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Extracorporeal Treatment for Barbiturate Poisoning: Recommendations From the EXTRIP Workgroup

*Robert Mactier, MD,[1] Martin Laliberté, MD, MSc,[2] Joelle Mardini, MD,[3] Marc Ghannoum, MD,[3] Valery Lavergne, MD, MSc,[4] Sophie Gosselin, MD,[5] Robert S. Hoffman, MD,[6,7] and Thomas D. Nolin, PharmD, PhD,[8,9] on behalf of the EXTRIP Workgroup**

The EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup conducted a systematic review of barbiturate poisoning using a standardized evidence-based process to provide recommendations on the use of extracorporeal treatment (ECTR) in patients with barbiturate poisoning. The authors reviewed all articles, extracted data, summarized key findings, and proposed structured voting statements following a predetermined format. A 2-round modified Delphi method was used to reach a consensus on voting statements, and the RAND/UCLA Appropriateness Method was used to quantify disagreement. 617 articles met the search inclusion criteria. Data for 538 patients were abstracted and evaluated. Only case reports, case series, and nonrandomized observational studies were identified, yielding a low quality of evidence for all recommendations. Using established criteria, the workgroup deemed that long-acting barbiturates are dialyzable and short-acting barbiturates are moderately dialyzable. Four key recommendations were made. (1) The use of ECTR should be restricted to cases of severe long-acting barbiturate poisoning. (2) The indications for ECTR in this setting are the presence of prolonged coma, respiratory depression necessitating mechanical ventilation, shock, persistent toxicity, or increasing or persistently elevated serum barbiturate concentrations despite treatment with multiple-dose activated charcoal. (3) Intermittent hemodialysis is the preferred mode of ECTR, and multiple-dose activated charcoal treatment should be continued during ECTR. (4) Cessation of ECTR is indicated when clinical improvement is apparent. This report provides detailed descriptions of the rationale for all recommendations. In summary, patients with long-acting barbiturate poisoning should be treated with ECTR provided at least one of the specific criteria in the first recommendation is present.
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Barbiturates frequently are implicated in poisoning. In 2008, they were the 15th most common class of drugs associated with fatal poisoning in the United States,[1] and barbiturate intoxication remains an important cause of morbidity and mortality today.[2] Recognition of the low therapeutic index of barbiturates and the high historical incidence of fatal and nonfatal barbiturate poisoning has led to strict guidelines dictating barbiturate prescription, and these guidelines have contributed to the decreased availability of barbiturates worldwide. The barbiturate most frequently associated with self-poisoning is phenobarbital, although cases of severe poisoning and death from other barbiturates continue to be reported worldwide.[2-21]

The EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup (www.extrip-workgroup.org), comprising international experts representing diverse specialties and professional societies, was assembled to provide recommendations on the use of extracorporeal treatment (ECTR) in poisoning. The rationale, background, objectives, and methods of the Workgroup have been reported previously.[22] We present

From [1]Renal Services, NHS Greater Glasgow & Clyde, Glasgow, Scotland, United Kingdom; [2]Department of Emergency Medicine, McGill University Health Centre, McGill University, Montréal; [3]Department of Nephrology, Verdun Hospital, University of Montreal, Verdun; [4]Department of Medical Biology, Sacre-Coeur Hospital, University of Montreal; [5]Department of Emergency Medicine, Medical Toxicology Service, McGill University Health Centre, McGill University, Montréal, QC, Canada; Division of Medical Toxicology, Departments of [6]Medicine and [7]Emergency Medicine, New York University School of Medicine, New York, NY; and [8]Department of Pharmacy and Therapeutics and [9]Department of Medicine, Renal Electrolyte Division, University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, PA.

**A list of the members of the EXTRIP Workgroup appears in the Acknowledgements.*

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Address correspondence to Thomas D. Nolin, PharmD, PhD, University of Pittsburgh School of Pharmacy, Department of Pharmacy and Therapeutics, 808 Salk Hall, 3501 Terrace St, Pittsburgh, PA 15261. E-mail: nolin@pitt.edu

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recommendations on the use of ECTR in patients with barbiturate poisoning based on a systematic review of relevant literature using a standardized evidence-based process.

