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REVIEW

Enhanced elimination in acute barbiturate poisoning – A systematic review

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Context. Despite a worldwide decline in barbiturate use, cases of acute poisoning with severe toxicity are still noted, particularly in developing countries. Severe poisonings often require prolonged admission to an intensive care unit, so enhanced elimination might be useful to hasten recovery. Information regarding the efficacy of these techniques for individual barbiturates is not available in standard textbooks. *Objective.* To determine the evidence supporting the effect of enhanced elimination and its role in the management of acute barbiturate poisoning. *Methods.* A systematic review was conducted using broad search criteria in three databases. All potentially relevant articles were obtained, and reference lists were manually reviewed. Ninety-four publications fulfilling inclusion criteria were located. Studies were classified as controlled or uncontrolled, and clinical and pharmacokinetic end points were manually extracted. If not directly stated, standard pharmacokinetic methods were used to calculate the clearance and efficiency of enhanced elimination techniques for each barbiturate and tabulated for direct comparison. *Prospective controlled clinical trials.* Two of the 94 publications were prospective controlled studies (only one stated that allocation was via blinded randomisation), and both assessed the effect of multiple-dose activated charcoal for acute phenobarbital poisoning. These studies demonstrated enhanced elimination with a decrease in elimination of half-life from approximately 80 to 40 h, but only one study reported clinical benefits. *Uncontrolled series and single case reports*. Sufficient data to determine the clearance due to enhanced elimination were available in only 52 of these papers. Barbiturate clearances by enhanced elimination varied markedly among studies. While extracorporeal modalities appeared to increase the direct clearance of many barbiturates, there was insufficient information to confirm a clinical benefit. *Conclusions.* There is limited evidence to support the use of enhanced elimination in the treatment of poisoning with most barbiturates. There is no role for urine alkalinisation, while multiple-dose activated charcoal may be useful for most phenobarbital and possibly primidone poisonings. Extracorporeal techniques appear to enhance elimination, but the clinical benefits, relative to the potential complications and cost, are poorly defined. Extracorporeal techniques such as haemodialysis and haemoperfusion can be considered for patients with life-threatening barbiturate toxicity such as refractory hypotension.

Keywords Pentobarbital; Phenobarbital; Barbiturate; Pharmacokinetics; Dialysis

Introduction

Barbiturates were widely prescribed and frequently used for intentional self-poisoning prior to development of the less toxic benzodiazepines.[1–3] Thousands of patients died during the 1950s and 1960s from barbiturate poisoning.[4,5] Since benzodiazepines have become the hypnosedative of choice, barbiturate poisoning (especially with the short-acting hypnosedative compounds) is much less common. Today, although phenobarbital appears to be the most common barbiturate associated with self-poisoning, cases of severe poisoning and death from other barbiturates continue to be reported worldwide.[6–12] This is particularly the case in developing countries where barbiturate anticonvulsants are widely used because they are both cheap and effective.[13,14] Despite a lower incidence of severe barbiturate poisoning in the United States, they are still the 15th most common medication class associated with fatal poisoning.[12]

Toxicity varies within the class largely in terms of the onset and duration of action. For example, short-acting barbiturates induce a very rapid onset of coma, but if no complications develop, patients will recover fairly quickly, whereas patients with significant poisoning by long-acting agents such as phenobarbital will require ventilatory support in an intensive care unit for many days.[15]

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With the exception of centres who use high-dose barbiturates for neuroprotection or status epilepticus,[16] the collective experience (and comfort) of clinicians for managing patients with severe barbiturate toxicity is fading. The importance of supportive care in the management of poisoned patients is undisputed. Analeptic stimulants including caffeine, amfetamines and strychnine are not beneficial and possibly harmful.[4,15,17,18] Since there is no specific antidote, treatments that enhance the elimination of the drug may be considered by clinicians treating a patient with severe poisoning. The aim of enhanced elimination is to decrease the duration of coma and ventilatory support in intensive care, the severity of hypotension, and mortality.[15,19,20] Enhanced elimination techniques have probably been administered for poisoning due to barbiturates more than any other class of drugs.

The potential usefulness of enhanced elimination is largely a function of the relative increase in clearance [(endogenous + enhanced clearance)/endogenous clearance]. Therefore, this is influenced not only by the rate of enhanced clearance but also by the endogenous clearance that varies greatly in this drug class. Except for the long-acting phenobarbital, there is minimal (if any) specific information on management of poisonings with barbiturates in most toxicology references. This may cause confusion regarding the optimum management of short-acting barbiturate poisoning and the potential for over-treatment and associated adverse effects.

