

Kardiotoksičnost in več-organska odpoved zaradi zastrupitve z valproatom

Cardiotoxicity and multiorgan system failure caused by valproate poisoning: case report and review of the literature

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Izvleček

V prispevku je prikazan primer hude zastrupitve z valproatom, ki je povzročila večorgansko odpoved. Gre za prvo poročilo hude prizadetosti srca, ki se je kazala z atrijsko fibrilacijo, difuzno inverzijo T valov, podaljšanjem QT_c intervala in porastom markerjev nekroze miokarda. Bolnica je popolnoma okrevala po 7 dneh terapije, ki je vsebovala lavažo želodca, aktivno oglje, manitol in hemodializo. Po zastrupitvi ni bilo opaziti patoloških ehokardiografskih sprememb in tudi mesec dni po odpustu z obremenitvenim testiranjem nismo izžvali ishemičnih sprememb ali aritmij.

Abstract

We report the case of severe valproate intoxication presenting as multiorgan failure. This is the first report to describe severe cardiac involvement, in which a 19-year-old woman developed atrial fibrillation, diffuse T wave inversion and QT_c interval prolongation with elevated specific biochemical markers of myocardial damage. After 7 days of treatment, including supportive care, gastric lavage, activated charcoal, mannitol and hemodialysis, the patient recovered completely. After the poisoning there were no pathological echocardiographic changes and one month after discharge exercise stress testing did not provoke ischemia or arrhythmias.

INTRODUCTION

Valproic acid (VPA) or sodium valproate was primarily used as an antiepileptic drug, but recently its indications have expanded to include the treatment of schizoaffective disorder, schizophrenia, and bipolar affective disorder and migraine prophylaxis¹. The expanded use of VPA has resulted in the rise of adverse effects and self-poisonings². From 1992 to 2001, VPA prescription increased 2.5-fold, making VPA the leading anticonvulsant over the older antiepileptics carbamazepine and phenytoin³. There are several case reports of severe toxicity and three retrospective case series, giving the false impression that VPA has significant toxicity and a narrow therapeutic index. On the other hand, an earlier French series and more recent US poison centre studies and Australian studies demonstrated only mild toxicity in the majority of cases^{2,3,4}. It is clear that only large amounts of VPA can cause severe toxicity, such as doses over 400 mg kg⁻¹. We report a case of severe cardiotoxicity after VPA poisoning which, to the authors' knowledge, has not previously been reported in literature.

Case report

A 19-year-old woman was admitted to the ICU because of severe drowsiness, confusion and hemodynamic instability after ingesting 200 tablets of extended-release valproic acid (VPA) (Depakine Chrono 500 mg - Sanofi Synthelabo). On admission, her heart rate was 120 bpm, blood pressure 90/55 mm Hg and respiratory rate 32 breaths per minute. The initial serum VPA level was 5150 µmol/L as measured by a fluorescent polarization immunoassay (Abbott AxSYM, Illinois, USA). A full blood count, serum electrolytes, blood urea nitrogen, serum creatinine and liver function tests were initially normal. Arterial blood gas on admission showed a pH of 7.27, pCO₂ of 4.1 kPa and pO₂ of 6.3 kPa. These findings were consistent with severe hypoxemia and metabolic acidosis associated with high concentration of unmeasured anions. The serum lactate concentration was elevated at 5.6 mEq/L.

The initial treatment included gastric lavage, decontamination with multiple doses of activated charcoal, oxygen and iv fluids. With continuous monitoring of oxygen saturation by pulse oximetry (SpO₂), we adjusted the flow rates and oxygen concentration of her face mask. We used 0,28 to 0,60 inspired fraction of oxygen (F_IO₂). Since the patient was hemodynamically unstable, we administered 3900 to 4300 mL of fluids per day during the first 5 days to increase cardiac output. The lowest mean arterial pressure was 60 mmHg, for a short period of time; most of the time it was above 65 mmHg. Despite symptomatic treatment, the signs of the central nervous system depression progressed to stupor and agitation on day 2, when the diagnosis of cerebral oedema was confirmed with a CT scan. Consequently, on days 2 and 3 the treatment consisted of repeated mannitol infusions.

On day 2 the patient's temperature rose to 38.3 °C and laboratory tests revealed hyperammonemia with an NH₃ of 210 µmol/L and signs of hepatotoxicity with elevations of aminotransferases (AST 4.91 µkat/L, ALT 1.56 µkat/L and γGT 1 µkat/L) and a slightly increased INR (1.42). Pancreatic enzymes were elevated with an amylase of 7.4 µkat/L and lipase of 14.6 µkat/L. We also observed rhabdomyolysis with an elevated CK of 152 µkat/L and myoglobin of 843 µg/L. On days 2 and 3 the patient additionally developed signs of cardiotoxicity with numerous paroxysms of atrial fibrillation with a rapid ventricular rate around 180 bpm and inversion of the T wave in leads V3–V6, II, III and aVF. On day 2 we observed a prolonged QTc interval, with a peak value of 462 ms. The patient also had elevated cardiac enzymes: the peak CK-MB level was 93.7 µg/L and the peak troponin T (TnT) level was 0.7 µg/L. On day 3, mild pancytopenia developed (Hb 99 g/L, platelet count 100x10⁹/L and white blood cell count 3.3 x10⁹/L).

