] are tachycardia and altered mental status that could lead to coma. EKG changes like prolonged QT have also been described. With the exception of the altered mental status, other events as EKG changes were not presented by our patient. Moreover, venlafaxine is not dialyzed and the rapid improvement of our patient after dialysis suggests that her clinical picture was caused by the overdose with another drug. This way, the symptoms our patient presented were more likely caused by a valproate overdose. Another point in favor of valproate intoxication would be hyperammonemia, which has not been described in overdoses with the other drugs.

In our case the exact initial valproic acid concentration is unknown; we only know that it exceeded 352 mg/L. The concentration just before HD was 286 mg/L. However, the poor clinical situation with hemodynamic instability and low conscious level led us to search for other therapeutic alternatives. The case we are describing happened in 2014, when no clear recommendations were present for the use of HD in valproate poisoning since the EXTRIP recommendations were published in 2015. At a first instance the SmPC was revised without finding any clear reference to the use of HD. A quick literature review of similar published cases was conducted to take a therapeutic decision, with many reservations, to use intermittent HD for the elimination of valproate. In 2016 we had another case of valproate poisoning in our centre (with peak concentration of 847 mg/L), with no updates on treatment of overdose in the valproate SmPC at that point. However, the EXTRIP workgroup recommendations had been published and since that patient was in coma and with high peak valproate concentration levels, the decision to use HD for the elimination of the drug was immediate, and with good results.

EXTRIP workgroup recommendations are based on case reports, case series and an observational study. As the own authors mention, there are important limitations as the absence of a control group and publication bias. Nonetheless, it is evident that extracorporeal techniques have proven to be successful for the elimination of valproate in its overdose. We believe that rather than looking for a valproate concentration cut-off point, the clinical course (both neurological and hemodynamic) should set the indication for dialysis as long as it is not contraindicated. Furthermore, with the available data in literature it could be considered as hardly ethical to design a study with a control group.

Valproate SmPC was last modified in the EU in June 2018 to contraindicate its use in women of childbearing potential, unless conditions of Pregnancy Prevention Programme are met, due to a high risk in malformations and development problems in newborns whose mothers used valproate [27]. Since the update was centered on this subject, the section on overdose has not been changed as we previously mentioned, with no clear recommendations on the use of HD and with different recommendations in each country belonging to the EU. Thus, the question arises whether the overdose section in the SmPC is of use to health practitioners in cases of serious intoxications as the case we describe. Taking into account the available published case reports, case series and the EXTRIP workgroup recommendations,

it would not seem unreasonable to give a specific and clear recommendation in the SmPC on the use of HD in cases with elevated peak concentrations or severe clinical manifestations that do not improve with gastrointestinal decontamination.

Conclusion

In conclusion, we describe another case of valproate intoxication that although by taking into account peak concentration levels would not be considered serious, the patient's poor clinical situation required a more intensive treatment with HD. Once more HD was effective in the treatment of valproate intoxication with an evident clinical improvement in less than 24 hours. The most recent cases reported on the use of dialysis for valproate intoxication should lead to a revision of valproate SmPC to include clear recommendations on the use of dialysis in cases of overdose particularly when either coma or liver failure are present.

Conflict of Interest

No conflicts of interest to declare.

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