To determine the role of enhanced elimination in the management of acute poisoning of currently available barbiturates, a systematic review was conducted to describe the likely change in clearance from these techniques and the evidence for clinical benefits. This was prompted by a case of severe pentobarbital poisoning in which treatments for enhanced elimination were used in an attempt to facilitate recovery (Appendix). These treatments were administered due to the difficulty in finding specific information on the management of acute pentobarbital poisoning in a timely manner. In contrast, information regarding the management of phenobarbital poisoning was available, so the same recommendations were applied in this case.

Methods

A systematic database search was conducted to locate all clinical trials assessing the efficacy of enhanced elimination techniques in patients with acute barbiturate self-poisoning. We searched in Medline and Embase (www.embase.com; last accessed 19 September 2010) using the following exploded terms: [(barbiturates OR barbit* OR pentobarbit* OR secobarbital OR quinalbarbitone OR amobarbital OR amylobarbitone OR butabarbital OR secbutobarbitone OR primidone OR phenobarb*) AND (poison* OR poison OR poisoning OR overdose) AND (elimination OR clearance OR dialysis OR renal-dialysis OR haemodialysis OR hemoperfusion OR haemoperf* OR hemoperf* OR charcoal OR MDAC OR urine OR urinary OR alkalinisation OR alkalinization OR NaHCO3 OR bicarbonates OR hydrogen-ion-concentration)]. We also searched in The Cochrane Central Register of Controlled Trials (http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html; last accessed 7 March 2010) using the terms [barbit* AND (renal OR elimination OR clearance)]. Studies in patients older than 16 years with acute poisoning published in English with clinical or pharmacokinetic end points were obtained. Excluded studies were those prior to 1960 (to allow for sufficiently developed dialysis technology) and those evaluating the effect of peritoneal dialysis or non-charcoal haemoperfusion. Reference lists were hand searched to locate additional studies. Where a study was non-controlled, changes in clinical outcomes were not considered.

A total of 4993 publications were identified in the searches; of which, 95 publications that fulfilled the inclusion criteria were identified.

Given the variable absorption and disposition kinetics in overdose,[21,22] only values of direct clearance were extracted. The exception to this was prospective controlled trials using multiple doses of activated charcoal because direct clearance cannot be calculated with this intervention. If direct clearance was not stated in the publication, then it was calculated using standard pharmacokinetic equations. In the case of extracorporeal techniques, the extraction ratio was calculated as follows:

$$\text{Extraction ratio} = [(\text{inlet concentration}) - (\text{outlet concentration})]/(\text{inlet concentration})$$

Direct clearance with extracorporeal techniques was determined by multiplying the extraction ratio by plasma flow through the system (haematocrit was assumed to be 0.45 if this was not stated). Direct clearance could also be calculated for extracorporeal techniques and enhanced urinary elimination as follows:

$$\text{Clearance} = \text{amount removed (milligram/hour)}/\text{plasma pre-treatment concentration (milligram/litre)},$$

except in the case in which the amount removed was reported after a prolonged treatment, the mean of the pre- and post-concentrations was used in place of the pre-treatment plasma concentration. If direct clearance was calculated a number of times in the same individual, then the mean value was included in the analysis.

Enhanced elimination was considered potentially useful if the endogenous plasma clearance of barbiturates was increased by 30% or more,[23] compared with reported estimates of baseline endogenous clearance for that barbiturate.[23–29]

We did not determine the percentage of ingested dose removed in this systematic review. While this is a practical end point, particularly for drugs with a larger volume of distribution,[21] it was not assessed due to uncertainty

regarding the accuracy of the ingested dose (a large range of possible doses are commonly reported) and bioavailability in overdose.[22]

Case study of acute pentobarbital poisoning

By way of example, a method for quantifying pentobarbital clearance for a patient with severe toxicity is demonstrated in the Appendix. Serum, urine and dialysate effluent specimens were analysed using gas chromatography with mass spectrometry by Central Sydney Laboratory Service, Royal Prince Alfred Hospital, Australia.

Prospective controlled clinical trials

Two prospective controlled clinical trials in patients with acute barbiturate toxicity were identified.[30,31] They investigated the effect of multiple-dose activated charcoal and/or urine alkalinisation (UA) on phenobarbital poisonings. Control subjects were randomly assigned in one study[31] and with an unstated method of allocation in the other study.[30] In both studies, there was a similar decrease in the mean apparent plasma half-life, from ~80–90 h in patients not receiving multiple-dose activated charcoal to 36–38 h in those who did receive multiple-dose activated charcoal. However, there were important differences between these studies.

In 1984, Pond et al.[31] reported the results of a blinded randomised controlled trial in 10 patients. Five patients received multiple-dose activated charcoal (17 g every 6 h) and five single-dose activated charcoal. No improvement in clinical outcomes was reported, which may have been contributed to by co-consumption of alcohol and phenytoin in some patients.

