



Extracorporeal Treatment in Phenytoin Poisoning: Systematic Review and Recommendations from the EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup

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The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup conducted a systematic literature review using a standardized process to develop evidence-based recommendations on the use of extracorporeal treatment (ECTR) in patients with phenytoin poisoning. The authors reviewed all articles, extracted data, summarized 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. 51 articles met the inclusion criteria. Only case reports, case series, and pharmacokinetic studies were identified, yielding a very low quality of evidence. Clinical data from 31 patients and toxicokinetic grading from 46 patients were abstracted. The workgroup concluded that phenytoin is moderately dialyzable (level of evidence = C) despite its high protein binding and made the following recommendations. ECTR would be reasonable in select cases of severe phenytoin poisoning (neutral recommendation, 3D). ECTR is suggested if prolonged coma is present or expected (graded 2D) and it would be reasonable if prolonged incapacitating ataxia is present or expected (graded 3D). If ECTR is used, it should be discontinued when clinical improvement is apparent (graded 1D). The preferred ECTR modality in phenytoin poisoning is intermittent hemodialysis (graded 1D), but hemoperfusion is an acceptable alternative if hemodialysis is not available (graded 1D). In summary, phenytoin appears to be amenable to extracorporeal removal. However, because of the low incidence of irreversible tissue injury or death related to phenytoin poisoning and the relatively limited effect of ECTR on phenytoin removal, the workgroup proposed the use of ECTR only in very select patients with severe phenytoin poisoning.

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INDEX WORDS: Phenytoin; poisoning; toxicity; EXTRIP (Extracorporeal Treatments in Poisoning); recommendations; indications; extracorporeal treatment (ECTR); hemodialysis; hemoperfusion; renal replacement therapy (RRT); pharmacokinetics; toxicokinetics; dialyzability.

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup is composed of international experts representing diverse specialties and professional societies (Item S1, available as online supplementary material, contains a list of the represented societies) to provide recommendations on the use of extracorporeal treatments (ECTRs) in poisoning. The rationale, background, objectives, methodology, and its initial recommendations have been published previously.¹⁻¹³ In this Special Report, we present a

systematic literature review and evidence-based recommendations for the use of ECTR in phenytoin poisoning.

PHARMACOLOGY AND TOXICOKINETICS

Phenytoin is a hydantoin derivative that is used as a first-line agent in the control of tonic-clonic and psychomotor seizures and in preventing and treating neurosurgery-associated seizures.¹⁴⁻¹⁶ The main site of action of phenytoin is the motor cortex, stabilizing

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transmembrane ion flux and reducing post-tetanic potentiation of synapses.¹⁴ Specifically, phenytoin inhibits sodium channels by reducing their capacity for recovery after inactivation.^{14,17} Phenytoin also increases the brain concentration of the cerebral cortex inhibitor gamma-aminobutyric acid (GABA).^{14,15}

Phenytoin has a molecular mass of 252 Da and binds extensively to plasma proteins (binding = 90%), a percentage that remains unchanged after overdose,^{18,19} but decreases slightly to 75% to 80% in patients with kidney failure, hypoalbuminemia, or cytochrome P450 (CYP) 2C9 genetic polymorphism.²⁰ The unbound or “free” form is responsible for its clinical and toxicologic effects.^{21,22} The reported time to peak plasma concentrations in therapeutic dosing is 1.5 to 3 hours for standard formulations and 4 to 12 hours for extended-release formulations. However, oral absorption of phenytoin is slow and variable and can be delayed and unpredictable during overdose. Peak plasma concentrations have been observed up to 96 hours after ingestion in the overdose setting.²³⁻²⁵

Phenytoin has a volume of distribution of 0.6 to 0.8 L/kg and is predominantly metabolized by the CYP enzyme system to inactive metabolites. The drug exhibits Michaelis-Menten kinetics; as such, increased doses may produce a larger than expected increase in plasma concentrations and prolonged elimination.^{14,21,26} Less than 1% of phenytoin is eliminated unchanged in urine, although its metabolites, including 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH), are renally excreted. At therapeutic concentrations, the endogenous clearance of phenytoin is 23 mL/min²⁷ and its apparent elimination half-life is approximately 22 (range, 7-42) hours.^{14,21} In overdose, the apparent elimination half-life increases; in one case, it was reported to be as long as 103 hours.²⁸ This explains why massive phenytoin ingestions may lead to prolonged toxicity and extended hospital stays. The physicochemical characteristics and pharmacokinetic properties of phenytoin are presented in [Box 1](#).