As the signs of severe intoxication did not respond to supportive care, we started hemodialysis on day 2. The serum VPA concentration was 3241 µmol/L at the initiation of hemodialysis. The highest blood urea was 4,8 mmol/L and the highest creatinine was

116 $\mu\text{mol/L}$; both were recorded on day 2 before hemodialysis commenced. The patient was dialysed for 5 hours using a high-flux polyamide hemodialysis membrane (Gambro, 1.7m², Hechingen, Germany). Hemodialysis was difficult to perform because of hemodynamic instability. During hemodialysis we had to continuously infuse 0.9% saline into the patient. After dialysis, the VPA concentration on day 3 was 1205 $\mu\text{mol/L}$ and no further rebound in the serum VPA concentration was observed.

The signs of cardiotoxicity resolved on day 5, at which stage we did not observe any pathologic electrocardiographic or echocardiographic changes. The patient completely recovered during the 7-day treatment in ICU. Exercise stress testing performed one month after discharge did not provoke ischemia or arrhythmias.

DISCUSSION

Severe overdose with VPA most frequently manifests as central nervous system depression^{5,6}, which we also observed in our patient. There is no firm correlation between the dose of VPA and the site or severity of organ dysfunction, although concentrations above 5800 $\mu\text{mol/L}$ are more likely to lead to coma, respiratory depression, metabolic acidosis or hypotension². The case we describe confirms that the clinical signs of intoxication are delayed with extended release formulations; this is because enteric-coated tablets prolong the dissociation process and cause a long absorption phase – the dissociation of divalproex sodium into the valproate ion is necessary before absorption occurs⁷. The delayed clinical picture is also a consequence of toxic metabolites (2-EN-VPA, 4-EN-VPA and propionic acid), which mediate dose-related and idiosyncratic adverse effects, particularly on the central nervous system and liver^{5,6,8,9}.

Beside cerebral edema manifested as stupor and agitation, our patient had other already reported clinical and laboratory findings of multiorgan fail-

ure present, namely liver failure manifesting as hyperammonemia and raised liver enzymes; elevated pancreatic enzymes; acidosis^{5,10}; hypoxemia, which may have been the consequence of a direct toxic effect of VPA on the lungs⁵; pancytopenia, which can be explained by bone marrow toxicity¹¹, although an immunological mechanism has been suggested¹²; rhabdomyolysis with asymptomatic elevation of CK and myoglobin. Undoubtedly saline infusion and mannitol administration increasing urine flow and protect the kidney tubules from myoglobinuric damage. We also observed cardiovascular abnormalities including hypotension, tachycardia, paroxysms of atrial fibrillation with a rapid ventricular rate, repolarization abnormalities and prolongation of QT_c interval. The presence of symmetrical T-wave inversion is often considered to be an indication of transmural myocardial ischemia, and the elevation of both cardiac troponin T (TnT) levels and the MB fraction of CK (CK-MB) in our case indicated that there was myocardial damage. Such abnormalities could only be explained by VPA cardiotoxicity, which makes this case particularly interesting. We propose that the mechanism of cardiotoxicity was impairment of myocardial fuel oxidation^{13,14}. There are reports that VPA inhibits β fatty acid oxidation, which is the primary energy-providing pathway of the myocardium in a normal physiological situation. VPA also suppresses the oxidation of several carbohydrates, including lactate, whose contribution to meeting the energy needs of the heart needs to be increased during shock. Withdrawal of energy-providing substrates causes a decline in contractile function. To the authors' knowledge, there are only a few reports of hypotension and tachycardia after intoxication with VPA, and these signs can be explained by the negative inotropic action of VPA, which has been proven on isolated heart preparations¹⁵. Tachycardia and loss of atrial systole during atrial fibrillation also contribute to adverse hemodynamic changes. We observed a prolonged QT_c interval, which has been previously described and can be explained by inhibition of the potassium current I_{Kr} in ventricular myocytes by VPA¹⁶.

There is a general agreement that the treatment of VPA toxicity includes supportive care with the administration of oxygen, iv fluids, gastric lavage and decontamination with multiple doses of activated charcoal to prevent the prolonged absorption of extended-release VPA formulations ^{2,5}. We used repeated mannitol infusions to treat the cerebral edema, as recommended by previous authors ⁶. On day ², multiorgan failure developed and consciousness was further impaired, so we began hemodialysis. Hemodialysis and hemoperfusion have recently been suggested as successful therapeutic modalities in serious VPA toxicity ^{12,17}. The protein binding is maximal at therapeutic drug concentrations; at toxic concentrations of VPA, high concentrations of free drug are available for removal by hemodialysis, and hemodialysis efficiently removes free drug ¹⁸. After hemodialysis, we observed resolution of the stupor and agitation, milder hypoxemia, less tachycardia

and reduction in the paroxysms of atrial fibrillation. The signs and symptoms of multiorgan failure completely recovered during the seven days of intensive treatment.

CONCLUSION

Multiorgan failure and cardiotoxicity are rare and life-threatening consequences of VPA toxicity but they can be successfully treated with early supportive care and hemodialysis.

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