In 2001, Ebid and Abdul-Rahman[30] reported the results of a controlled trial in 30 patients; the method of allocation was unstated. Ten patients received multiple-dose activated charcoal (50 g every 4 h), 10 received UA, and 10 received both multiple-dose activated charcoal and UA. An improvement in clinical outcomes such as time to extubation and duration of ventilation was reported in the first group relative to both the other groups (including combined treatment). However, the time to extubation was reported to be shorter than the duration of mechanical ventilation that was not adequately explained in the publication. Although the baseline characteristics of patients in this study were similar, conclusions about the effectiveness of enhanced elimination from this study are limited by the high risk of biases introduced in selection of the control group and the lack of any mechanistic explanation that could support these clinical findings.

Clearance by enhanced elimination in uncontrolled series and single case reports

Of the 94 publications that fulfilled inclusion criteria, sufficient data to determine the clearance due to enhanced elimination were available in only 52 (55%) of these. Extracorporeal treatments included haemoperfusion, haemodialysis, haemofiltration and haemodialfiltration. For the purposes of this review, the last three modalities are collectively termed haemodialysis, although it is acknowledged that there are important differences between these techniques. Barbiturate clearances by enhanced elimination varied markedly between studies as shown in Table 1 and Fig. 1. In the case of phenobarbital for which the most data are available, the range of clearance values from each study reported over 50 years are shown in Fig. 2. Although some authors suggested clinical improvements (such as resolution of coma, improved ventilation or facilitated discharge from hospital) with extracorporeal treatments compared to previous cases, we considered this information to be inadequate to confirm this observation. Only 22 studies (23%) stated whether at least one of the reported patients had taken barbiturates prior to the overdose, so that the potential influence of induced metabolism on clinical end points appeared, in general, inadequately considered.

Guidelines for the use of extracorporeal elimination

There is limited information to guide the use of enhanced elimination techniques in patients with acute barbiturate poisoning. Multiple-dose activated charcoal may be useful for acute poisoning with phenobarbital and possibly primidone (which is largely metabolised to phenobarbital) to hasten recovery, while UA appears to be ineffective in all types of barbiturate poisoning. These recommendations regarding UA and multiple-dose activated charcoal are consistent with those of joint consensus statements by the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists.[87,88] These groups have not developed position statements regarding extracorporeal elimination.

In the absence of quality data from randomised controlled trials, guidelines for the use of extracorporeal elimination must be empirically derived. The clinical manifestations, natural history of acute barbiturate poisoning and available pharmacokinetic data should all be considered; these are discussed later. However, taken together, it appears that extracorporeal enhanced elimination is of limited efficacy for most barbiturates. Potentially it may be considered in patients who develop life-threatening poisoning, which will be discussed later (Table 2).

Clinical manifestations and natural history of acute barbiturate poisoning

Barbiturate overdose manifests as sedation, while severe poisoning causes coma, areflexia, apnoea, hypotension and/or hypothermia.[1–4,32,33,89–91] Patients poisoned with short-acting barbiturates generally regain consciousness within 24–48 h[4,17] although not consistently.[91] Morbidity appears to be higher in elderly patients and those with prior cardiac, respiratory or renal disease.[15]

The overall in-hospital mortality from barbiturate poisoning is fairly low (generally <0.5–2%) with supportive

Table 1. Barbiturate physicochemistry, pharmacokinetics and efficacy of enhanced elimination techniques.*

Barbiturate	Duration of action (h)	Elimination half-life (h)	pK_a	MW	Volume of distribution (L/kg)	Major route of clearance	Endogenous clearance (mL/min)†	PB (%)	HD clearance (mL/min)	HP clearance (mL/min)	Urinary enhanced clearance (mL/min)‡	Increase in clearance from HP and HD
Short acting												
Pentobarbital[1,24–27,32–43]	>3–4	15–48	7.9	226	0.5–1	Hepatic (1–6% renal)	20–37	35–70	8–85	49–115	<15	HD: 21–425%; HP: 132–575%
Secobarbital (quinalbarbitone)[15,24,34,37,38,40–53]	>3–4	15–40	7.9	238	1.4–1.9	Hepatic (3–6% renal)	5–53	45–70	17–65	36–163	<15	HD: 32–1300%; HP: 68–3260%
Intermediate acting												
Amobarbital[1,2,24,37,38,43,46–50,54,55]	>4–6	8–42	7.7	226		Hepatic (10–12% renal)	37		17–95	32–145	<8	HD: 46–257%; HP: 86–392%
Butobarbital (secbutabarbital)[1,2,24,36,37,40,46–48,50,53–56]	>4–6	34–42	7.8	212		Hepatic (<12% renal)	18	26	93–99	17–162	<12	HD: 517–550%; HP: 94–900%
Long acting												
Barbital[40,44,45,53,57–63]	6–12	5–88	7.7	184	0.4–0.6	Hepatic (30–35% renal)	3–7	5–25	43	80–210	<15	HD: 614–1433%; HP: 1142–7000%
Primidone (metabolised in part to phenobarbital)[40,64–66]	6–12	3–22	13	218	0.5–1	Hepatic (15% renal)	40	0–95	Y	98		HP: 245%
Phenobarbital[1,2,19,34,36–38,40–43,45–48,50,53–57,61,62,64–82]	>6–12	80–120	7.2	232	0.25–1.2	Hepatic (25–30% renal)	4–9	20–60	23–174, Y	26–290	<17	HD: 255–4350%; HP: 289–7250%