OVERVIEW OF PHENYTOIN POISONING

US Poison Control Centers documented 2,850 phenytoin exposures in 2013, of which 528 had a clinical outcome defined as moderate or worse, including 1

Box 1. Physicochemical and Pharmacokinetic Properties of Phenytoin

Molecular mass: 252 Da
Oral bioavailability: 90%
Protein binding: 90% (70%-80% in hypoalbuminemia)
Volume of distribution: 0.6-0.8 L/kg
Therapeutic range ^a : 10-20 µg/mL (39.6-79.2 µmol/L)
Toxic ingestion: ≥20 mg/kg
Toxic plasma concentrations: ≥20 µg/mL (≥79 µmol/L)

^aTo convert units, 1.0 µg/mL = 3.96 µmol/L.

death.²⁹ Oral overdose is characterized by cerebellar and vestibular effects, including multidirectional nystagmus, dizziness, nausea, vomiting, and ataxia.^{30,31} Severe overdose may result in coma and marked respiratory depression.^{30,31} To our knowledge, there is no previously published literature on the frequency of clinical effects for phenytoin overdoses. Thus, we performed a search in the National Poison Data System from 2000 to 2014 for single-substance phenytoin exposures coded with a serious outcome (major effect or death).³² Of 734 retrieved cases, respiratory arrest was reported in 3.1%; respiratory depression, in 5.7%; and coma, in 16.1%. The other most common signs and symptoms include seizures (44.1%), drowsiness/lethargy (39%), ataxia (25.1%), confusion (23.2%), nystagmus (17.8%), agitation/irritability (15.4%), hypotension (12.5%), and slurred speech (11.4%). Cardiac arrest was present in 3.5% of cases and 29 patients died.

Death or irreversible injury following phenytoin poisoning is infrequent, but still reported.³³⁻³⁵ Intravenous overdose produces similar systemic effects to oral overdose, but cardiotoxicity, including hypotension, bradycardia, arrhythmias, and even asystole, can occur.^{36,37} These side effects are thought to be caused by the diluent (propylene glycol) rather than phenytoin itself.^{38,39}

Fosphenytoin, the intravenous prodrug of phenytoin, is designed with an extra phosphate linkage enhancing its water solubility. It comes as an injection, dissolved in sterile water and tromethamine buffer. In vivo, fosphenytoin is converted into phenytoin by losing the phosphate group. Though there is limited information on the toxicity of fosphenytoin, data from US poison centers from 2000 to 2014 on 208 single-substance fosphenytoin exposures showed the most common symptoms, including seizures (22.6%), drowsiness/lethargy (22.6%), no symptoms (17.3%), hypotension (14.9%), other (13%), ataxia (11.1%), agitation/irritability (9.1%), confusion (8.2%), vomiting (8.2%), and nystagmus (7.7%).³² In the 25 cases classified as serious (major effects or death), seizures remained the most common symptom at 44%, followed by hypotension (32%), bradycardia (24%), and respiratory arrest (20%). Cardiac arrest was noted in 12% of serious cases. Case reports demonstrate that the most serious acute complication of massive intravenous fosphenytoin overdoses is cardiovascular in nature (hypotension, bradyarrhythmias, conduction disturbances, and even asystole). The signs and symptoms of classic phenytoin poisoning (coma, ataxia, drowsiness, and seizures) manifest as the toxicity progresses.⁴⁰⁻⁴⁵

