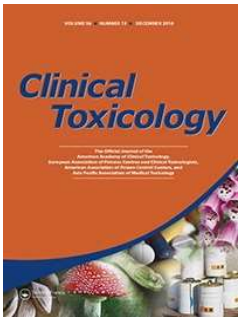

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LETTER TO THE EDITOR

Delayed and prolonged coma following valpromide poisoning in a 4-year-old girl

To the Editor,

Valpromide, a valproic acid (VPA)-derived amide, is used as antiepileptic and mood stabilizer drug. At pharmacological doses, serum valpromide concentrations are low due to its rapid metabolism to VPA [1]. Valpromide, usually considered as a prodrug, is also pharmacologically active with potent anticonvulsant effects. However, its direct toxicity remains poorly understood.

A 4-year-old girl was found in bed playing with valpromide tablets used by her mother. Four hours later, she suddenly became comatose (Glasgow coma score, 3) and was transported to the intensive care unit. On admission, laboratory tests showed arterial pH 7.23, $PaCO_2$ 6.8 kPa (*N*, 4.8–5.8), PaO_2 8.2 kPa (*N*, 10.0–13.0), blood lactate 3.1 mmol/L (*N*, 0.6–2.4), bicarbonate 21.4 mmol/L, anion gap 4 mmol/L AST/ALT, 25/7 IU/L, creatinine, 23 µmol/L and ammonium 20 µmol/L (*N*, 10–50). She was intubated, received inhaled epinephrine/budesonide to treat bronchospasm and L-carnitine to reverse presumed valproic-induced hyperammonemia, and benefited from a 2-h hemodialysis session at H12 to enhance the toxicant elimination. Ammonia remained normal (17 µmol/L at D2). After 48 h of mechanical ventilation, she progressively woke up with normal neurological examination and blood gases allowing extubation.

Toxicological screening tests using liquid chromatography coupled to diode array detector and liquid chromatography tandem mass spectrometry (LC-MS/MS) found valpromide (serum concentration, 89 mg/L at H5.5; therapeutic range, no published data [1]; limit of quantification, 2 mg/L) and cetirizine (serum concentration, 440 µg/L; therapeutic range, 20–400 µg/L; toxicity threshold, > 2000 µg/L). VPA was quantified using an automated chemistry analyzer (Cobas-c502 analyzer™, Roche) at 134 mg/L (therapeutic range, 50–100 mg/L; toxic threshold, 150 mg/L; limit of quantification 2.8 mg/L). Valpromide and VPA peaked at H12 at 153