pK_a, dissociation constant, for each increase in pH of one unit from the pK_a, the proportion of drug ionised increases by one order of magnitude; MW, relative molecular mass; PB, protein binding; HD, haemodialysis, haemofiltration or haemodialfiltration; HP, charcoal haemoperfusion.[38,75,76,83] Values are for charcoal HP because the resin cartridge is no longer marketed[23]; Y, clearance appears to be significant, given that dose adjustments are required in patients receiving regular therapy and dialysis.

*The barbiturates included in this table are those noted to be important causes of death from intentional self-poisoning.[6,84] Multiple-dose activated charcoal (MDAC) is not shown because studies in overdose patients are limited to phenobarbital.

†Based primarily on studies in volunteers administered therapeutic doses. The clearance may be expected to increase in patients who consume these drugs regularly due to hepatic enzyme autoinduction.[24,85] These values are higher than those determined in an older study in patients with acute poisoning; however, the assay in that study was unable to differentiate metabolites from the parent compound.[86]

‡From urine alkalinisation with or without diuresis. In general, there was limited information on the specificity of the analytical methods used in these studies, and because of significant interference by metabolites, these values are likely to overstate the true urine clearance.

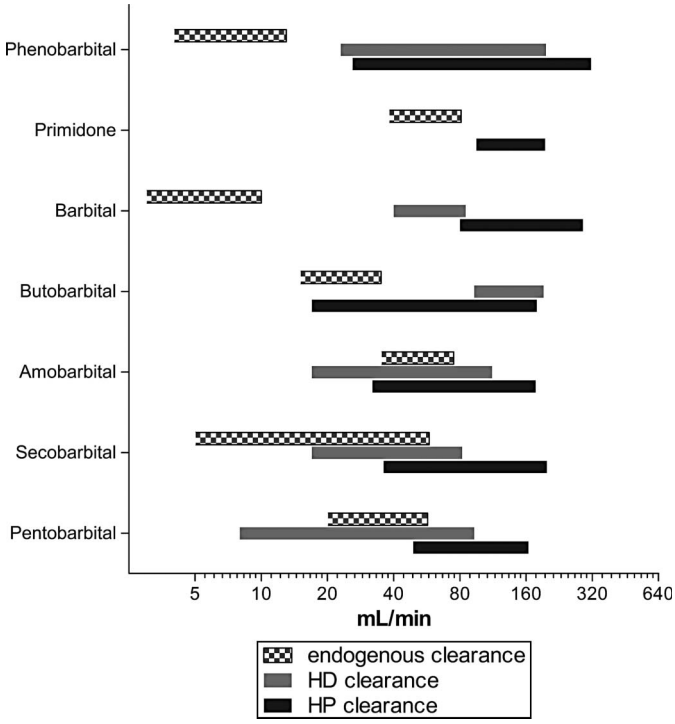

Fig. 1. Comparison of endogenous clearance to the range of clearances reported from haemodialysis or haemoperfusion for specific barbiturates.

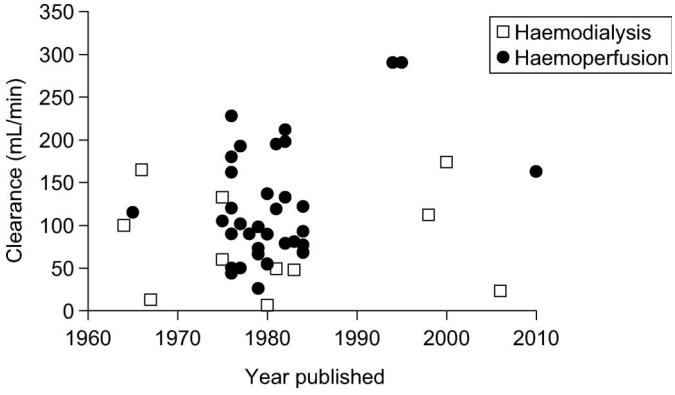

Fig. 2. Variability in reported phenobarbital clearance by extracorporeal treatments over 50 years.

care,[2,17–19,92] but this may increase in patients with severe poisoning,[2,3,91] despite adequate supportive care.[34,91] This may relate to hypoxic damage prior to medical care or organ failure (particularly renal) from persistent hypotension.[4,15,35,36,57,92,93] Hypotension may be secondary to reduced vascular resistance or direct myocardial depression,[35,94] and this in turn may decrease intrinsic clearance and prolong toxicity.[35,95] Death and morbidity may also occur from complications associated with prolonged admission, or iatrogenic complications from forced diuresis, gastric lavage or central venous access (Table 3).[17,36,57,92,96–98] Given the potential for complications, careful consideration should be given prior to initiating enhanced elimination.

