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CASE REPORT

Valproic acid intoxication: sense and non-sense of haemodialysis

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ABSTRACT

Introduction: Valproic acid is increasingly used in the treatment of epilepsy, and also prescribed for bipolar affective disorders, schizoaffective disorders, schizophrenia and migraine prophylaxis. We describe two case reports involving valproic acid intoxication with ingestion of ethanol.

Methods: One patient was treated by supportive care, one patient received haemodialysis.

Results: From analysis of plasma concentrations before and during haemodialysis (pre- and post-filter) it is shown that valproic acid can be effectively eliminated by haemodialysis when plasma levels are way above 100 μg/ml. In the literature, plasma protein binding is reported to be around 90% for levels within the therapeutic range. In our patient plasma protein binding was around 50% after treatment with haemodialysis.

Conclusion: These findings make haemodialysis in valproic acid intoxication a sensible therapeutic option with increasing efficiency when plasma concentration is high. Furthermore our findings suggest that lowering valproic acid concentrations to a therapeutic level by haemodialysis does not necessarily result in an immediate, simultaneous increase in plasma protein binding of valproic acid.

INTRODUCTION

Valproic acid (VPA) is increasingly used in the treatment of epilepsy, and is also prescribed for bipolar affective disorders, schizoaffective disorders, schizophrenia and migraine prophylaxis.[1,2] Patients with these diseases are prone to self-poisoning. Self-poisoning with VPA may lead to coma, respiratory failure, renal failure, acute pancreatitis, central nervous system depression, hepatotoxicity, leucopenia, thrombocytopenia, and drowsiness.[3-5] Although some side affects of VPA are not dose-dependent, toxic effects are associated with daily doses above 1800 mg[6] and blood levels above 100 μg/ml.[7] VPA has a low molecular weight of 144 daltons and a small distribution volume (0.1 to 0.5 l/kg). VPA is metabolised in the liver and excreted in the urine. At therapeutic levels (50 to 100 μg/ml), VPA is almost completely bound (90 to 95%) to plasma proteins with, as a consequence, a limited free drug fraction.[8] Thus, at the therapeutic serum level, drug removal obtained through haemodialysis (HD) is negligible. However, in case of VPA overdose, the free drug fraction increases as VPA protein binding sites become saturated, and plasma concentration of the drug increases significantly.[8-10] In this situation, HD may be a useful tool for eliminating VPA. We report two cases of VPA self-poisoning. We studied the natural course in one patient and the effect of HD in the other patient.

CASE 1

A 38-year-old man with a history of psychiatric disease was found naked and unconscious. Empty medication strips were found on the ground beside him. Sixty tablets of valproic acid (Depakine® chrono) were missing.
He arrived in the emergency room in coma, with a Glasgow

coma score of 3. He had a regular heart rate of 92 beats/min, blood pressure of 100/45 mmHg, temperature of 36 °C, and a respiratory rate of 20 breaths/min. Blood toxicology revealed ethanol values of 1.1%. The serum valproic acid (VPA) concentration on admission was 846 µg/ml (therapeutic range 50 to 100 µg/ml).
Initial treatment included enteral activated charcoal, nasal oxygen, and fluid therapy. The patient was admitted to the intensive care unit. He was rehydrated, and $MgSO_4$, and L-carnitine were administered intravenously.[11]
Haemodialysis (HD via a right femoral venous catheter) was initiated 3.5 hours after admission and was performed for 4.5 hours. During this HD session, the blood flow rate was 300 ml/min, and dialysate flow rate was 500 ml/min. Blood samples for determination of VPA and free VPA concentrations were drawn at one, two, three and four hours after dialysis initiation both pre- and post-filter. A fluoresence polarisation immunoassay (FPIA; Cobas Integra, Mannheim, Germany) was used for analysis of total VPA concentrations in plasma. After ultrafiltration, free VPA concentrations were determined by a specific and sensitive gas chromatography method with flame ionisation detection (GC-FID), with a limit of detection of 1.5 µg/ml. Percentage plasma protein binding of VPA was calculated as 100 x (total VPA concentration – free VPA concentration)/total VPA concentration.
After HD, the serum VPA concentration decreased from 723 to 313 µg/ml. Eighteen hours after the start of HD the VPA concentration had decreased to 86 µg/ml (*figure 1*). During dialysis, the patient showed stable haemodynamic parameters. He regained consciousness and no toxic effects, including hepatotoxicity, occurred. His subsequent hospital course was uncomplicated.