PHARMACOKINETICS OF BARBITURATES

All barbiturates are derivatives of barbituric acid and are classified according to their pharmacokinetic properties into long-acting and short-acting agents (consisting of ultrashort-, short-, and intermediate-acting agents).[23] Each barbiturate has a unique structure that relates to its effective duration of action. Short-acting barbiturates are more protein bound and lipid soluble than their long-acting counterparts; have a more rapid onset, higher pKa (logarithmic acid dissociation constant), and shorter duration of action; and are metabolized nearly exclusively in the liver.[16,23-26] Conversely, long-acting barbiturates accumulate less extensively in tissue (ie, their volume of distribution is smaller), are less lipid soluble, and are excreted as active drugs by the kidneys more readily. For example, the long-acting agent phenobarbital is a weak acid and approximately 20%-25% is excreted unchanged in urine, whereas <5% of pentobarbital is excreted unchanged.[16,24] Consequently, long-acting agents are more amenable to enhanced removal using urinary alkalinization; historically, forced alkaline diuresis was used in cases of moderate phenobarbital poisoning. Table 1 summarizes physicochemical and pharmacokinetic data for barbiturates.

Table 1. Physicochemical and Pharmacokinetic Properties of Barbiturates

	Long Acting	Short Acting
Representative barbiturate	Phenobarbital	Pentobarbital
Molecular weight (Da)	232	226
pKa	7.2	7.9
Volume of distribution (L/kg)	0.25-1.2	0.5-1.0
Protein binding (%)	20-60	35-70
Elimination half-life (h)	80-120	15-48
Duration of action (h)	6-12	3-4
Total endogenous clearance (mL/min)	5-12	18-39
Hepatic clearance (mL/min)	4-9	18-37
Renal clearance (mL/min)	1-3	0.2-2
MDAC clearance (mL/min)	84	NA
HD clearance (mL/min)	23-174	8-85
HP clearance (mL/min)	26-290	49-115
PD clearance (mL/min)	4-8	4-8
ET clearance (mL/min)	7	NA
Potentially fatal ingested dose (g)	>5	>3
Potentially fatal serum concentration (mg/L)	80	50

Note: Data from.[16,25,26,105,135]

Abbreviations: ET, exchange transfusion; HD, intermittent hemodialysis; HP, hemoperfusion; MDAC, multiple dose activated charcoal; NA, not available; PD, peritoneal dialysis; pKa, logarithmic acid dissociation constant.

Hepatic metabolism is the main route of endogenous clearance of all barbiturates. They are well-known inducers of the hepatic cytochrome P450 (CYP) enzyme system and thus increase the metabolic clearance of medications that are CYP substrates.[23] Barbiturates undergo CYP-mediated metabolism and exhibit autoinduction, which leads long-term users to develop tolerance. Although tolerance to the sedative-hypnotic effects of barbiturates develops, tolerance to the serum drug concentration associated with lethal toxicity (ie, respiratory failure) does not appear to develop. Thus, long-term users tolerate a higher dose but not a higher serum concentration before being at risk of lethal toxicity and will be at greater risk of drug withdrawal if concentrations are reduced rapidly using ECTR.[23,27] When barbiturates are combined with other central nervous system (CNS) depressants, such as alcohol, opiates, or benzodiazepines, overdose is even more dangerous due to additive depressant effects on the CNS and respiratory system.

OVERVIEW OF BARBITURATE POISONING

In the United States, United Kingdom, and most other developed countries, intermediate-acting barbiturates such as butobarbital, secobarbital, and amobarbital are no longer licensed for use and can be prescribed only to patients who already take these drugs for intractable insomnia. Pentobarbital is used clinically as well as in veterinary practice and thus may be acquired and used for intentional poisoning.[4] Therefore, the current recommendations focus on only barbiturates that are licensed for use at this time and use phenobarbital and pentobarbital as the representative barbiturates for long- and short-acting agents, respectively.

Comprehensive clinical assessment is necessary when considering whether patients have a severe enough overdose to warrant ECTR. In particular, it is essential to evaluate the severity of barbiturate poisoning objectively, based primarily on its toxic effects observed in the CNS, pulmonary, and cardiovascular systems.[28]

- *CNS effects.* Barbiturates mainly act in the CNS, though they may affect other organ systems indirectly. Direct effects include sedation and hypnosis at lower dosages. Symptoms of a moderate overdose typically include sluggishness, lack of coordination, slow speech, faulty judgment, and drowsiness. Shallow respiration and coma occur in severe poisoning.[28]
- *Pulmonary effects.* Barbiturates suppress the medullary respiratory center to induce respiratory depression. Patients with underlying chronic obstructive pulmonary disease are more susceptible to respiratory

depression even at doses that would be considered therapeutic in healthy individuals. Death from barbiturate overdose often is due to aspiration pneumonia caused by respiratory depression.[29,30]

- *Cardiovascular effects.* Cardiovascular depression is possible after medullary vasomotor centers are depressed. Individuals with congestive heart failure are more vulnerable to cardiovascular effects. Cardiac vascular tone and contractility are compromised at higher doses. This may cause hypotension and can decrease the effectiveness of ECTR by reducing cardiac output.