Pharmacokinetic considerations of enhanced elimination for acute barbiturate poisoning

Barbiturates are usually categorised by their duration of action (ultrashort, short, intermediate or long acting), a system based on the duration of anaesthesia in rabbits or rats.[24] This has only a partial correlation with half-life, with tissue binding and distribution to peripheral compartments accounting for some of the differences. The relevance of this classification in the prognosis or management of human poisonings has not been well defined.

Given the lack of advice for specific agents, many may treat all barbiturate poisonings in the same manner as phenobarbital (as occurred in the case described in the Appendix), particularly if information to the contrary is not readily available. This is clearly inappropriate. The physicochemical and pharmacokinetic properties of each barbiturate determine the efficacy of enhanced elimination techniques (Tables 1 and 4).[23] It can be easily visualised, as shown in Table 1 and Figs. 1 and 2, that while endogenous clearance greatly varies between drugs, the reported clearances with haemodialysis and haemoperfusion overlap substantially and are similar for all barbiturates. While haemoperfusion appears to be marginally more efficient, clearance decreases when the duration of the treatment exceeds 2–3 h.[37] Substantial variability between case reports for each barbiturate's enhanced clearance is noted in Table 1 and Figs. 1 and 2, which may reflect differences in the application of these techniques, including blood and dialysate flow rates, turbulence of flows, type of membrane, blood pressure and duration of treatment. Techniques that are expected to be most effective for enhanced elimination of barbiturates are those administered to normotensive patients with a maximum blood flow and rate of effluent production. However, as barbiturate clearance with haemodialysis techniques can be maintained for much longer periods and approach those of haemoperfusion, both treatment recommendations and further research should focus on optimised haemodialysis.

Enhanced elimination has been stated to be potentially useful if the technique increases endogenous clearance by 30% or more.[23] Furthermore, the extent to which the increase in clearance is likely to be useful depends on the half-life and the rate of endogenous clearance. For example, a 30% increase in clearance of a drug with a longer half-life (e.g. 120 h) may have clinical benefits, whereas for a drug with a shorter half-life (e.g. 24 h) is unlikely to be clinically important. Compared to other barbiturates, the long-acting agents including barbital, phenobarbital and primidone have longer plasma half-lives and lower endogenous clearance. Therefore, haemodialysis/haemoperfusion will exert a greater increase in clearance and will be more likely to have clinical benefit.

There are limitations to the method that we have used in this review to quantify the effect of a treatment. Evaluation of the effect of an enhanced elimination treatment on the basis of the percentage increase in total clearance requires consideration of

Table 2. Empirical recommendations for the use of enhanced elimination techniques in patients with barbiturate exposure on the basis of the severity of poisoning. There are no adequate controlled trials supporting these recommendations.

Severity of poisoning	Potential role for enhanced elimination
Mild–moderate (sedation, haemodynamics and respiration not requiring supportive measures)	• No enhanced elimination
Major (coma, supported respiration and/or haemodynamics)	• Phenobarbital or primidone – multiple-dose activated charcoal • All barbiturates – consider charcoal haemoperfusion or haemodialysis in patients who are elderly or have advanced chronic respiratory disease
Life-threatening despite intensive supportive care, i.e. persistent hypotension despite inotropes with end-organ dysfunction such as oliguria. There are limited data to support these recommendations. However, since death appears likely in these patients if the barbiturate load is not reduced, the most highly efficient enhanced elimination techniques should be considered.	• Charcoal haemoperfusion if available, particularly if blood concentrations are rising. • If haemoperfusion is unavailable or contraindicated, consider haemodialysis. While there is limited information to support the use of haemoperfusion or haemodialysis in poisoning with short-acting barbiturates, some drug may be cleared from the central compartment, decreasing the concentration in contact with the heart, improving blood pressure.

