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

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ABSTRACT

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 pre-determined format. A two-round modified Delphi method was used to reach a consensus on voting statements, and the RAND/UCLA Appropriateness Method was employed to quantify disagreement. 51 articles met 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 selected cases of severe phenytoin poisoning, (Neutral recommendation, 3D). ECTR is suggested if prolonged coma is present or expected (2D) and it would be reasonable if prolonged incapacitating ataxia is present or expected (3D). If ECTR is used, it should be discontinued when clinical improvement is apparent (1D). The preferred ECTR modality in phenytoin poisoning is intermittent hemodialysis (1D), but hemoperfusion is an acceptable alternative if hemodialysis is not available (1D). In summary, phenytoin appears to be amenable to extracorporeal removal. However, because of the low incidence of irreversible tissue injury or fatality 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.

INTRODUCTION

The Extracorporeal Treatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Item S1) to provide recommendations on the use of extracorporeal treatments (ECTRs) in poisoning (www.extrip-workgroup.org). The rationale, background, objectives, methodology, and its initial recommendations have been published previously.[1-13] 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 the prevention and treatment of seizures associated with neurosurgery.[14-16] The main site of action of phenytoin is the motor cortex, where it stabilizes transmembrane flux of ions and reduces post-tetanic potentiation of synapses.[14] Specifically, phenytoin inhibits sodium channels by reducing their capacity for recovery after inactivation.[14,17] Phenytoin also increases brain concentrations of gamma-aminobutyric acid (GABA), which has an inhibitory action in the cerebral cortex.[14,15]

Phenytoin has a molecular mass of 252 Da, and it binds extensively to plasma proteins (binding = 90%), a percentage that stays unchanged after overdose[18,19] but decreases slightly to 75-80% 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 toxicological 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 had a volume of distribution of 0.6-0.8 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, phenytoin's endogenous clearance is 23 mL/min[27] and its apparent elimination half-life is approximately 22 hours (range 7 to 42 hours).[14,21] In overdose, the 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 Table 1.

Overview of Phenytoin Poisoning

US Poison Control Centers documented 2,850 phenytoin exposures in 2013, 528 of which had a clinical outcome defined as moderate outcome or worse, including one fatality.[29] Oral overdose is characterized by cerebellar and vestibular effects including multi-directional 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. In response, 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 effects or fatalities).[32] Of the 734 retrieved cases, respiratory arrest

was reported in 3.1%, respiratory depression in 5.7%, coma in 16.1% and ataxia in 25.1%. The other most common signs and symptoms include seizures (44.1%), drowsiness/lethargy (39%), confusion (23.2%), nystagmus (17.8%), agitation/irritable (15.4%), hypotension (12.5%) and slurred speech (11.4%). Cardiac arrest was present in 3.5% of the cases and 29 patients died.

Mortality 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, dysrhythmias 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 (13.0%), ataxia (11.1%), agitated/irritable (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 44.0% followed by hypotension (32.0%), bradycardia (24%), and respiratory arrest (20%). Cardiac arrest was noted in 12.0% of serious cases. Case reports demonstrate that the most serious, acute complication of massive IV fosphenytoin overdoses is cardiovascular in nature (hypotension, bradydysrhythmias, conduction disturbances and even asystole). The signs and symptoms of a classic phenytoin poisoning (coma, ataxia, drowsiness, 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 usage and liver disease,[46] while morbidity is correlated to ataxia.[47] While therapeutic concentrations of total plasma phenytoin are reported to be 10-20 mcg/mL, free phenytoin concentrations (1-2 mcg/mL therapeutic; > 5 mcg/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]

The 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 (e.g., 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 phenytoin's effects. While multiple-dose activated charcoal (MDAC) increases elimination of phenytoin,[50-52] the data are conflicting regarding the improvement of clinical outcome in phenytoin overdose. In some studies MDAC failed to demonstrate a beneficial effect on time to resolution of phenytoin toxicity,[53-55] while in other studies MDAC seems to improve the clinical course.[56] For the moment, MDAC is not routinely recommended for the treatment of phenytoin ingestions,[57] but may be considered in selected cases.[58,59] Current toxicology resources do not routinely recommend ECTR for phenytoin poisoning, claiming unproven benefit on clinical outcomes.[60-62]

METHODS

A Predetermined methodology, incorporating recommendations from The Appraisal of Guidelines for Research and Evaluation (AGREE)[63] and Grading of Recommendation Assessment, Development and Evaluation (GRADE),[64] was used and is described in detail elsewhere.[2] The primary literature search was conducted on July 12th 2012 in Medline, Embase and Cochrane library (Review and Central).