Evaluating the severity of barbiturate overdose objectively requires quantifying the serum barbiturate concentration (particularly phenobarbital). A simultaneous urine drug screen and blood ethanol concentration might confirm the presence of co-ingested drugs, which could influence the clinical assessment of the patient. Serum concentrations confirm the diagnosis of poisoning and help determine whether to institute ECTR, but are not reliable in predicting the duration or severity of toxicity.[28] The therapeutic range for anticonvulsant activity of phenobarbital is 10-25 mg/L. Serum concentrations $>$ 50 mg/L may induce coma and concentrations $>$ 80 mg/L may be fatal.[2]

Optimal supportive care is mandatory in all cases of barbiturate poisoning. In general, interventions to enhance elimination should provide substantially greater elimination than endogenous mechanisms alone to be considered effective and must produce clinical benefit to justify the costs and potential risks of the intervention.[22] The use of multiple-dose activated charcoal (MDAC) may enhance the elimination of barbiturates,[31-33] but only limited improvement in clinical outcome has been reported.[32] Gastric emptying appears to decrease in the setting of barbiturate toxicity,[34] so patients may be at increased risk of impaction and gut perforation with the use of MDAC, as well as being at higher risk of aspiration. MDAC (15-20 g taken orally every 6 hours) should be administered only after the airway is protected and hemodynamic stabilization has been addressed. Urinary alkalinization is no longer recommended as first-line treatment in cases of barbiturate poisoning because it does not increase renal clearance significantly and MDAC is considered superior.[32,35,36]

METHODOLOGY FOR EXTRIP EVALUATION

The EXTRIP evaluation methodology is described in detail elsewhere[22] and was evaluated and validated during the preparation of recommendations for the use of ECTR in severe thallium poisoning.[37] The process is summarized briefly next.

A literature search of the different forms of ECTR used in barbiturate poisoning during 1951-2013 was performed. Articles were obtained initially by the preliminary search database. Thereafter, a specific search, last accessed on January 18, 2014, retrieved other articles from MEDLINE, EMBASE, the Cochrane Library (Review and Central), conference proceedings, meeting abstracts, and Google Scholar. The bibliographies of all articles were manually reviewed. The search strategy was as follows: (barbiturate OR barbit OR phenobarb* OR pentobarbit* OR secobarbital OR quinalbarbitone OR amobarbital OR amylobarbitone OR butabarbital) AND (toxicity OR poison* OR intoxication OR overdose) AND (hemoperfusion OR haemoperfusion OR hemofiltration OR haemofiltration OR hemodialysis OR haemodialysis OR hemodiafiltration OR haemodiafiltration OR dialysis OR plasmapheresis OR plasma exchange OR exchange transfusion OR CRRT OR renal replacement therapy OR extracorporeal therapy).

The group members completed the literature search, reviewed articles, extracted data, summarized findings, and proposed structured voting statements using a predetermined format. All non–English language publications were translated into English for extraction of clinical data. The level of evidence for clinical recommendations (Box 1) and dialyzability were determined using established criteria.[22] The strength of these recommendations was evaluated by a 2-round modified Delphi method for each proposed

Box 1. Strength of Recommendation and Level of Evidence Scaling on Clinical Outcomes

Strength of recommendation (consensus based)

Level 1 = Strong recommendation. (The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.)

Level 2 = Weak recommendation. (The course of action is considered appropriate by the majority of experts but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.)

Level 3 = Neutral position. (The course of action could be considered appropriate in the right context.)

No recommendation = No agreement was reached by the group of experts.

Level of evidence (based on the GRADE system)

Grade A = High level of evidence (the true effect lies close to our estimate of the effect)

Grade B = Moderate level of evidence (the true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different)

Grade C = Low level of evidence (the true effect may be substantially different from our estimate of the effect)

Grade D = Very low level of evidence (our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect)