Table 3. Potential adverse effects of methods to increase elimination.[22]*

Urine alkalinisation	Multiple-dose activated charcoal	Haemodialysis	Haemoperfusion	Haemo(dial)filtration
Electrolyte abnormalities; hypercarbia; vasoconstriction	Transient constipation or occasional bowel obstruction; vomiting; aspiration	Procedural complications†	Procedural complications†; thrombocytopenia; leukopenia; hypocalcaemia‡	Procedural complications†

*Forced diuresis is no longer employed because of low efficacy and potential for complications and is therefore not discussed here.
†Complications from damage to vessels from attempted cannulation and hypotension, blood loss, haematomas, air embolism and metabolic disequilibria such as electrolyte changes may be noted in these techniques.[23]
‡Decreased with coated charcoal cartridges,[34,36] but clearance is influenced by the type of coating used.[44] The platelet count usually decreases 30–50% after each 4–8 h haemoperfusion treatment.[23]

Table 4. Factors that determine the total amount of drug removed by enhanced elimination.[22]*

Urine alkalinisation	Multiple-dose activated charcoal	Haemodialysis†	Haemoperfusion†	Haemo(dial)filtration†
Significant renal excretion; weakly acidic (p*K*a 3.5–7.4); small V_d	Long half-life; small V_d; enterohepatic circulation; delayed absorption; poorly bound to plasma proteins	MW < 500–15,000; water soluble; small V_d (< 1 L/kg); poorly bound to plasma proteins and rapid redistribution; single-compartment kinetics; low endogenous clearance (< 4 mL/min/kg)	Adsorbed by activated charcoal‡; small V_d (< 1 L/kg); poorly bound to plasma proteins; single-compartment kinetics; low endogenous clearance (< 4 mL/min/kg)	MW less than cutoff of the filter fibres, usually < 40,000; small V_d (< 1 L/kg); poorly bound to plasma proteins; single-compartment kinetics; low endogenous clearance (< 4 mL/min/kg)

MW, molecular weight; p*K*a, dissociation constant; V_d, apparent volume of distribution, a V_d < 1 L/kg is generally considered small.
*Forced diuresis is no longer employed because of low efficacy and potential for complications and is therefore not discussed here.
†Clearance is also influenced by flow rate[35] and blood pressure if haemoperfusion/haemodialysis/continuous arteriovenous haemodialysis is used.[4,23]
‡Barbiturates have strong adsorbent affinity to charcoal.[38] The cartridge becomes markedly less efficient after a certain period of use, noted when the concentration difference between inlet and outlet decreases, at which point a replacement cartridge is required.[44,45,60,73,75,83]

cases where endogenous clearance is altered. In this review, we have calculated the potential effect of enhanced elimination compared to endogenous clearance that was mostly calculated from volunteer studies. Dose-dependent pharmacokinetics have been demonstrated for some drugs, but this is poorly described in the case of barbiturates.[22] Endogenous clearance may be reduced in patients with severe hepatic and potentially renal dysfunction, so enhancing elimination in such

patients may be more useful. In contrast, patients who regularly take barbiturates will have induced hepatic metabolism and higher endogenous clearance; hence, they will be less likely to benefit from enhanced elimination techniques. Of the studies identified in this systematic review, only 23% mentioned whether the patient had previously taken the barbiturate, and often there were minimal details regarding duration. Thus, there is much variability in the baseline clearance of patients with acute self-poisoning,[99] so comparison with endogenous clearances determined by volunteer studies, as shown in Table 1, does not provide precise estimates of the extent to which clearance might be increased for an individual patient.

Despite these potential problems, this review demonstrates the benefits of pharmacokinetic end points being reported in cases assessing the effect of enhanced elimination techniques in patients with acute poisoning. Clinical studies into the clinical benefits of such interventions are only worth considering when a significant increase in clearance can be demonstrated. In pharmacokinetic studies, the effect of enhanced elimination on clearance is best determined by directly measuring the proportion of drug eliminated via the technique compared with the (often estimated) exposure.[83] Unfortunately, the exposure is not accurately known in many cases. Although potentially it can be estimated by measuring the total amount of drug or metabolites eliminated in the urine and effluent, this is rarely done.

An alternative method is to measure the percent of drug extracted across the dialyser with a single pass, although this should be performed on a number of occasions during the lifetime of the cartridge to determine how clearance changes with use. Again, efficiency of this technique should ideally be determined by relating clearance back to the estimated exposure. For example, high plasma clearances were noted from these techniques in cases previously, but the proportion removed from the body was less than 10–15% per treatment.[32,35,38] Delayed initiation of therapy, high tissue binding and slow redistribution to the central compartment contribute to this low proportion. Therefore, early high-efficiency extracorporeal treatments during the absorption phase may remove a larger proportion of drug, although often this is not practical.