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), and Google Scholar was performed, as well as the bibliography of each article obtained during the literature search.

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 (Table 2) 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 pre-determined format.

The strength of recommendations was evaluated by a two-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 15th 2014 using the methodology described above; new articles and the updated data summary were submitted to every participant who then updated their votes.

RESULTS

Results of the literature search are presented in Figure 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 trial (RCT) or observational studies were identified.

Clinical Outcomes

The evidence of a clinical effect of ECTR in phenytoin poisoning is comprised only 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 published in 1958 when hemodialysis was used to treat a boy poisoned with phenytoin.[66] An aggregate description of clinical outcomes of reported cases is presented in Table 3. The average phenytoin ingestion and peak total concentration were 6.8 grams and 69.8 mcg/mL, respectively. The majority of patients presented with some level of impaired consciousness, and most reported cases were treated using either hemodialysis 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 chronic protracted course or long-term sequelae.[33,35,66,80,84] In others, incapacitating ataxia was still present one week after exposure.[70,81] Although the natural history of severely poisoned patients not treated with ECTR suggests survival,[111,112] irreversible neurological conditions may incur in those most at risk.[23-25] In our cohort, survival was noted in some patients who reportedly ingested 10 grams or greater,[33,67,69,71,84] and who had peak total phenytoin concentrations over 90 mcg/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 fatality 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 (HP) and therapeutic plasma exchange (TPE) would theoretically be most likely to efficiently remove phenytoin. TPE can readily remove phenytoin from the vascular compartment, albeit at a

slow rate; on average TPE removes 5-10% of total body load of phenytoin during a single 2-3 hour exchange[93,95,99,102] and can provide clearances up to 20 mL/min (Table 4).[78,113] Initial clearances with charcoal HP 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 have been tested *in vitro*, their application in clinical practice is unknown.[109]

Historical reports suggest a lack of an effect of diffusive techniques including intermittent hemodialysis (HD) because of phenytoin's significant protein binding.[36,67,71,76,90,92,94] However, encouraging results have been shown with high-efficiency filters,[110] especially in patients presenting with conditions known to reduce protein binding (e.g., hypoalbuminemia, kidney disease); clearance may exceed 100 mL/min in uremic patients.[103] Clearances are inferior but nevertheless considerable in patients who have normal protein binding, although the workgroup acknowledged that additional study is required to confirm this.[19,86] One report describes a patient who ingested 3.6 grams 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 4) and the toxicokinetic grading of all patients (Table 5) demonstrate the superiority of both HP and high-efficiency HD over all other techniques. The advantages of HP over HD for phenytoin removal are less clear; in patients who underwent both techniques, HP was superior to HD in one report,[82] and inferior in the other.[86] The addition of a charcoal column in series after a dialysis filter appears to enhance clearance of both HP or HD alone, but requires further study.[86]

Supplementation of albumin into the dialysate does not appear to substantially enhance removal of phenytoin.[74,110] The data on other liver support therapies, like molecular adsorbent recirculating systems (MARS), are limited: in one case, the apparent phenytoin elimination half-life during MARS was 8.4 h, 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 (ET),[76] peritoneal dialysis (PD),[68,69] and continuous renal replacement therapy (CRRT)[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 the criteria established previously,[9] the dialyzability of phenytoin is "slightly dialyzable" or "not dialyzable" for less efficient techniques like ET, PD, CRRT, and conventional HD techniques using less efficient cuprophane membranes. Phenytoin is "slightly" to "moderately dialyzable" with TPE and "moderately dialyzable" to "dialyzable" for HP, high-efficiency HD, and liver support therapies, especially if the patient presents with a condition that is associated with decreased protein binding (e.g., hypoalbuminemia, malnutrition, 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 MDAC with respect to enhanced elimination of phenytoin. In three 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 1**.

