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Special Report

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/min[27] 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 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.

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)

[a]To convert units, 1.0 μg/mL = 3.96 μmol/L.

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