Clinical considerations of enhanced elimination for acute barbiturate poisoning

To reliably determine whether enhanced elimination techniques improve clinical outcomes, prospective controlled trials are needed. A few trials have been conducted in patients with acute barbiturate poisoning, so the clinical usefulness of any technique is not defined. The two very small controlled studies assessing multiple-dose activated charcoal had conflicting evidence on whether it is effective at improving clinical outcomes from phenobarbital poisoning.[30,31] For these reasons, recommendations for use are mostly empiric.

Mortality is low from barbiturate poisoning with supportive care alone. The main aim of enhanced elimination is to reduce the duration of admission or to minimise complications of prolonged intubation and intensive care admission. To date, such benefits have not been confirmed.[11] It has been proposed that haemodialysis may be utilised in patients with high barbiturate concentrations, for example, when the concentration is greater than 100–200 mg/L for phenobarbital or 40–50 mg/L for short-acting agents.[3,11,19,54,67,100] These concentrations were proposed on the basis of observational studies, but the true risk–benefit of enhanced elimination is not confirmed. Variability in clinical severity of poisoning at similar barbiturate concentrations occurs,[11,91,101] but higher concentrations are often associated with more severe poisoning.[10,92,102,103] Delays in treatment while waiting for the drug concentration to be determined may compromise patient outcomes,[100] so treatments are often commenced on the basis of clinical assessment.

Because of the potential for complications, requirement for experienced staff, expense of extracorporeal enhanced elimination and natural history of toxicity, there are a few clinical reasons to justify the use of enhanced elimination in acute barbiturate poisoning. We believe that patients with acute severe or life-threatening barbiturate poisoning with refractory hypotension and oliguria, despite the current absence of data, should receive a treatment to enhance elimination. Similar to discussions regarding life-threatening tricyclic anti-depressant poisoning, it cannot be excluded that a prompt clinical improvement may occur when haemoperfusion or haemodialysis is administered to hypotensive patients due to clearing of barbiturate from the central circulation.[20] Of course, hypotensive patients are often intolerant of intermittent high-flow dialysis, so continuous modalities may be preferred; unfortunately, this compromises clearance.[68] Patients unlikely to tolerate prolonged ventilation such as the elderly or those with advanced lung disease or patients with impaired capacity for drug clearance such as liver failure may also benefit. Suggestions for the use of enhanced elimination in acute barbiturate poisoning are summarised in Table 2, but it should be noted that supporting clinical data are limited. More data on barbiturate clearance by haemodialysis using high-flux filters are required, as these are now more widely available.

Clinical deterioration following an initial improvement may occur when high-flux haemodialysis or haemoperfusion is ceased, requiring multiple treatments to be performed.[4,20,38,44,45,58,83] This occurs due to drug redistribution from the peripheral compartment into the central circulation, which may be minimised by slowly tapering the initial flow rate or by use of continuous techniques.[20,23,35,38,68]

Barbiturate withdrawal

Another potential complication from enhanced elimination is precipitation of barbiturate withdrawal in patients who habitually use these drugs. This is often noted after 48–72 h

and may be severe, manifesting as seizures and/or delirium.[104–107] In patients susceptible to withdrawal, clinicians must consider when enhanced elimination techniques should be stopped and maintenance of phenobarbital commenced. Pharmacokinetic approaches where the apparent plasma elimination half-life is estimated may identify patients who regularly consume barbiturates, particularly when an adequate drug history is unavailable. For example, patients with phenobarbital poisoning with an apparent elimination half-life less than 50 h are more likely to develop withdrawal symptoms.[104,105]

Conclusions

The priority in the management of barbiturate poisoning is supportive care. Patients who receive prompt medical care soon after the exposure generally have favourable outcomes. While haemoperfusion and haemodialysis may increase the clearance of short-acting barbiturates such as pentobarbital, the clinical significance of this appears limited. This is not clearly stated in many standard toxicology references; instead, discussion is largely centred around phenobarbital, which is the most commonly ingested barbiturate. Multiple-dose activated charcoal may be used for enhanced elimination in severe phenobarbital or primidone poisonings. Haemoperfusion or high-flux haemodialysis can be trialled in elderly patients with severe poisoning or patients remaining hypotensive despite maximal supportive care. Ongoing observations are required to monitor for rebound toxicity and barbiturate withdrawal, particularly for short-acting barbiturates and those who habitually use these drugs.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Appendix. Example of pharmacokinetic methods for calculating the effect of enhanced elimination techniques on drug clearance

Case report

A previously healthy young woman attempted suicide by parenteral administration of 20 mL of a veterinary euthanasia solution containing pentobarbital 325 mg/mL; there was some extravasation. She was retrieved promptly by paramedics and her Glasgow Coma Score dropped to four on arrival at the local hospital 10 min later where she was intubated and ventilated. Her systolic blood pressure remained 70–80 mmHg despite fluid resuscitation, so a noradrenaline infusion was commenced. Sodium bicarbonate (25 mmol/h) was initiated for UA, and active warming was commenced for hypothermia (32.8°C). On day 2, there were absent brainstem and peripheral tendon reflexes, and the electroencephalogram (EEG) was isoelectric. Standard toxicology references did not clarify the efficacy of enhanced elimination for pentobarbital, so UA (pH=7.5–8) continued, and multiple-dose activated charcoal and continuous veno-venous haemodialfiltration (blood flow, 160 mL/min; standard dialysate fluids, 25 mL/min) were commenced. Blood, urine and dialysate effluent samples were obtained for analysis.