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

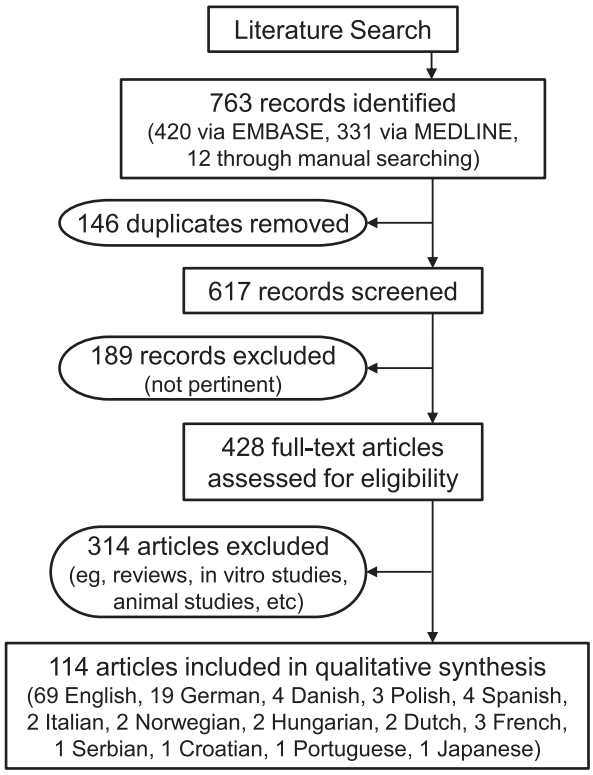

Figure 1. Summary of literature search on use of extracorporeal treatment in barbiturate poisoning (1951-2013).

voting statement, and the RAND/UCLA Appropriateness Method was used to quantify disagreement between voters, as reported previously.[22] Blinded votes were compiled, returned, and discussed during a conference. The same representatives from the list of participating societies (Item S1) performed a second vote after the conference. Then, recommendations were graded as previously described.[22] The results of the voting and grading process led to the statements that are reported here as the EXTRIP recommendations.

RESULTS OF THE LITERATURE SEARCH

Study Selection

A total of 617 articles were identified. After screening for eligibility criteria, 114 articles that comprised 74 case reports[6-14,17-19,21,38-95] (describing ≤2 patients) and 40 case series[3,5,20,96-132] (describing ≥3 patients) were suitable for extraction of clinical data and thus included in the final analysis. We included only clinical studies of ECTR that reported patient survival or mortality outcomes; review articles, in vitro studies, and animal studies were excluded (Table 1).[133] Results of the literature search, including the reason studies were excluded, are presented in Fig 1.

Clinical Outcomes

The clinical data were subdivided into 3 time periods that largely reflect the major eras of barbiturate poisoning and ECTR techniques during the 60-year search period (Table 2). An improvement in level of consciousness and reduction in duration of coma during ECTR was reported in the majority of cases published in 1951-2013 that involved hemodialysis (HD), hemodiafiltration (HDF), hemoperfusion, peritoneal dialysis (PD), exchange transfusion, therapeutic plasma exchange (TPE; plasmapheresis), and combinations of hemoperfusion and HD, although the improvement usually was delayed (>1 day) or absent in most cases of patients receiving PD, exchange transfusion, or TPE. There were 69 deaths in the 538 patients treated with ECTR (Table 2), indicating significant patient mortality in severe barbiturate poisoning even if patients received ECTR. These data also may indicate that ECTR was being reserved for use in patients at significant risk of death due to barbiturate poisoning. During the last 20 years, HD remained the most common mode of ECTR for barbiturate poisoning, and there were still 7 deaths in 67 patients despite the use of more modern ECTR techniques (Table 2).

Table 2. Number of Articles, Patients, and Deaths Related to Barbiturate Poisoning, by ECTR Modality (1951-2013)

	1951-1970	1971-1990	1991-2013	Total
HD articles	33	15	10	58
Patients	165	106	58	329
Deaths	34	16	6	56
HP articles	0	36	4	40
Patients	0	167	4	171
Deaths	0	9	0	9
HD + HP articles	1	3	1	5
Patients	1	4	1	6
Deaths	0	0	0	0
HDF & CVVHDF articles	0	0	4	4
Patients	0	0	4	4
Deaths	0	0	1	1
PD articles[a]	4	7	0	11
PD patients	4	13	0	17
PD + HP/HD patients	2	6	0	8
Deaths	2	1	0	3
TPE & ET articles	0	1	2	3
Patients	0	1	2	3
Deaths	0	0	0	0
Total number of articles[a]	38	62	21	114[a]
Total patients	172	297	69	538
Total deaths	36	26	7	69

Abbreviations: CVVHDF, continuous venovenous hemodiafiltration; ECTR, extracorporeal treatment; ET, exchange transfusion; HD, intermittent hemodialysis; HDF, intermittent hemodiafiltration; HP, hemoperfusion; PD, peritoneal dialysis; TPE, therapeutic plasma exchange.

[a]Seven of 11 articles about PD reported multiple modalities, so were also included in previous HD, HP, or HD + HP categories, resulting in an overall total of 114 articles.