1. General statement regarding use of ECTR

- ECTR would be reasonable in selected cases of severe phenytoin poisoning (Neutral recommendation - 3D)

Rationale: Phenytoin is a widely used pharmaceutical, and toxicity following an 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 MDAC remains controversial.[50,55] In severe cases, incapacitating and prolonged ataxia may occur, which can progress to stupor and coma. ECTR not only removes phenytoin from the blood compartment, but also simultaneously from the CSF, its toxic compartment.[83] This may be the reason why several reports describe a marked improvement in the 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 of 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 of 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 to decrease related mortality. Several participants postulated that ECTR might decrease mechanical ventilation time, ICU 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 above. 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 above, potential clinical benefit, risks, and the economic considerations and resource utilization, 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 those patients that 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 phenytoin's zero order kinetics, 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, where supportive management can be preferred over ECTR. In other words, ECTR can be considered in selected cases where 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 (e.g., kidney failure, hypoalbuminemia).

2. Indications for ECTR

- **ECTR is suggested if prolonged coma is present or expected (2D)**
- **ECTR would be reasonable if prolonged incapacitating ataxia is present or expected (3D)**
- **We recommend NOT to perform ECTR solely based on a suspected dose of phenytoin ingested (1D)**
- **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 (e.g., ingestion, intravenous), measurement of toxin in body fluids, technical examinations, and clinical symptoms and signs.

The workgroup agreed that there were too many uncertainties related to the dose of phenytoin 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 an acute phenytoin exposure includes supportive measures, proper gastrointestinal decontamination with single dose activated charcoal and possibly MDAC. If the ingestion history is confirmed and the clinician suspects that major toxicity might ensue, then early communication with a toxicologist and nephrologist for consideration of possible ECTR may be warranted. This may be impossible in the event of IV overdose, given the rapid absorption and distribution (within minutes) and ensuing toxicity from the diluent.

Monitoring of 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 symptomatology than on an arbitrary serum phenytoin concentration threshold. Prophylactic ECTR (i.e., ECTR before the appearance of symptoms) can be considered in poisons where irreversible or life-threatening clinical toxicity is expected (e.g., methanol, theophylline) but the workgroup did not endorse this approach for phenytoin.

Signs and symptoms following phenytoin poisoning are primarily neurologic. As stated earlier, phenytoin poisonings generally have a good prognosis and should be managed with supportive therapy. Coma in phenytoin poisoning is not due to a structural CNS 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 ICU stays, warranting consideration of the risks of 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 utilization.

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 like nystagmus did not warrant ECTR.

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

3. Cessation of ECTR

- **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.

4. Choice of ECTR

- **Intermittent hemodialysis is the preferred ECTR in phenytoin poisoning (1D)**
- **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 to less efficient cuprophane or polyacrylonitrile filters;[103] intermittent HD is the most widely available modality of dialysis worldwide; more physicians and nurses are experienced with HD, with lesser risks of delay and uncertainty; the complication rate with HD appears favorable in comparison to HP, especially with regard to thrombocytopenia during HP, as described in some of the patients included in the cohort;[18,73,88] the cost of HD favors it over HP. This is largely explained by the cost of monitoring and treating complications as well as the lower cost of dialysis filters versus charcoal cartridges, which need to be replaced regularly because of saturation of their adsorptive capacity.

Based on the fact that phenytoin is highly protein bound, a more efficient membrane and the 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 HP as an acceptable and useful alternative, as there is reliable data on its efficacy. HD and HP can also be used simultaneously in series with some clinical benefit.[86,87] Peritoneal dialysis, albumin dialysis, exchange transfusion (ET) and therapeutic plasma exchange would not offer comparable results to HD or HP and are currently not recommended by EXTRIP for phenytoin poisoning. Continuous techniques, offer markedly lower clearances and removal rates compared to intermittent techniques.

CONCLUSION

The EXTRIP workgroup presents its 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 in whom prolonged coma is present

or expected, ECTR is suggested to accelerate elimination of phenytoin and to theoretically reduce ICU stay and its associated morbidity. The preferred choice of ECTR is high-efficiency intermittent hemodialysis. 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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Table 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 mcg/mL (39.6-79.2 μmol/L)
Toxic ingestion	≥ 20 mg/kg
Toxic plasma concentrations	≥ 20 mcg/mL (79 μmol/L)

[a]To convert units 1.0 mcg/mL = 3.96 μmol/L

Table 2. Strength of recommendation and level of evidence scaling for clinical outcomes

Strength of recommendation (consensus-based)	Level of evidence (based on GRADE system)
Level 1 = Strong recommendation "We recommend…" *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 "We suggest…" *The course of action is considered appropriate by the majority of experts but some degree of dissension exists amongst the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.* Level 3 = Neutral recommendation "It would be reasonable…" *The course of action could be considered appropriate in the right context* No recommendation *No agreement was reached by the group of experts*	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*

Adapted from Lavergne V, Nolin TD, Hoffman RS, et al. The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: guideline methodology. *Clin Toxicol (Phila).* 2012;50(5):403-413.