The onset of symptoms usually occurs within minutes of intravenous administration and within 1 to 2 hours of ingestion, although the latter can be delayed or

prolonged for up to a week due to prolonged absorption and saturable metabolism. Factors on admission that correlate with length of stay include disorientation and unarousability, concurrent phenothiazine use, and liver disease,⁴⁶ whereas morbidity is correlated to ataxia.⁴⁷ While therapeutic concentrations of total plasma phenytoin are reported to be 10 to 20 µg/mL, free phenytoin concentrations (1-2 µg/mL therapeutic; >5 µg/mL toxic) are more accurate in predicting clinical effects.⁴⁸ However, there is little correlation between the phenytoin concentration at presentation and the severity of toxicity or length of stay.⁴⁷

Management of patients with phenytoin toxicity is largely supportive, including airway protection and correction of hypotension with intravenous fluids. Advanced cardiac life support guidelines should be followed when indicated. Gastrointestinal decontamination (eg, single-dose activated charcoal) should be given if the patient presents shortly after ingestion and has no contraindications, although there is no evidence that this alters the clinical course.⁴⁹ There are no antidotes available to reverse the effects of phenytoin. Although multiple-dose activated charcoal increases phenytoin elimination,⁵⁰⁻⁵² data are conflicting regarding improvement in clinical outcome in phenytoin overdose. In some studies, multiple-dose activated charcoal failed to demonstrate a beneficial effect on time to resolution of phenytoin toxicity,⁵³⁻⁵⁵ whereas in other studies, it seems to improve the clinical course.⁵⁶ For the moment, multiple-dose activated charcoal is not routinely recommended for the treatment of phenytoin ingestions,⁵⁷ but may be considered in select cases.^{58,59} Current toxicology resources do not routinely recommend ECTR for phenytoin poisoning, claiming unproven benefit on clinical outcomes.⁶⁰⁻⁶²

METHODOLOGY FOR EXTRIP EVALUATION

A predetermined methodology, incorporating recommendations from AGREE (the Appraisal of Guidelines for Research and Evaluation)⁶³ and GRADE (Grading of Recommendation Assessment, Development and Evaluation),⁶⁴ was used and is described in detail elsewhere.² The primary literature search was conducted on July 12, 2012, in MEDLINE, EMBASE, and the Cochrane Library (including the *Cochrane Database of Systematic Reviews* and CENTRAL [Cochrane Central Register of Controlled Trials]).

The search strategy was: [phenytoin OR dilantin] AND [toxicity OR poison* OR intoxication OR overdos*] 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].

A manual search of conference proceedings of the European Association of European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and the North American Congress of Clinical Toxicology (NACCT) annual meetings (2002-2014) was performed; in addition, Google Scholar was searched and the bibliography of each article obtained during the literature search was reviewed for relevant articles.

A subgroup of EXTRIP completed the literature search, reviewed each article, extracted data, and summarized findings. The level of evidence assigned to each clinical recommendation and dialyzability were determined based on established criteria.² The potential benefits of the procedure were weighed against its cost, availability, related complications, and alternative treatments. All this information was submitted to the entire workgroup for consideration, along with structured voting statements based on a predetermined format.

The strength of recommendations was evaluated by a 2-round modified Delphi method for each proposed voting statement, and a RAND/UCLA Appropriateness Method was used to quantify disagreement between voters, as previously described.^{2,65} Anonymous votes with comments were sent to the epidemiologist, who then compiled and returned a summary to each participant. The workgroup met in person to exchange ideas and debate statements. A second vote was later conducted and these results were used in determining the core EXTRIP recommendations. The literature search was updated on November 15, 2014, using the methodology described. New articles and the updated data summary were submitted to every participant, who then updated their votes.

RESULTS OF THE LITERATURE SEARCH

Study Selection

Results of the literature search are presented in Fig 1. A total of 546 articles were identified after removal of duplicates. In the final analysis, 51 studies were included for qualitative analysis: 30 case reports or case series (31 patients),^{18,19,33,35-37,66-89} 17 pharmacokinetic studies (54 patients),⁹⁰⁻¹⁰⁶ 1 animal experiment,¹⁰⁷ and 3 in vitro studies.¹⁰⁸⁻¹¹⁰ No randomized controlled trials or observational studies were identified.

