Netherlands
The Journal of Medicine

EDITORIAL

Enhanced extracorporeal elimination of valproic acid in overdose

R. Engbersen[1], C. Kramers[2]

Department of [1]General Internal Medicine/Clinical Pharmacology, [2]Department of Pharmacology and Toxicology, University Medical Centre St Radboud, PO Box 9101, 6500 HB Nijmegen, the Netherlands

The treatment of the poisoned patient has been based on three main approaches: use of supportive nonspecific therapy, if available administration of antidotes and removal of the offending drug from the body. Gastric lavage and binding of nonabsorbed drug by activated charcoal are often used in an attempt to eliminate the intoxicating agent from the body. In addition, elimination of already absorbed drug can sometimes be enhanced by the induction of brisk diuresis coupled to manipulation of urine pH (e.g. alkalinise for salicylates) or applying extracorporeal techniques such as haemodialysis, haemofiltration or haemoperfusion.[1] In this issue of the journal Meek *et al*.[7] describe the application of haemodialysis in a patient with severe valproic acid (VPA) overdose and demonstrate an increased elimination after the start of haemodialysis.

It is likely that valproic acid overdose will become an increasing problem due to the extended therapeutic application of this drug in psychiatric patients. Valproic acid is currently not only used in epilepsy treatment but also in the treatment of bipolar disorders and migraine prophylaxis.[2] Most cases of overdose can be managed by supportive care with the use of single- and multiple-dose activated charcoal. Since absorption from the gastrointestinal tract is rapid and almost complete, a single-dose activated charcoal is expected to be sufficient for VPA overdose. However, absorption can be delayed after overdose, especially when enteric-coated formulations are ingested (as with Depakine® chrono in both presented cases) and in these cases multiple-dose activated charcoal is recommended.[3] Prospective studies in the management of the poisoned patient are lacking and available data are mainly from case reports or small retrospective studies using elimination kinetics as effect parameters (e.g. rapid decrease in serum concentrations). However, with a few exceptions (acetaminophen, ethylene glycol and theophylline) serum drug levels do not correlate well with the degree of toxicity or prognosis, probably reflecting the poor correlation with tissue concentrations at the receptor site or the individual differences in drug sensitivity.[1,4] Given the fact that most complications of intoxication occur in the initial hours and the inevitable delay in starting extracorporeal techniques, it is unclear whether these techniques are able to influence outcome at all. Therefore, no guidance based on evidence can be given in when to use extracorporeal elimination in drug overdose. Certain pharmacokinetic parameters of the ingested drug are nonetheless a prerequisite.[1] To be effectively eliminated by haemodialysis a substantial amount of the drug present in the body has to be available for extraction from the plasma compartment. This is favoured by a small volume of distribution (<1 l/kg), a low degree of protein binding and a low molecular weight (<500 daltons) which enables the drug to rapidly cross the dialysis membrane by diffusion. Furthermore, to add a clinically notable effect the drug clearance by dialysis has to be high, relative to the endogenous clearance of the drug. Gwilt and Perrier suggested that the amount of drug removed by haemodialysis can be estimated by dividing the percentage of free drug in plasma by the apparent volume of distribution (litre per kg of body weight).[5] When this fraction is greater than 80, six hours of dialysis should remove a significant amount (20 to 50%) of drug, when less than 20 only an insignificant amount (<10%) will be removed after six hours of dialysis. Except for its high protein binding (which is over 90%) VPA fulfils these criteria.[6] As discussed by Meek *et al*.[7]

the high protein binding of VPA results in free drug concentrations that are too small to use haemodialysis effectively under normal circumstances. Indeed, a negligible effect of haemodialysis on serum VPA concentrations has been demonstrated at therapeutic concentrations.[8] However, at increasing drug concentrations of VPA, protein binding becomes saturated thereby increasing the amount of drug available for diffusion, making dialysis a feasible option.[9] Elimination of highly protein-bound drugs can be enhanced by the use of haemoperfusion, which enables direct contact between blood and an absorbent, mostly charcoal. Special charcoal cartridges have to be available and unlike haemodialysis no correction of electrolytes and acid-base disorders are possible. Early haemoperfusion devices produced significant side effects, such as pyrogenic reactions, haemolysis, thrombocytopenia, and reduced fibrinogen concentrations.[1] These adverse effects have been largely overcome with modern preparatory methods.

Continuous haemofiltration techniques (arteriovenous or venovenous) have been advocated for drugs with a high tissue binding and hence volume of distribution.[10] After clearance of the plasma compartment these drugs tend to give a rebound effect by rapid diffusion from the tissue compartment into plasma. These techniques could therefore be an advantage for overdose of drugs with strong tissue binding (e.g. digoxin and tricyclic antidepressants). Since only limited data are available about the value of these continuous techniques and no comparison with repeated haemodialysis exists, no definitive conclusions can be drawn. The notion that extracting the responsible toxin from the plasma by extracorporeal techniques should improve the prognosis of the patient is intrinsically appealing. However, the lack of solid data on outcome means that the decision to use extracorporeal elimination techniques should be guided by whether removal of a substantial fraction of the drug from the body is possible and be carefully balanced with the risks of applying extracorporeal techniques (e.g. bleeding, infection). In this context the article by Meek *et al.*[7] provides favourable evidence for the use of haemodialysis in VPA intoxication.

REFERENCES

1. Garella S. Extracorporeal techniques in the treatment of exogenous intoxications. Kidney Int 1988;33:735-54.
2. Sztajnkrycer MD. Valproic acid toxicity: overview and management. J Toxicol Clin Toxicol 2002;40:789-801.
3. Ingels M, Beauchamp J, Clark RF, Williams SR. Delayed valproic acid toxicity: a retrospective case series. Ann Emerg Med 2002;39:616-21.
4. Chadwick DW. Concentration-effect relationships of valproic acid. Clin Pharmacokinet 1985;10:155-63.
5. Gwilt PR, Perrier D. Plasma protein binding and distribution characteristics of drugs as indices of their haemodialyzability. Clin Pharmacol Ther 1978;24:154-61.
6. Zaccara G, Messori A, Moroni F. Clinical pharmacokinetics of valproic acid—1988. Clin Pharmacokinet 1988;15:367-89.
7. Meek MF, Broekroelofs J, Yska JP, Egbers PHM, Boerma EC, Voort PHJ van der. Valproic acid intoxication: sense and non-sense of hemodialysis. Neth J Med 2004;62:333-36.
8. Marbury TC, Lee CS, Bruni J, Wilder BJ. Haemodialysis of valproic acid in uremic patients. Dial Transplant 1980;9:961-4.
9. Bowdle AT, Patel IH, Levy RH, Wilensky AJ. Valproic acid dosage and plasma protein binding and clearance. Clin Pharmacol Ther 1980;28:486-92.
10. Golper TA, Bennett WM. Drug removal by continuous arteriovenous haemofiltration. A review of the evidence in poisoned patients. Med Toxicol Adverse Drug Exp 1988;3:341-9.