Spontaneous respirations and some reflexes returned on day 3, but there were no improvements in other clinical parameters. By day 4, she was drowsy but obeying commands. The noradrenaline infusion was weaned, and dialysis, the bicarbonate infusion and multiple-dose charcoal were all ceased. No complications or neurological sequelae were noted at recovery.

Pentobarbital concentrations and correlation with clinical status are shown in Fig. 3. A blood sample at 60-h

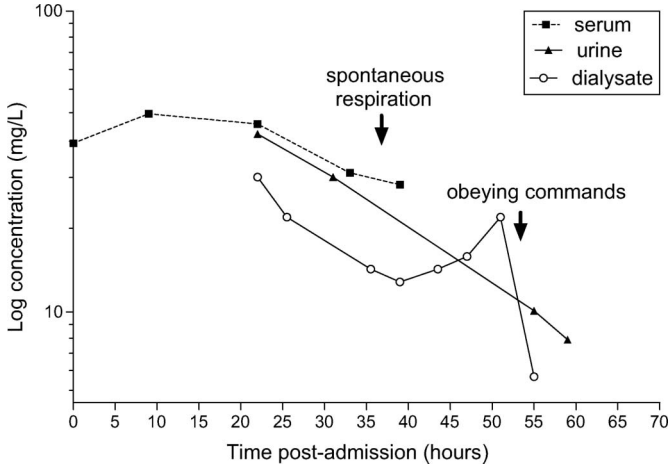

Fig. 3. Pentobarbital concentrations and correlation with clinical status.

post-admission unfortunately was not analysed due to a logistic error. It is not clear why the dialysate pentobarbital concentration increased towards the end of the dialysis period. Contributing factors may have included the increase in blood pressure (to 170/95 mmHg) due to increased alertness and agitation prior to extubation, a change in protein binding, an increase in plasma concentration due to incomplete surgical debridement (additional urine and plasma samples may have clarified this) or an undocumented change in dialysis flow rates.

Renal clearance (CL_R)

$$\mathrm{CL_R} = C_u \times Q_u / C_p = 1.7\,\mathrm{mL/min}\,,$$

where C_u is the concentration in urine, Q_u is the average urine flow rate during the sampling period and C_p is the corresponding plasma concentration.

Given the physicochemical properties of pentobarbital (Tables 1 and 4), it is not predicted that UA would increase urine clearance beyond that of the endogenous rate. This is confirmed in this patient.

Dialysis clearance (CL_D)

$$\mathrm{CL_D} = C_d \times Q_d / C_p = 9.2\,\mathrm{mL/min}\,,$$

where C_d is the concentration in dialysate, Q_d is the average flow rate of dialysate during the sampling period and C_p is the corresponding plasma concentration.

Based on these measured clearances, treatment with haemodialfiltration represents more than a 125% increase over average endogenous clearance, which suggests that it may be useful. However, this was a low rate of clearance from haemodialfiltration compared to others in the literature (Table 1 and Fig. 1). The patient began to regain consciousness within 48 h of admission, similar to other reports in the literature without an extracorporeal treatment. Overall, the benefit of dialysis in this patient appears limited.

Total amount of pentobarbital excreted by enhanced elimination techniques

Renal: $\Sigma(C_u \cdot Q_u)$ for each collection interval=65 mg over 39 h

Dialysis: $\Sigma(C_d \cdot Q_d)$ for each collection interval=740 mg over 33 h

While the exact exposure to pentobarbital is not known in this patient, these amounts are very low and suggest that UA was ineffective and that haemodialysis contributed to total clearance to a limited extent. The effect of multiple-dose charcoal (if any) during this period cannot be quantified in this or other case reports.

Notes on pentobarbital

The lethal dose of pentobarbital is estimated to be 2–10 g.[5,40] For neuroprotection, pentobarbital concentrations are maintained at 25–40 mg/L,[26,85] which is characterised by sedation, mild hypotension and an isoelectric EEG,[25] as noted in our patient. Patients generally regain consciousness from an acute poisoning after 24–48 h[3,35,69] with a plasma pentobarbital concentration of 11–13 mg/L.[32,40] Pentobarbital assays are not widely available, so clinical features are the most important in the assessment of poisoning severity and recovery.