Clinical Outcomes

The evidence of a clinical effect of ECTR in phenytoin poisoning consists exclusively of case reports and case series, which are inherently anecdotal, limited by a lack of controls, and susceptible to publication bias. Therefore, the quality of the evidence for all recommendations was graded as very low.

Clinical data from 30 reports and 31 patients were retrieved; the first reported case of ECTR was

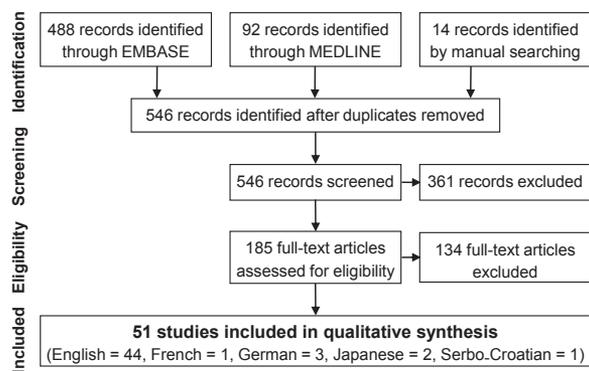


Figure 1. Summary of the literature search on the use of extracorporeal treatment (ECTR) in phenytoin poisoning.

published in 1958 when hemodialysis (HD) was used to treat a boy poisoned with phenytoin.⁶⁶ An aggregate description of clinical outcomes of reported cases is presented in Table 1. Average phenytoin ingestion and peak total concentration were 6.8 g and 69.8 $\mu\text{g/mL}$, respectively. The majority of patients presented with some level of impaired consciousness, and most reported cases were treated using either HD and/or hemoperfusion.

In the studied cohort, most patients experienced some improvement during or shortly after ECTR, which was occasionally dramatic when using an efficient ECTR.^{19,71,77,79,87} Conversely, some patients experienced no apparent benefit from ECTR and developed a protracted course or long-term sequelae.^{33,35,66,80,84} In others, incapacitating ataxia was still present 1 week after exposure.^{70,81} Although the natural history of severely poisoned patients not treated with ECTR suggests survival,^{111,112} irreversible neurologic conditions may incur in those most at risk.²³⁻²⁵ In our cohort, survival was noted in some patients who reportedly ingested ≥ 10 g^{33,67,69,71,84} and who had peak total phenytoin concentrations >90 $\mu\text{g/mL}$.^{33,35,66,70,75,87,88} Complications associated with ECTR included thrombocytopenia after hemoperfusion^{18,88} and peritonitis following peritoneal dialysis that led to death.⁷⁴ The other death appeared unrelated to phenytoin toxicity and followed bowel infarction.⁸⁶

Dialyzability

Phenytoin is a small molecule (252 Da) and has a small volume of distribution of 0.6 to 0.8 L/kg.^{18,19,27} However, because of its extensive binding to plasma proteins (90%), hemoperfusion and therapeutic plasma exchange would theoretically be most likely to efficiently remove phenytoin. Therapeutic plasma exchange can readily remove phenytoin from the vascular compartment, albeit at a slow rate; on average, therapeutic plasma exchange removes 5% to 10% of total body load of phenytoin during a single

Table 1. Aggregate Clinical Outcomes of the 31 Overdose Patients Described in Case Reports or Case Series

Clinical Measure	Aggregated Outcomes
Demographics	
Age, y	26.7 [0.1-77]
Male sex	63%
Phenytoin exposure	
Amount ingested, g	6.8 [1-21.5]
Peak total phenytoin concentration, $\mu\text{g/mL}$	69.8 [15-200.7]
Time from ingestion to presentation, h	18.1 [1-120]
Toxic symptoms	
Altered consciousness	90%
Seizure (≥ 1)	19%
Respiratory failure	32%
Dysarthria/ataxia	26%
Other treatments	
Mechanical ventilation	26%
Multiple dose-activated charcoal	20%
Extracorporeal treatment, no. of patients	
HD	7
Hemoperfusion	7
Continuous renal replacement therapy	0
HD and hemoperfusion in series	3
Therapeutic plasma exchange	3
Exchange transfusion	1
Peritoneal dialysis	6
Liver support therapy (MARS)	1
>1 extracorporeal treatment	3
Outcome	
Sequelae	13%
Death	7%

Note: Values for continuous variables are given as mean [range]. Other values are given as counts or percentages, as indicated.