CASE 2

A 37-year-old man with a history of epilepsy (treated with Depakine® chrono) following a road traffic injury 14 years previously, multiple suicide attempts, and alcohol dependence, arrived in the emergency room with a Glasgow coma score of 6. He had a regular heart rate of 80 beats/min, blood pressure of 105/70 mmHg, temperature of 36.8 °C, and a respiratory rate of 15 breaths/min. Blood toxicology revealed an ethanol level of 2.8%. The serum valproic acid (VPA) concentration on admission was 260 µg/ml (therapeutic range, 50 to 100 µg/ml). Initial treatment included enteral activated charcoal, nasal oxygen and fluid therapy. The patient was admitted to the intensive care unit. He was treated with supportive care. After 24 hours, his serum VPA concentration decreased to 186.9 µg/ml; 48 hours thereafter the VPA concentration had decreased to 52.9 µg/ml (*figure 1*). It is shown in this case that the half-life of VPA is prolonged in supratherapeutic ranges (e.g. approximately 24 hours). The patient remained haemodynamically stable. His subsequent hospital course was uncomplicated.

DISCUSSION

Valproic acid (VPA) is used in the treatment of epilepsy and psychiatric disorders. We have reported two cases of VPA self-poisoning and have studied the natural course in one patient and the effect of HD in the other. The patient who was treated with HD showed a better elimination rate than the patient on supportive care. However, HD is not totally free from complications and is not widely or

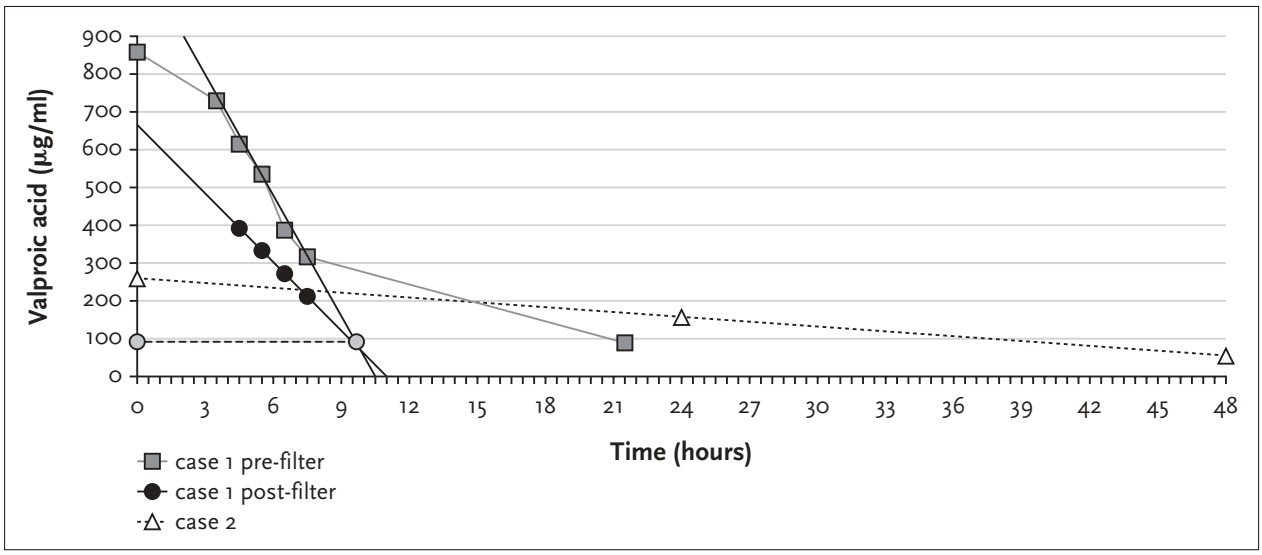

Figure 1
Valproic acid concentration vs time
In case 1 the pre- and post-haemodialysis filter VPA levels are shown. Case 2 represents serum levels. The line at 100 µg/ml is drawn to determine the level were the elimination fraction is zero (see text).

rapidly available in most hospitals. The most common complications during HD are hypotension (20 to 30%), cramps (5 to 20%), nausea and vomiting (5 to 15%), headache (5%), chest pain (2 to 5%), back pain (2 to 5%), itching (5%), and fever and chills (<1%).[12]

On the other hand, if HD is not applied in acute VPA self-poisoning, risks are taken. Self-poisoning with VPA may lead to coma, respiratory failure, renal failure, acute pancreatitis, central nervous system depression, hepatotoxicity, leucopenia, thrombocytopenia, and drowsiness.[3-5] Hepatotoxicity may be asymptomatic with elevated serum liver enzymes, or may present as fatal hepatic failure.[5,7] Therefore, at very high plasma levels the risks of HD may outweigh the risks of prolonged toxic VPA levels if supportive care is given without HD. However, VPA is poorly water-soluble, suggesting that it would be poorly dialysed from the blood into the dialysate. In contrast, the volume of distribution (0.1 to 0.5 l/kg) and low molecular weight suggest it would be effectively removed from circulation by dialysis. According to the current literature, at therapeutic levels VPA circulates almost completely protein bound.[8] The protein binding decreases to 70 and 35% when drug concentrations are >150 μg/ml, and >300 μg/ml, respectively.[10,13] The toxicokinetics, as derived from the literature on VPA, are summarised in *table 1*.[14-16]