To date, there are no randomized controlled trials of ECTR in humans with barbiturate poisoning. Two randomized controlled trials and a single case series using MDAC in patients with serum phenobarbital concentrations > 100 mg/L documented enhanced elimination of phenobarbital with MDAC use, but did not demonstrate clinical benefit in patient outcomes.[31-33] However, in a study in rats and dogs exposed to a lethal dose of sodium pentobarbital and then randomized to either charcoal hemoperfusion or an empty control circuit, the treated groups showed significantly decreased mortality rates: 58% to 14% in rats and 100% to 15% in dogs.[134] These data suggest that ECTR may be more beneficial than MDAC alone in barbiturate poisoning. Observational data also provide limited evidence of the benefit of ECTR over urinary alkalinization. Botti et al[3] assessed outcomes in an observational study of patients with a mean phenobarbital concentration of 116 mg/L. The mean duration of coma in 16 patients treated with HD was 12.2 hours with no deaths, whereas the mean duration of coma in 9 patients treated with urine alkalinization was 61.3 hours with one death. In the only other observational study of ECTR in barbiturate poisoning, Srinivas et al[5] reported a median phenobarbital concentration of 83.4 mg/L in 9 patients treated with both urine alkalinization and HD with 2 deaths, compared to a median concentration of 75.5 mg/L and no death in 9 patients treated with urine alkalinization alone. This study is difficult to interpret because all participants had ingested "moderate" overdoses (ie, the phenobarbital ingested dose was <3 g) and it was limited by confounding by indication. Nevertheless, this study suggests that there is no benefit from treatment with HD in moderate phenobarbital overdoses.

Dialyzability

On the basis of the literature reviewed, the EXTRIP Workgroup concluded that it considered long-acting barbiturates dialyzable (level of evidence: B) and short-acting barbiturates moderately dialyzable (level of evidence: C).

Rationale

Predefined criteria were used to assess dialyzability.[22] The determination of barbituate dialyzability is supported by a large number of case reports over a period of 60 years during which the modalities and efficacy of ECTR changed considerably. Variability in reported clearance with HD and hemoperfusion most likely reflects variation in achieved blood and dialysate flow rates, choice of dialyzer or hemoperfusion device, and duration of ECTR. Most of the case reports used reasonable pharmacokinetic methods

Table 3. Barbiturate Ingestion, Clinical Presentation, Serum Barbiturate Concentrations, and Outcomes in Individual Case Reports of Barbiturate Poisoning in the Modern ECTR Era (1991-2013)

ECTR Modality	Study	Barbiturate Ingested (dose, if reported)	Main Clinical Features	C_p (mg/L)	Post-ECTR C_p (mg/L)	Died (Y/N)
HD	Morikawa et al[6] (1992)	Pheno	Coma	88	39	N
HD	Soylemezoglu et al[7] (1993)	Pheno	Coma	120	64	N
HD	Quan & Winter[8] (1998)	Pheno	Coma	223	130, 87[a]	N
HD	Palmer[9] (2000)	Pheno	Coma	147	53	N
HD	Jacobs & Brivet[10] (2004)	Pheno	Coma	180	80, 46[a]	N
HD	Thompson & Aks[12] (2007)	Pheno	Coma	152	90	N
HD	Hoyland et al[21] (2013)	Pheno	Coma	115	84, 55[a]	N
HP	Kamijo et al[13] (2002)	Amobarb (15 g)	Hyperthermia	87	38	N
HP	Bouma et al[14] (2004)	Pheno	Coma	112	55, 30[a]	N
HP	Lin & Jeng[94] (1994)	Pheno	Coma	80	3.4	N
HP + MDAC	Roberts et al[19] (2011)	Pheno (6 g)	Coma	95	50	N
HD + HP	Morikawa et al[6] (1992)	Pheno	Respiratory arrest	76	13	N
HDF	van de Plas et al[17] (2006)	Pheno	Coma	120	30	N
CVVHDF	Lal et al[11] (2006)	Pheno (4.8 g)	Coma + AKI	106	41	N
CVVHDF	Bironneau et al[18] (1996)	Pento (20 g)	Coma + AKI	198	65	Y
CVVHDF	Roberts & Buckley[16] (2011)	Pento (6.5 g)	Coma	60	NA	N
ET	Wehner et al[93] (1991)	Pheno (0.3 g)	Coma	117	68	N
ET	Sancak et al[95] (1999)	Pheno (0.2 g)	Coma	112	51	N

Abbreviations: AKI, acute kidney injury; amobarb, amobarbital; C_p, peak serum concentration; CVVHDF, continuous venovenous hemodiafiltration; ECTR, extracorporeal treatment; ET, exchange transfusion; HD, intermittent hemodialysis; HDF, intermittent hemodiafiltration; HP, hemoperfusion; MDAC, multiple-dose activated charcoal; NA, not available; pento, pentobarbital; pheno, phenobarbital.