Abbreviations: HD, intermittent hemodialysis; MARS, molecular adsorbent recirculating system.

2- to 3-hour exchange^{93,95,99,102} and can provide clearances up to 20 mL/min (Table 2).^{78,113} Initial clearances with charcoal hemoperfusion surpass this range but are subsequently limited by saturation of the column, which usually occurs within 2 hours.^{72,114} Although some sorbent adsorption columns were tested in vitro, their application in clinical practice is unknown.¹⁰⁹

Historical reports suggest a lack of an effect of diffusive techniques including intermittent HD because of the significant protein binding of phenytoin.^{36,67,71,76,90,92,94} However, encouraging results were shown with high-efficiency filters,¹¹⁰ especially in patients presenting with conditions known to reduce protein binding (eg, hypoalbuminemia and kidney disease); clearance may be >100 mL/min in uremic patients.¹⁰³ Clearances are inferior but nevertheless considerable in patients who have normal protein binding, although the workgroup

Table 2. Clearance of Various ECTRs From Included Articles

ECTR	No. of Patients	Clearance, mL/min	References
Conventional HD	10	16.7 [6.5-42]	71, 90-92
High-efficiency HD	3	68.1 [44.3-112]	19, 86, 103
Charcoal hemoperfusion	4	28.8 [18-42]	72, 73, 83, 86
HD & hemoperfusion in series	1	58.4	86
Therapeutic plasma exchange	14	18.5 [7.8-43]	75, 78, 80, 81, 93, 95-99, 102
Peritoneal dialysis	6	3.3 [0.2-10.6]	36, 68, 69, 74, 76, 94
Exchange transfusion	1	3.1	76
Continuous RRT	4	6.5 [0.9-13]	100, 104

Note: Clearance values are given as mean [range].

Abbreviations: ECTR, extracorporeal treatment; HD, intermittent hemodialysis; RRT, renal replacement therapy.

acknowledged that additional study is required to confirm this.^{19,86} One report describes a patient who ingested 3.6 g of phenytoin who was treated with HD.¹⁹ A total of 547 mg of phenytoin was extracted in approximately 6 hours. Overall, the aggregate ECTR clearance (Table 2) and toxicokinetic grading of all patients (Table 3) demonstrate the superiority of both hemoperfusion and high-efficiency HD over all other techniques. The advantages of hemoperfusion over HD for phenytoin removal are less clear; in patients who underwent both techniques, hemoperfusion was superior to HD in one report⁸² and inferior in the other.⁸⁶ The addition of a charcoal column in series after a dialysis filter appears to enhance clearance of both hemoperfusion or HD alone, but requires further study.⁸⁶

Supplementation of albumin in the dialysate does not appear to substantially enhance phenytoin removal.^{74,110} The data for other liver support

Table 3. Toxicokinetic Grading Attributed to Individual Patients

	HD						CRRT	TPE	ET	LST
	PD	HP	Conv	High-eff	+ HP (in series)					
Dialyzable	0	2	0	2	1	0	0	0	1	
Moderately dialyzable	0	2	0	2	0	0	7	0	0	
Slightly dialyzable	1	0	5	0	0	2	7	1	0	
Not dialyzable	5	0	4	0	0	2	2	0	0	

Note: Values shown are number of patients graded.

Abbreviations: Conv, conventional; CRRT, continuous renal replacement therapy; ET, exchange transfusion; HD, intermittent hemodialysis; high-eff, high efficiency; HP, hemoperfusion; LST, liver support therapy; PD, peritoneal dialysis; TPE, therapeutic plasma exchange.

therapies, such as molecular adsorbent recirculating systems, are limited: in one case, the apparent phenytoin elimination half-life during molecular adsorbent recirculating systems was 8.4 hours, which is not shorter than what can be achieved with more conventional and less expensive alternatives.³⁷ Further studies are needed to confirm the role of liver support therapies, especially considering their cost. Other ECTRs show limited phenytoin clearance (<10 mL/min),¹¹³ including exchange transfusion,⁷⁶ peritoneal dialysis,^{68,69} and continuous renal replacement therapy,^{100,104} and are therefore of very limited use in phenytoin poisoning.

