Sodium valproate poisoning

A case report

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Summary

A case of a severe overdose of sodium valproate (more than 10 times the therapeutic requirement) is discussed. The patient presented with central nervous, respiratory and cardiovascular depression and was treated with supportive therapy and haemoperfusion. However, on available data it would appear that haemoperfusion did not make a significant contribution towards the patient's recovery.

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Case report

A 38-year-old man was admitted to the Respiratory Intensive Care Unit at Tygerberg Hospital after an overdose of sodium valproate (SV). The time lapse between the ingestion of the drug and admission and the amount of drug taken were unknown.

On examination the patient was in coma; the pupils were dilated and reacted poorly to light. There was general hypotonia and no abnormal reflexes. He was hypoventilating (3-4 breaths/min), there was central cyanosis, the left lung was dull on percussion, and rhonchi and wheezing were present. There was a sinus bradycardia (40/min), and the patient was hypotensive (blood pressure 70/40 mmHg). Blood gas measurements confirmed the clinical picture of alveolar hypoventilation (partial arterial pressure of O_2 9,9 kPa; partial pressure of CO_2 9,9 kPa; pH 7,28; base excess –12; inspired O_2 fraction (FiO_2) 0,21). The chest radiograph showed patchy consolidation of the left lung and there were nonspecific ST-T changes on the ECG.

The patient was intubated and ventilated to correct the alveolar hypoventilation. Positive end-expiratory pressure was utilized to minimize the venous shunt and ventilation-perfusion defects (arterio-alveolar oxygen tension difference 7,1 kPa) and to allow for an FiO_2 of less than 0,5. Central venous pressure was 18 cm H_2O and dopamine 5 $\mu g/kg/min$ was given for the first 8 hours to improve myocardial contractility. Theophylline was infused at 4 mg/kg over 30 minutes and continued at 0,7 mg/kg/h. The cardiopulmonary condition improved and, since the pulmonary physician was not sure whether the patient had aspirated solid material, a bronchoscopy was performed to clear

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the left lung; this revealed only mucopurulent material in the bronchi.

The blood level of SV was 1 080 $\mu g/ml$ on admission and haemoperfusion was performed for 8 hours (activated charcoal, 150-200 ml/min). The change in blood levels of SV are shown in Fig. 1. The patient regained consciousness shortly after he had been haemoperfused for the second time for 5 hours 18 hours after admission and he was weaned from the ventilator 35 hours after admission. Follow-up liver and kidney function tests and haematological investigations revealed no abnormalities.
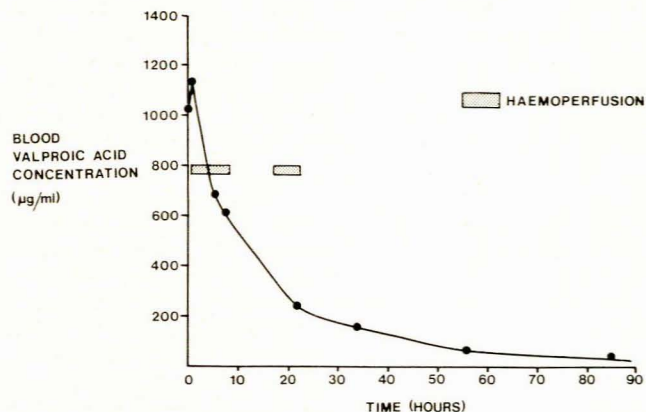

Fig. 1. The decrease in blood SV concentration in relation to time in hours.

Discussion

Self-poisoning is an important complication of epilepsy[1] and the only commonly prescribed anticonvulsant for which the effects of an overdose are well known is phenobarbitone.[2] Specifically, there is insufficient reliable data on the effect of SV in above-normal dosages and from cases reviewed by the Poisons Unit, Guy's Hospital, London,[3] it is reasonable to conclude that plasma concentrations 5 - 6 times the maximum therapeutic concentration (therapeutic blood concentration 50-100 $\mu g/ml$) are unlikely to be accompanied by symptoms other than nausea, vomiting and dizziness. With a massive overdosage where plasma concentrations reach 10 - 20 times the normal therapeutic requirements, central nervous system and respiratory depression can be expected to occur — as in this case.