[a]Values correspond to concentrations after first and second ECTR sessions, respectively.

(ie, serial measurements, appropriate calculations in dialysate, and correct interpretation) but used older ECTR technology. Because there is a trend for reported clearance rates to improve over time, we restricted our assessment of dialyzability to data from the last 20 years to reflect the use of ECTR in the modern era. A summary of this evidence is provided in Table 3.[6-19]

The 3 case series of barbiturate poisonings treated with ECTR in the past 20 years provide no detailed pharmacokinetic or toxicokinetic data.[3,5,20] However, the largest series reported that 24 of the 30 patients were in a grade 4 coma before HD treatment was initiated; in these patients, 40% of the barbiturate was removed during a 4- to 6-hour HD session and 4 patients died despite 1 (n = 25) or 2 (n = 5) sessions of intermittent HD.[20] Although PD was used in several patients, its measured barbiturate removal was always inferior to HD in a comparable time frame; in patients receiving multiple modalities, calculated clearance values in patients undergoing PD were several-fold lower than in those receiving hemoperfusion or HD, and rarely surpassed 10 mL/min.[105,123] Exchange transfusion appeared to accelerate barbiturate elimination only marginally in 2 poisoned infants,[93,95] which is consistent with a pharmacokinetic study showing phenobarbital clearance to be 7 mL/min.[135] TPE has a mild effect on barbiturate clearance.[136,137]

Long-Acting Barbiturates

Evidence from the 1991-2013 literature indicates that long-acting barbiturates are dialyzable (level of evidence: B). In one report, high-flux HD resulted in phenobarbital clearance rates up to 188 mL/min (average, 174 mL/min) during a 4-hour dialysis session.[9] The phenobarbital half-life during HD was 3.2 hours, compared with half-lives of 29 hours prior to dialysis (ratio, 0.11) and 57 hours after dialysis (0.06).[9] A single hemoperfusion session (5 hours; Gambro Adsorba 30C cartridge; blood flow rate, 300 mL/min) successfully removed >30% of an ingested phenobarbital dose, with extracorporeal clearance as high as 163 mL/min.[19] Treatment with continuous arteriovenous hemoperfusion for 8 hours resulted in a phenobarbital clearance of 290 mL/min.[15]

Short-Acting Barbiturates

ECTR appears to be less effective in removing short-acting barbiturates than their long-acting counterparts. Urinary alkalinization does not enhance the clearance of short-acting agents, whereas extracorporeal techniques enhance their clearance only minimally because they have a larger volume of distribution and greater lipid solubility. Endogenous clearance in adults is 20-60 mL/min for most of this group of barbiturates and overlaps with ECTR clearance with HD, HDF, or hemoperfusion.[16] Continuous venovenous HDF (CVVHDF) treatment (AN69 filter; blood flow rate, 100-150 mL/min; dialysate flow rate, 16.6 mL/min; average ultrafiltration rate, 750 mL/h) for 48 hours leads to a median pentobarbital clearance of 7.6 mL/min during ECTR and ~15% removal of the ingested dose.[18] Similarly, extracorporeal pentobarbital clearance of 9.2 mL/min with CVVHDF (blood flow rate, 160 mL/min; dialysate flow rate, 25 mL/min) was reported recently.[16] On the basis of 15% removal, short-acting barbiturates appear to be moderately dialyzable (level of evidence: C).

Box 2. Executive Summary of Recommendations

General Statement Regarding Suitability of ECTR
- ECTR is recommended in severe long-acting barbiturate poisoning. (*1D*)

Indications for ECTR
- If prolonged coma is present or expected (*1D*)
- If shock is present after fluid resuscitation (*1D*)
- If, despite MDAC treatment, toxicity persists (*1D*)
- If, despite MDAC treatment, serum barbiturate concentration rises or remains elevated (*2D*)
- If respiratory depression necessitating mechanical ventilation is present (*2D*)

Choice of ECTR
- Intermittent HD is the preferred mode of ECTR of severe barbiturate poisoning (*1D*)
- HP (*1D*) or CRRT (*3D*) are acceptable alternative modalities in adults if HD is not available

Cessation of ECTR
- Cessation of ECTR is indicated when clinical improvement is apparent (*1D*)

Note: Level 1 recommendations are considered strong and level 2 recommendations as weak; level 3 is considered a neutral position. Grades of evidence are based on quality of evidence, with A, B, C, and D corresponding to high, moderate, low, and very low quality of evidence, respectively. MDAC should be continued during ECTR (*1D*).