In summary, the best reported clearances that can be sustained are with HD, possibly in series with a charcoal cartridge. Based on criteria established previously,⁹ the dialyzability of phenytoin is “slightly dialyzable” or “not dialyzable” for less efficient techniques such as exchange transfusion, peritoneal dialysis, continuous renal replacement therapy, and conventional HD techniques using less efficient cuprophane membranes. Phenytoin is “slightly” to “moderately dialyzable” with therapeutic plasma exchange and “moderately dialyzable” to “dialyzable” for hemoperfusion, high-efficiency HD, and liver support therapies, especially if the patient presents with a condition that is associated with decreased protein binding (eg, hypoalbuminemia, malnutrition, and kidney disease). The workgroup preferred a conservative grading and therefore agreed with the following statement: phenytoin is moderately dialyzable (level of evidence = C). Again, it was acknowledged that more studies using contemporary ECTR technology and parameters, as well as performing more complete toxicokinetic measurements, especially quantification of removal in effluent fluid,⁹ are needed to support this observation.

There are no studies that specifically compare ECTR to multiple-dose activated charcoal with respect to enhanced elimination of phenytoin. In 3 case reports, ECTR appeared superior, although the toxicokinetic data are relatively incomplete and cannot be reliably interpreted.^{19,33,84}

RECOMMENDATIONS

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

General statement regarding use of ECTR

1: ECTR would be reasonable in selected cases of severe phenytoin poisoning. (Neutral recommendation; 3D)

Rationale

Phenytoin is a widely used pharmaceutical and toxicity following acute ingestion or in therapeutic

dosing is common.²⁹ Life-threatening symptoms are infrequent and usually resolve completely with appropriate supportive treatment. No antidotes currently exist to reverse the toxic effects of phenytoin and the use of multiple-dose activated charcoal remains controversial.^{50,55} In severe cases, incapacitating and prolonged ataxia may occur, which can progress to stupor and coma. ECTR removes phenytoin from the blood compartment, which results in its prompt elimination from the cerebrospinal fluid, the toxic compartment.⁸³ This may be the reason that several reports describe marked improvement in patients' levels of consciousness during or following ECTR.

Despite the absence of robust evidence, the workgroup considered the following arguments in evaluating the risks and benefits of ECTR in phenytoin poisoning: the risk for prolonged coma with mechanical ventilation is not negligible, complications associated with ECTR are infrequent and usually mild, high-efficiency intermittent ECTR can achieve rapid and substantial removal of phenytoin, and there is anecdotal evidence of clinical improvement following ECTR. Conversely, the mortality and long-term disability associated with phenytoin poisoning is very low; the cost of ECTR is not negligible, especially if the patient requires a transfer to another facility; and there is a theoretical risk for precipitating a seizure if phenytoin concentrations are abruptly lowered with ECTR in a patient with a known seizure disorder.

Given the lack of significant end-organ damage, the primary rationale for ECTR in phenytoin poisoning is to attenuate potential morbidity rather

than decrease related mortality. Several participants postulated that ECTR might decrease mechanical ventilation time, intensive care unit length of stay, and overall length of stay, which will in turn lessen financial cost. However, this effect would have to be weighed against the inherent risks and costs of ECTR mentioned. Unfortunately, there are no cost-benefit studies that confirm or refute this hypothesis. Other participants believed that active supportive measures are sufficient. Taking into account the relative uncertainty concerning the toxicokinetic results detailed, potential clinical benefit, risks, and economic considerations and resource use, the workgroup proposed a neutral recommendation on the use of ECTR in severe phenytoin poisoning, meaning that ECTR would be reasonable in the right context. Twelve participants voted for ECTR, 8 participants supported a neutral position, and 7 voted against ECTR (median vote = 5, disagreement index < 1). Therefore, ECTR should probably only be considered in patients who present following a massive ingestion, who exhibit life-threatening toxicity and/or are expected to have very prolonged symptoms, and in whom ECTR is considered to be safe. This case can be made for ECTR in a profoundly symptomatic patient who by virtue of the zero-order kinetics of phenytoin is likely to have a prolonged hospital stay. The opposite decision can be made for a moderately symptomatic patient needing a transfer to another center to receive ECTR, for which supportive management can be preferred over ECTR. In other words, ECTR can be considered in select cases in which the potential benefit seems to outweigh the risks. Further study is needed to determine the place of ECTR in the management of phenytoin toxicity in the subpopulation with decreased protein binding of phenytoin (eg, kidney failure and hypoalbuminemia).