Table 1
Toxicokinetics of VPA

Peak plasma level	50-100 μg/ml
Time to peak plasma level	1-4 hours
Volume of distribution	0.15-0.40 l/kg
Plasma protein binding	90%
Elimination half-life	7-15 hours
Excreted unchanged	1-3%

With supratherapeutic VPA concentrations, the free drug fraction increases as VPA protein binding sites become saturated, and HD may be an increasingly efficient tool to eliminate VPA and lower the free drug fraction. As shown in *figure 1*, the concentration differences between pre- and post-filter blood samples are greater in the high plasma concentration range than in the low plasma concentration range. This elimination fraction (EF) is shown in *table 2*. By extrapolating these results, we calculated that the EF will be zero with a plasma level of 100 μg/ml. Above this cut-off point of the VPA concentration, HD will contribute to VPA elimination. However, a low free drug fraction will decrease the effectiveness of HD.

Klotz and Antonin studied the pharmacokinetics and bioavailability of VPA.[10] At the therapeutic concentration of 80 μg/ml, the plasma protein binding of VPA was determined (the four-hour blood sample). They found that therapeutic concentrations of VPA revealed relatively strong plasma protein binding between 80 and 94% after a single iv bolus of 400 mg. The results were obtained from six healthy volunteers,[10] and used as a reference in numerous articles. In contrast, at a therapeutic level after intoxication, we found a lower protein bound fraction of around 50%. The reason for this finding is not completely clear.

We found an increase in protein binding with lowering of the total VPA concentration. This is in agreement with a case report by Franssen *et al.*[17] in which they describe a patient with a severe VPA intoxication successfully treated by HD and haemoperfusion. In that particular case, during two treatment sessions, protein binding of VPA rose from 32%, at the start, to 54%.[17] There may be two explanations for the fact that when lowering toxic total VPA concentrations to a therapeutic level by HD, protein binding does not immediately reach the normal level of around 90%. HD may increase free fatty concentrations, leading to an increase in free VPA concentrations by displacement of protein binding.[18] However, De Smet *et al.* reported that

Table 2
VPA concentrations, free fractions, and plasma protein binding in case 1

TIME (HOURS)	VPA SERUM CONCENTRATION PRE-FILTER (μG/ML)	FREE DRUG FRACTION (μG/ML) (% PLASMA PROTEIN BINDING)	VPA CONCENTRATION POST-FILTER (μG/ML)	FREE DRUG FRACTION POST-FILTER (μG/ML) (% PLASMA PROTEIN BINDING)	ELIMINATION FRACTION
0	846	398 (53%)			
3.5	723	425 (41%)	*		
4.5	616	358 (42%)	391	204 (48%)	36.5% ((616-391)/616)
5.5	535	313 (41%)	317	157 (50%)	40.7%
6.5	379	238 (37%)	265	112 (58%)	30.0%
7.5	313	165 (47%)	210 **	88 (58%)	32.9%
21.5	86	33 (59%)			

** Start of haemodialysis, ** end of haemodialysis.*

the use of heparin during dialysis may alter lipase activity in the blood sample collection tubes (the free fraction does not increase during HD when lipase activity is neutralised at the time of blood sampling), resulting in higher free fatty acid concentration competing with VPA for protein binding sites. Thus, during dialysis, measured free VPA concentrations may be higher than in reality, and previous reported increases are probably artefacts.[19]

It was shown earlier that the protein binding of VPA may alter due to age and concomitant medication.[20,21] However, neither of these factors were present in our patient. *Table 2* shows an increase in protein binding measurements and an ongoing decrease in VPA concentrations. It can be speculated that a further increase in protein binding would appear with decreasing VPA concentrations.

In conclusion, although it seems logical to use HD in VPA levels above 100 μg/ml, a decision will be made based upon the clinical situation and the possible disadvantages of HD. In practice, the cut-off point when to use HD will be higher than the 100 μg/ml as illustrated by our second case. In the first patient with a relatively high VPA level, HD was successfully applied, whereas in our second patient with a much lower VPA level, no forced elimination was performed. In addition, we have shown in our patient that the protein binding at high VPA levels, and after normalisation of the level by HD, differs from protein binding data at therapeutic levels under normal circumstances.

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