Table 3. Aggregate clinical outcomes of the 31 overdose patients described in case reports or case series

Demographics	Age in years [mean (range)]	26.7 (0.1-77)
	Male (%)	63.3%
Phenytoin exposure	Amount ingested (grams)	6.8 (1-21.5)
	Peak total phenytoin conc [mean (range)] (mcg/mL)	69.8 (15-200.7)
	Time from ingestion to presentation (hours)	18.1 (1-120)
Toxic symptoms (%)	Altered consciousness	90.3%
	Seizure (one or more)	19.4%
	Respiratory failure	32.3%
	Dysarthria/ataxia	25.8%
Other treatments (%)	Mechanical ventilation	25.8%
	MDAC	9.7%
ECTR (N)	HD	7
	HP	7
	CRRT	0
	HP-HD	3
	TPE	3
	ET	1
	PD	6
	Liver support therapy (MARS)	1
	More than 1 ECTR	3
Outcome (%)	Sequelae	12.9%
	Death	6.5%

HD, intermittent hemodialysis; HP, hemoperfusion; CRRT, continuous renal replacement therapy; HD-HP, intermittent hemodialysis and hemoperfusion in series; TPE, therapeutic plasma exchange; ET, exchange transfusion; PD, peritoneal dialysis; MARS, molecular adsorbent recirculating system.

Table 4. Clearance of various ECTRs from accepted articles

ECTR	Patients	Clearance (mL/min)		References
		Average	Range	
Conventional HD	10	16.7	6.5-42	[71,90-92]
High efficiency HD	3	68.1	44.3-112	[19,86,103]
Charcoal HP	4	28.8	18-42	[72,73,83,86]
HD-HP	1	58.4		[86]
TPE	14	18.5	7.8-43	[75,78,80,81,93,95-99,102]
PD	6	3.3	0.2-10.6	[36,68,69,74,76,94]
ET	1	3.1		[76]
CRRT	4	6.5	0.9-13	[100,104]

HD, intermittent hemodialysis; HP, hemoperfusion; HD-HP, intermittent hemodialysis and hemoperfusion in series; TPE, therapeutic plasma exchange; PD, peritoneal dialysis; ET, exchange transfusion; CRRT, continuous renal replacement therapies.

Table 5. Toxicokinetic grading attributed to individual patients

	Number of Patients Graded								
	PD	HP	HD (conv)	HD (high-eff)	HD-HP (in series)	CRRT	TPE	ET	LST
Dialyzable		2		2	1				1
Moderately dialyzable		2		2			7		
Slightly dialyzable	1		5			2	7	1	
Not dialyzable	5		4			2	2		

PD, peritoneal dialysis; HP, hemoperfusion; HD (conv), conventional intermittent hemodialysis; HD (high-eff), high efficiency intermittent hemodialysis; HD-HP, intermittent hemodialysis and hemoperfusion in series; CRRT, continuous renal replacement therapy; TPE, therapeutic plasma exchange; ET, exchange transfusion; LST, liver support therapy.

Box 1. Executive summary of recommendations

General statement regarding use of ECTR

- ECTR would be reasonable in selected cases of severe phenytoin poisoning (3D)

Indications for ECTR

- ECTR is suggested if prolonged coma is present or expected (2D)
- ECTR would be reasonable if prolonged incapacitating ataxia is present or expected (3D)
- We recommend NOT to perform ECTR solely based on suspected dose of phenytoin ingested (1D)
- We recommend NOT to perform ECTR solely based on serum phenytoin concentration (1D)