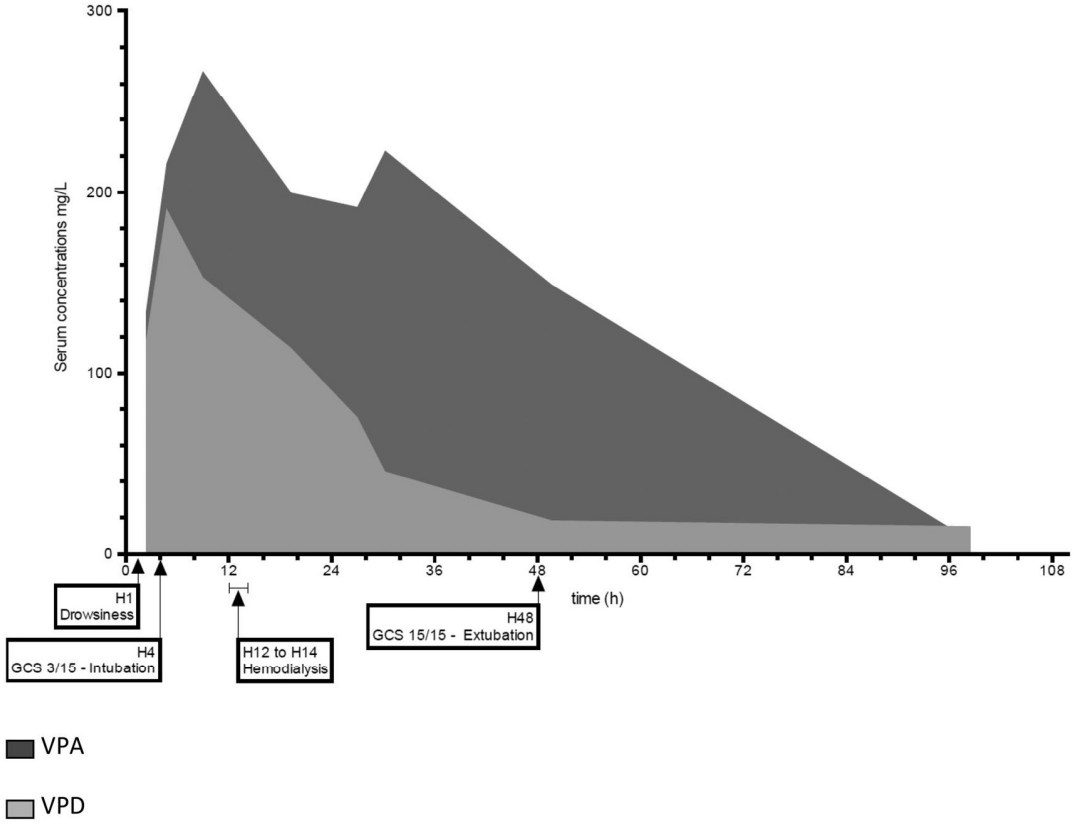

Figure 1. Valpromide (VPD) and valproic acid (VPA) concentrations following acute VPD overdose leading to delayed and prolonged coma.

and 267 mg/L, respectively, and were undetectable at H100 (Figure 1).

Similarly to VPA, valpromide poisoning mainly results in neurological, cardiovascular and metabolic disorders including hyperlactatemia and hyperammonemia [2,3]. However, delayed and prolonged consciousness impairment, as observed in our case, seems to characterize valpromide compared to VPA overdose. In a 163-case series of VPD overdoses, severe valpromide poisoning has been associated with lower VPA concentrations in comparison to VPA concentrations resulting from VPA overdoses (above 200 *versus* 850 mg/L) [3,4]. In our case, serum VPA peaked at 267 mg/L∼16 h post-ingestion and combined VPD/VPA-related effects could better explain the observed prolonged and marked coma. The apparent terminal half-lives of VPD and VPA were 14 and 28 h, respectively. Interestingly, we observed a rebound in VPA concentration around H36 concomitantly to an enhancement in VPD concentration fall. We hypothesized a possible acceleration in VPD metabolism to VPA although no other medication responsible for potential drug-drug interactions was administered at that time. Post-dialysis rebound in VPA concentration could also be considered but it usually happens much sooner than the 12–14 h after dialysis. By contrast, drug reabsorption from the GI track as gut motility returns when drug concentration falls was ruled out since the rebound was only in VPA while VPD concentration stayed flat.

No guideline exists to monitor valpromide concentrations in pharmacological conditions. In overdose, liver valpromide biotransformation to VPA can be saturated. Consequently, valpromide, a large volume of distribution lipophilic molecule evenly distributed between plasma, liver and brain [5], can accumulate. Thus, the higher distribution of valpromide compared to VPA in central nervous system, which is not a site of valpromide-to-VPA biotransformation, partly explains the more intense neurotoxicity observed. Valpromide, a powerful liver microsomal epoxide hydrolase inhibitor, is able to alter liver detoxification of co-ingested drugs taking this pathway and to result in drug–drug interactions [6].

Combining valpromide and VPA assays may improve diagnosis and prognosis evaluation in the valpromide-poisoned patient. Interestingly, both valpromide and VPA concentrations were determined in a fatal overdose at 194 and 14 mg/L, respectively [7]. In this case as in our patient, combined VPD/VPA assay was useful to avoid erroneous conclusions.

To conclude, valpromide overdose is rare in children and may result in life-threatening poisoning. We recommend measuring both valpromide and VPA concentration in valpromide poisoning due to prolonged neurotoxicity. Further investigations are needed to better understand valpromide kinetics in overdose.

Ethical approval

Data management was in agreement with the French data protection authority and our local ethics committee.

Disclosure statement

The authors report no declaration of interest.

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References

[1] Bialer M. Clinical pharmacology of valpromide. Clin Pharmacokinet. 1991;20(2):114–122.
[2] Payen C, Frantz P, Martin O, et al. Delayed toxicity following acute ingestion of valpromide. Hum Exp Toxicol. 2004;23(3):145–148.
[3] Spiller HA, Krenzelok EP, Klein-Schwartz W, et al. Multicenter case series of valproic acid ingestion: serum concentrations and toxicity. J Toxicol Clin Toxicol. 2000;38(7):755–760.
[4] Delhumau S, Le Roux G, Meyer G, et al. Surdosage en valpromide: comment interpréter le dosage plasmatique de l'acide valproïque? Toxicol Anal Clin. 2018;30(3):172.
[5] Blotnik S, Bergman F, Bialer M. Disposition of valpromide, valproic acid, and valnoctamide in the brain, liver, plasma, and urine of rats. Drug Metab Dispos. 1996;24(5):560–564.
[6] Kerr BM, Rettie AE, Eddy AC, et al. Inhibition of human liver microsomal epoxide hydrolase by valproate and valpromide: *in vitro/in vivo* correlation. Clin Pharmacol Ther. 1989;46(1):82–93.
[7] Bevalot F, Guinet T, Bottinelli C, et al. Limites du dosage de l'acide valproïque dans les intoxications au valpromide. Toxac. 2015;27(2):S35–S6.

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