Abbreviations: CRRT, continuous renal replacement therapy; ECTR, extracorporeal treatment; HD, hemodialysis; HP, hemoperfusion; MDAC, multiple-dose activated charcoal.

RECOMMENDATIONS

An executive summary of the EXTRIP recommendations is provided in Box 2.

General Statement Regarding Suitability of ECTR

1: ECTR is recommended in severe long-acting barbiturate poisoning. (*1D*)

Rationale

Both HD and hemoperfusion enhance elimination of barbiturates significantly, but the clinical benefits relative to the potential procedure-related complications and cost are not established. This literature review

identified no randomized controlled trials of any form of ECTR in patients with barbiturate poisoning; publications of ECTR with patient outcome data consisted mainly of 74 case reports (n = 87 patients) and 40 case series (n = 431 patients). The lack of control groups, presence of multiple confounders, heterogeneity of ECTR modality over more than 60 years, and publication bias complicate interpretation of the available data and its extrapolation into recommendations for ECTR.

In evaluating the risks and benefits of ECTR in barbiturate poisoning, the EXTRIP Workgroup took the following issues into account: (1) without ECTR, death after severe barbiturate poisoning is commonly reported despite full supportive care[2]; (2) there is no highly effective antidote or alternative therapeutic intervention to ECTR for barbiturate poisoning; (3) ECTR significantly enhances barbiturate removal compared to endogenous (renal and stool) elimination; (4) complications associated with ECTR in acute poisoning are infrequent, but occur; and (5) the cost of ECTR may be balanced by a reduction in duration of coma and treatment time in a critical care setting.

Based on these arguments, the EXTRIP Workgroup reached a consensus that the balance of the risk-benefit ratio in severe barbiturate poisoning supports the use of ECTR in patients who are clinically assessed as being at high risk (as defined in Recommendation 2 below). Therefore, we recommend using ECTR in patients with clinical signs and symptoms of a severe barbiturate overdose to reduce the duration of coma and incidence of complications such as pneumonia, cardiorespiratory compromise, and kidney failure.

The workgroup acknowledges that other interventions for enhancing the removal of barbiturates (eg, MDAC) should be used before and during ECTR. There have been 2 small randomized controlled trials of MDAC in phenobarbital poisoning,[32,33] and the American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists (AACT/EAPCCT) position paper on MDAC recommends that it is a useful adjunctive therapy and should be used in all significant cases of phenobarbital poisoning.[138] The combination of MDAC and ECTR should provide greater removal of the barbiturate body burden than either alone and may improve patient outcomes.

Indications for ECTR

2: ECTR is indicated to treat long-acting barbiturate poisoning when any of the following conditions are met:
- Prolonged coma is present or expected (*1D*)
- Shock is present after fluid resuscitation (*1D*)
- Despite MDAC treatment, toxicity persists (*1D*)
- Despite MDAC treatment, serum barbiturate concentration rises or remains elevated (*2D*)
- Respiratory depression necessitating mechanical ventilation is present (*2D*)

Rationale

The indications for ECTR represent the workgroup's consensus on the criteria that define a patient with severe life-threatening barbiturate overdose. Death from barbiturate poisoning is confined mainly to patients with prolonged coma with depression of autonomic control of respiratory and/or circulatory function and is more likely in patients with preexisting chronic lung disease. Therefore, the main indications to initiate ECTR are clinical signs and symptoms of severe poisoning that carry a poor prognosis and indicate either clinical deterioration or failure to improve with optimal medical therapy of poisoning. In such circumstances, ECTR can be justified despite a lack of evidence of benefit in randomized controlled studies because the prognosis without additional intervention likely is poor. The main reason for using ECTR in long-acting barbiturate poisoning is to reduce the duration and severity of complications.

ECTR will have the most benefit if it is initiated as soon as technically possible once at least one of the indications above is present, ideally within 24 hours of barbiturate exposure. Avoiding prolonged coma in barbiturate poisoning should reduce the risks associated with immobilization and mechanical ventilation, as well as the secondary issue of reducing health care costs associated with prolonged hospitalizations, particularly in the critical care setting.