Box 2. Executive Summary of Recommendations

General statement regarding use of ECTR

1: ECTR would be reasonable in selected cases of severe phenytoin poisoning. (3D)

Indications for ECTR

- 2.1: ECTR is suggested if prolonged coma is present or expected. (2D)
- 2.2: ECTR would be reasonable if prolonged incapacitating ataxia is present or expected. (3D)
- 2.3: We recommend *not* to perform ECTR solely based on suspected dose of phenytoin ingested. (1D)
- 2.4: We recommend *not* to perform ECTR solely based on serum phenytoin concentration. (1D)

Cessation of ECTR

3: ECTR should be discontinued when clinical improvement is apparent. (1D)

Choice of ECTR

- 4.1: Intermittent hemodialysis is the preferred ECTR in phenytoin poisoning. (1D)
- 4.2: Intermittent hemoperfusion is an acceptable alternative if intermittent hemodialysis is not available. (1D)

Abbreviation: ECTR, extracorporeal treatment.

Indications for ECTR

- 2.1: ECTR is suggested if prolonged coma is present or expected. (2D)
- 2.2: ECTR would be reasonable if prolonged incapacitating ataxia is present or expected. (3D)
- 2.3: We recommend *not* to perform ECTR solely based on a suspected dose of phenytoin ingested. (1D)
- 2.4: We recommend *not* to perform ECTR solely based on serum phenytoin concentration. (1D)

Rationale

The workgroup proposed that indications for ECTR initiation in any poisoning should be based on criteria that include exposure route (eg, ingestion and intravenous), measurement of toxin in body fluids, technical examinations, and clinical symptoms and signs.

The workgroup agreed that there are too many areas of uncertainty related to the phenytoin dose ingested to initiate ECTR based on this information alone, certainly for a toxin that usually results in minimal or no long-term damage. The preferred management for patients presenting after acute phenytoin exposure includes supportive measures and proper gastrointestinal decontamination with single-dose activated charcoal and possibly multiple-dose activated charcoal. If it is possible to confirm the ingestion history and the clinician believes that major toxicity might follow, early communication with a toxicologist and nephrologist for consideration of possible ECTR may be warranted. This may be impossible in the event of intravenous overdose given the rapid absorption and distribution (within minutes) and ensuing toxicity from the diluent.

Monitoring serum phenytoin concentrations can confirm an acute exposure and may be available in a time frame short enough to guide clinical decisions. Nevertheless, the workgroup suggested that the decision to initiate ECTR should be more dependent on symptoms than on an arbitrary serum phenytoin concentration threshold. Initiating ECTR before symptoms appear (prophylactic ECTR) can be considered after ingestion of poisons that are associated with irreversible or life-threatening clinical toxicity (eg, methanol and theophylline). However, the workgroup did not endorse this approach for phenytoin.

Signs and symptoms following phenytoin poisoning are primarily neurologic. As stated, patients with phenytoin poisoning generally have a good prognosis and should be managed with supportive therapy. Coma in phenytoin poisoning is not due to a structural central nervous system lesion and it is also not considered life-threatening in and of itself. However, coma following phenytoin poisoning may be prolonged and might necessitate protracted mechanical ventilation and intensive care unit stays, warranting consideration of the risks for complications of prolonged intubation and/or intensive care treatment. For that reason, ECTR was not strongly recommended for coma by the workgroup. ECTR seems indicated only for an expected prolonged coma with the rationale to attenuate coma-induced complications and resource use.