Cessation of ECTR

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

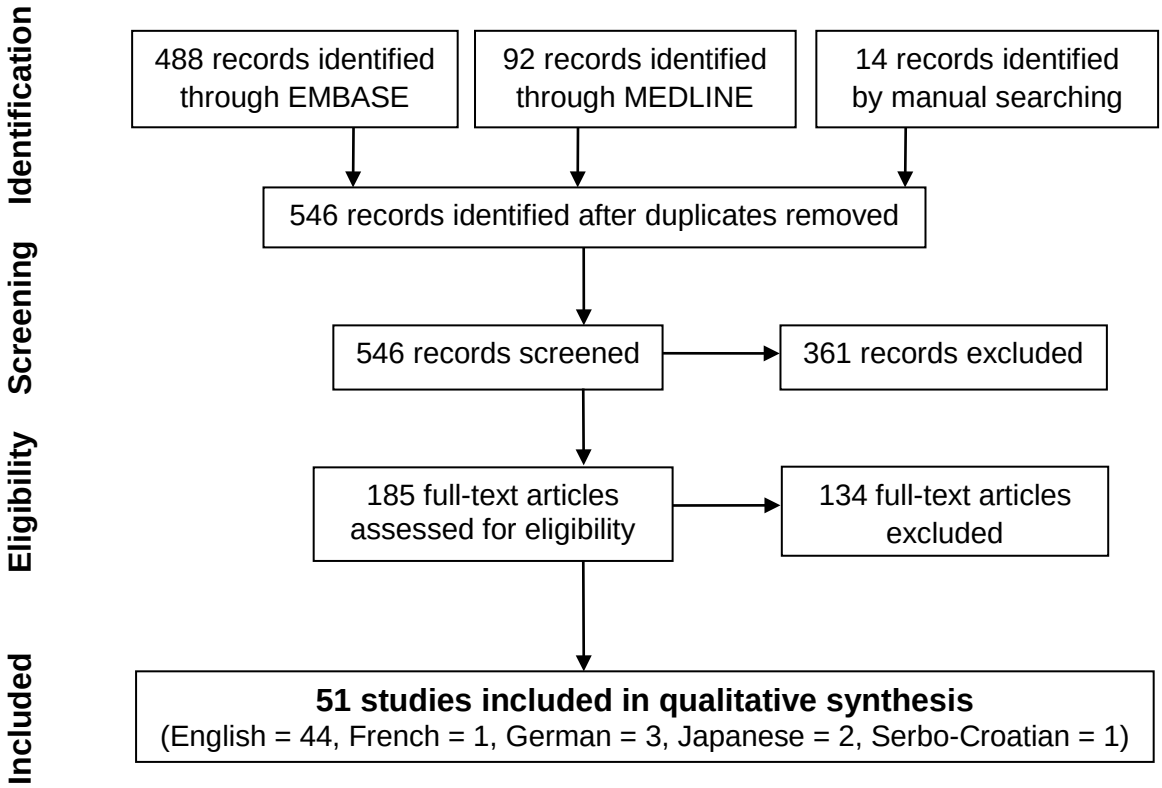
Choice of ECTR

- Intermittent HD is the preferred ECTR in phenytoin poisoning (1D)
- Intermittent HP is an acceptable alternative if intermittent HD is not available (1D)

Figure legend

Figure 1. Summary of literature search on use of ECTR in phenytoin poisoning.

Figure 1.


Identification
Screening
Eligibility
Included
488 records identified through EMBASE
92 records identified through MEDLINE
14 records identified by manual searching
546 records identified after duplicates removed
546 records screened
361 records excluded
185 full-text articles assessed for eligibility
134 full-text articles excluded
51 studies included in qualitative synthesis
(English = 44, French = 1, German = 3, Japanese = 2, Serbo-Croatian = 1)

Supplementary Material

Item S1. Represented Societies

Item S1. Societies represented in EXTRIP

American Academy of Clinical Toxicology
American College of Emergency Physicians
American College of Medical Toxicology
American Society of Nephrology
American Society of Pediatric Nephrology
Asia Pacific Association of Medical Toxicology
Australian and New Zealand Intensive Care Society
Australian and New Zealand Society of Nephrology
Brazilian Association of Poison Control Centers and Clinical Toxicologists
Brazilian Society of Nephrology
Brazilian Society of Toxicology
Canadian Association of Poison Control Centres
Canadian Association of Emergency Physicians
Canadian Society of Nephrology
Chinese College of Emergency Physicians
Chinese Medical Doctor Association
European Association of Poison Centres and Clinical Toxicologists
European Renal Best Practice
European Society of Emergency Medicine
European Society of Intensive Care Medicine
French Language Society of Resuscitation
German Society of Nephrology
International Pediatric Nephrology Association
International Society of Nephrology
Latin American Society of Nephrology and Hypertension
National Kidney Foundation
Pediatric Continuous Renal Replacement Therapy
Pediatric Critical Care Medicine
Quebec Association of Emergency Physicians
Quebec Association of Specialists in Emergency Medicine
Quebec Society of Nephrology
Renal Association
Society of Critical Care Medicine
Spanish Clinical Toxicology Foundation

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