While the EXTRIP Workgroup accepted the clinical indications of severe barbiturate poisoning outlined as criteria for initiating ECTR, we did not consider ingested dose and serum barbiturate concentrations to be reliable indicators of the need for ECTR. This stems from the fact that estimates of the ingested dose are often inaccurate, and there is uncertainty regarding what constitutes a potentially fatal dose or fatal serum drug concentration. This uncertainty is due at least in part to interpatient variability in the dose-effect relationship in barbiturates, which results from metabolism autoinduction and the acquired tolerance associated with long-term use.[23] Nevertheless, establishing drug concentrations and estimations of ingested dose is useful in confirming the diagnosis and potential severity of poisoning and in supporting the use of ECTR if other indications are present. Furthermore, if a massive ingested dose or high serum concentrations are recorded, early referral to a unit capable of performing ECTR should be considered. Consequently, the EXTRIP Workgroup recommends that a decision to perform ECTR should

not be based on ingested dose only (*1D*) and suggests that a decision to perform ECTR should not be based solely on the serum concentrations of a long-acting barbiturate (*2D*). That being said, it is unlikely that patients would exhibit one of the indications for ECTR unless concentrations were >100 mg/L.[28]

No consensus was reached regarding ECTR use in short-acting barbiturate poisoning, likely because of the shorter duration of action and reduced dialyzability of this class of barbiturates.

Choice of ECTR

3.1: Intermittent HD is the preferred mode of ECTR of severe barbiturate poisoning. (*1D*)
3.2: HP (*1D*) or CRRT (*3D*) are acceptable alternative modalities in adults if HD is not available.

Rationale

ECTRs such as HD and hemoperfusion may be performed in selected patients who are assessed as having life-threatening barbiturate poisoning. It is difficult to rank ECTR modalities in terms of efficacy in barbiturate poisoning, but based on changes in barbiturate elimination half-life during ECTR, HD is equivalent to hemoperfusion, both of which are superior to CVVH, which is in turn superior to PD. The recommendation for prioritizing HD over hemoperfusion is based on the considerations reported by Shannon.[139] HD removes electrolytes and water and replaces bicarbonate if the patient has co-existing kidney failure. Also, HD clearance rates remain relatively stable over time with no need to replace the dialyzer, whereas hemoperfusion columns need to be exchanged regularly to maintain clearance. HD is associated with less risk of thrombocytopenia or hypocalcemia and has lower heparin requirements than hemoperfusion. High-flux HD or HDF are predicted to provide better barbiturate clearances than historical reports. Hemoperfusion may not be available locally or there may be no prior experience with its use. HD is less costly than hemoperfusion, and hemoperfusion cartridges are not available in some countries.

The case for the use of HD instead of continuous renal replacement therapy (CRRT) depends mainly on the fact that continuous techniques provide lower clearance rates due to lower dialysate and/or blood flow rates. The use of CRRT instead of HD or hemoperfusion will depend on whether either of the latter forms is available because many critical care units provide only continuous modalities. HD may not be a feasible option in neonates, and case reports have described both recovery and no recovery after the use of exchange transfusion to treat severe barbiturate poisoning in neonates.[93,95] When HD is used, it is important to check serum biochemistries after therapy to ensure that potential complications such as hypokalemia, hypophosphatemia, or alkalemia have not developed. PD and TPE should not be used to treat barbiturate poisoning because achievable clearances are low (Table 1).[133]

Cessation of ECTR

4: Cessation of ECTR is indicated when clinical improvement is apparent. (*1D*)

Rationale

Cessation of ECTR should be based on clinical efficacy and response to barbiturate removal (ie, resolution of coma), rather than completing a specific duration of ECTR or reaching a specific drug concentration. This approach should ensure that ECTR is not discontinued before clinical benefit is observed and also reduce the risk of lowering drug concentrations too rapidly, which would increase the risk of withdrawal effects in long-term barbiturate users. Drug concentrations should be monitored in order to document the efficacy of drug removal rather than to determine the timing of ECTR cessation. This approach may not be applicable if the patient has taken a mixed overdose of other sedative drugs, especially drugs that are not removed effectively by ECTR, such as tricyclic antidepressants.

CONCLUSIONS

Optimal and full supportive care remains the mainstay of treatment in all cases of barbiturate poisoning. There is limited evidence to support the additional use of ECTR despite its use in severe cases of barbiturate poisoning for more than 60 years. Based on a risk-benefit assessment, modern ECTR techniques should be reserved for use in patients in whom one or more criteria of a life-threatening toxicity are present following an overdose of a long-acting barbiturate. ECTR should be initiated as soon as technically feasible after an indication is present. Intermittent HD is the preferred mode of ECTR of severe barbiturate poisoning, but intermittent hemoperfusion or continuous renal replacement modalities are valid alternatives if intermittent HD is not available.

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SUPPLEMENTARY MATERIAL

Item S1: Societies represented in EXTRIP.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.04.031) is available at www.ajkd.org

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