There was less support for ECTR in prolonged incapacitating ataxia. These patients can easily be managed in a non-intensive care setting and therefore would not use excessive resources, thus undermining the economic considerations. More benign symptoms such as nystagmus do not warrant ECTR.

Seizures may occur in phenytoin poisoning and are very difficult to differentiate from seizures in a patient with a seizure disorder. Some workgroup participants advocated the use of alternative anticonvulsants instead of ECTR in these patients, whereas other

participants drew attention to the risk of dialyzing not only phenytoin, but also other anticonvulsants in patients with seizure disorders. No agreement was reached on the use of ECTR in a patient with phenytoin poisoning if multiple seizures occur.

Cessation of ECTR

-
- 3: ECTR should be discontinued when clinical improvement is apparent. (1D)
-

Rationale

Because the recommendations for ECTR initiation are solely based on clinical symptoms, it is logical and reasonable to pursue ECTR until clear clinical improvement is present. Given the relatively modest clearances obtained with high-efficiency ECTRs, prolonged ECTR or a repeat session may be required. Phenytoin concentrations may rebound after ECTR, especially after a high-efficiency procedure.^{19,33,72,75,84} Although this is rarely a concern if caused by redistribution from deeper compartments, it may cause clinical morbidity if rebound is related to ongoing absorption, which has been reported as extensive in some cases.³³ It is therefore proposed to monitor clinical status and phenytoin concentrations serially over 24 hours after ECTR to help assess the need for subsequent sessions.

Choice of ECTR

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- 4.1: Intermittent hemodialysis is the preferred ECTR in phenytoin poisoning. (1D)
 4.2: Intermittent hemoperfusion is an acceptable alternative if intermittent hemodialysis is not available. (1D)
-

Rationale

According to the workgroup, intermittent HD is the preferred modality of ECTR in phenytoin poisoning. This recommendation is supported by the following arguments: clearance of phenytoin has increased dramatically with the use of high-flux synthetic membranes compared with less efficient cuprophane or polyacrylonitrile filters¹⁰³; intermittent HD is the most widely available modality of dialysis worldwide; more physicians and nurses have experience with HD, which leads to fewer risks from delay or uncertainty; the complication rate with HD seems to be less than with hemoperfusion, especially with regard to thrombocytopenia, which was described in some patients who underwent hemoperfusion included in the cohort^{18,73,88}; and HD is generally less expensive than hemoperfusion. The difference in cost is mainly due to the increased cost associated with monitoring and treating complications in hemoperfusion, as well as dialysis filters being less expensive than charcoal

cartridges, which also need to be replaced regularly because their adsorptive capacity becomes saturated.

Because phenytoin is highly protein bound, a more efficient membrane and optimization of both blood flow and effluent (dialysate and/or ultrafiltration) flow will have relatively minor but nevertheless significant effects on phenytoin clearance and are recommended.^{91,100,110,115}

If HD is not available, the workgroup recommended hemoperfusion as an acceptable and useful alternative because there are reliable data for its efficacy. HD and hemoperfusion can also be used simultaneously in series with some clinical benefit.^{86,87} Peritoneal dialysis, albumin dialysis, exchange transfusion, and therapeutic plasma exchange would not offer comparable results to HD or hemoperfusion and are currently not recommended by EXTRIP for phenytoin poisoning. These types of continuous techniques result in much lower clearances and removal rates in comparison to intermittent techniques.

CONCLUSION

This article presents the EXTRIP Workgroup recommendations for extracorporeal treatments in phenytoin poisoning. The great majority of cases can be treated with supportive care that may include single- or multiple-dose activated charcoal. In patients for whom prolonged coma is present or expected, ECTR is suggested to accelerate elimination of phenytoin and theoretically reduce the intensive care unit stay and its associated morbidity. The preferred choice of ECTR is high-efficiency intermittent HD. The workgroup advises to weigh the costs and risks associated with ECTR against the possible benefits in phenytoin toxicity and to individualize decisions to perform ECTR.

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SUPPLEMENTARY MATERIAL

Item S1. Represented professional societies.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2015.08.031>) is available at www.ajkd.org

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