There is no general consensus about the treatment of SV overdose and forced diuresis, haemodialysis or haemoperfusion have been suggested.[3] It is possible that haemoperfusion may result in a more effective clearance of SV, but at present, except for that of Mortensen et al.,[4] no reports of its application are documented. These authors suggested that haemodialysis, haemoperfusion and glucose infusion contributed towards the successful treatment of a patient whose blood levels of SV were 2 120 $\mu g/ml$. However, other authors[3,5] suggest that supportive therapy alone is sufficient in treating these patients.
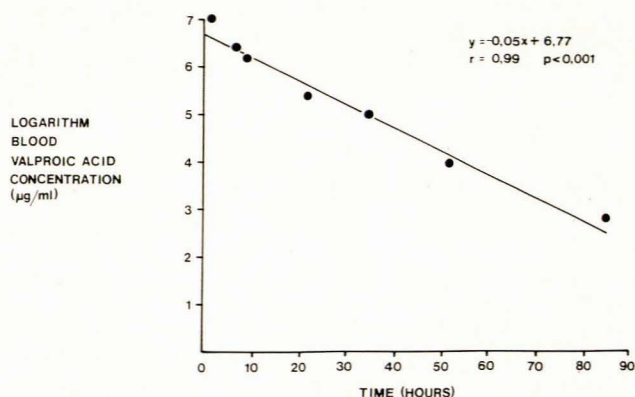
Fig. 2. A semilogarithmic plot of the data from Fig. 1. The straight line obtained confirms the first-order kinetics of SV notwithstanding the two periods of haemoperfusion indicated on Fig. 1.

It would appear that on our patient's admission the SV was still in the distribution phase, since the second value recorded was higher than the first (see Fig. 1). However, more and earlier data points would be required to verify this impression.

In general, Fig. 1 suggests a first-order kinetic process. First-order kinetics are characterized by a differential equation that defines a proportionality constant (k).[6] This constant (/min) relates the rate of change to plasma concentration:

$$dCp/dt = k\ Cp(t)$$

where dCp/dt = change in plasma concentration at time t; $Cp(t)$ = plasma concentration at time t; and k = proportionality constant.

If k is solved for the various segments of the curve in Fig. 1, it yields a constant 0,001/min except for the final part of the curve where the value is equal to 0,0006/min or, by approximation, 0,001/min. This k value implies a 0,1% decay in plasma concentration per minute. Clearly the amount of drug removed from the plasma in the initial phases was greater than that

removed in the final phases, but the *fraction* removed (i.e. normalized to the absolute level) is constant. Plotting the available data on a semilogarithmic scale yields a straight line (Fig. 2). Furthermore, utilizing the basic formula:

$$\log Cp(t) = \log Cp(o) - \frac{kt}{2,303}$$

a slope of 0,05 (hours v. log) was obtained. This is equal to the k of 0,001 (min v. log). A regression analysis performed on the data (h v. log blood concentration) gave $y = 0,05x + 6,77$ and $r = 0,99$. The latter was tested for significance using $t =$

$$r\sqrt{\frac{n-2}{1-r^2}}$$

and the r value was significant at the 0,1% level (degrees of freedom = 5).

In conclusion, we would suggest that haemoperfusion did not alter the first-order kinetics of SV elimination. If haemoperfusion was effective, it would have altered (during the periods of haemoperfusion at least) the elimination curve as demonstrated in Fig. 1 and supportive measures seem to suffice in the treatment of SV overdose. More data points would certainly serve to increase the accuracy of the exponential curve although, notwithstanding this limitation, we would not suggest haemoperfusion as an adjuvant in the treatment of an overdose of SV.

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