

ORIGINAL ARTICLE

Extracorporeal treatment for theophylline poisoning: Systematic review and recommendations from the EXTRIP workgroup

MARC GHANNOUM,¹ TIMOTHY J. WIEGAND,² KATHLEEN D. LIU,³ DIANE P. CALELLO,⁴ MELANIE GODIN,⁵ VALÉRY LAVERGNE,⁶ SOPHIE GOSSELIN,⁷ THOMAS D. NOLIN,⁸ and ROBERT S. HOFFMAN⁹; ON BEHALF OF THE EXTRIP WORKGROUP

¹Department of Nephrology, Verdun Hospital, University of Montreal, Verdun, Canada

²The University of Rochester Medical Center and Strong Memorial Hospital, Rochester, USA

³Division of Nephrology, Department of Medicine, University of California, San Francisco, USA

⁴Department of Emergency Medicine, Morristown Medical Center, Morristown, New Jersey, USA

⁵Division of Nephrology, Department of Medicine, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada

⁶Department of Medical Biology, Sacre-Coeur Hospital, University of Montreal, Montreal, Canada

⁷Department of Emergency Medicine, Medical Toxicology Service, McGill University Health Centre, McGill University, Montreal, Canada

⁸Department of Pharmacy and Therapeutics, Center for Clinical Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA

⁹Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, New York, USA

Background. The Extracorporeal Treatments in Poisoning workgroup was created to provide evidence-based recommendations on the use of extracorporeal treatments (ECTRs) in poisoning. Here, the workgroup presents its systematic review and recommendations for theophylline. **Methods.** After a systematic review of the literature, a subgroup reviewed articles, extracted data, summarized findings, and proposed structured voting statements following a pre-determined format. A two-round modified Delphi method was chosen to reach a consensus on voting statements and the RAND/UCLA Appropriateness Method was used to quantify disagreement. Anonymous votes were compiled, returned, and discussed. A second vote determined the final recommendations. **Results.** 141 articles were included: 6 in vitro studies, 4 animal studies, 101 case reports/case series, 7 descriptive cohorts, 4 observational studies, and 19 pharmacokinetic studies, yielding a low-to-very-low quality of evidence for all recommendations. Data on 143 patients were reviewed, including 10 deaths. The workgroup concluded that theophylline is dialyzable (level of evidence = A) and made the following recommendations: ECTR is recommended in severe theophylline poisoning (1C). Specific recommendations for ECTR include a theophylline concentration [theophylline] > 100 mg/L (555 µmol/L) in acute exposure (1C), the presence of seizures (1D), life-threatening dysrhythmias (1D) or shock (1D), a rising [theophylline] despite optimal therapy (1D), and clinical deterioration despite optimal care (1D). In chronic poisoning, ECTR is suggested if [theophylline] > 60 mg/L (333 µmol/L) (2D) or if the [theophylline] > 50 mg/L (278 µmol/L) and the patient is either less than 6 months of age or older than 60 years of age (2D). ECTR is also suggested if gastrointestinal decontamination cannot be administered (2D). ECTR should be continued until clinical improvement is apparent or the [theophylline] is < 15 mg/L (83 µmol/L) (1D). Following the cessation of ECTR, patients should be closely monitored. Intermittent hemodialysis is the preferred method of ECTR (1C). If intermittent hemodialysis is unavailable, hemoperfusion (1C) or continuous renal replacement therapies may be considered (3D). Exchange transfusion is an adequate alternative to hemodialysis in neonates (2D). Multi-dose activated charcoal should be continued during ECTR (1D). **Conclusion.** Theophylline poisoning is amenable to ECTRs. The workgroup recommended extracorporeal removal in the case of severe theophylline poisoning.

Keywords: Dialysis, Methylxanthines, Theophylline

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*The EXTRIP workgroup also includes the following: Kurt Anseeuw, Ashish Bhalla, Emmanuel A. Burdmann, Paul I. Dargan, Brian S. Decker, Tais F. Galvao, David S. Goldfarb, Lotte C. Hoegberg, David N. Juurlink, Jan T. Kielstein, Martin Laliberté, Yi Li, Robert MacLaren, Robert Mactier, Bruno Mégarbane, James B. Mowry, Véronique Phan, Darren M. Roberts, Kevin M. Sowinski, James F. Winchester, Christopher Yates.

Address correspondence to Dr. Robert S. Hoffman, Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, New York University School of Medicine, 455 First Ave, Room 123, New York, NY 10016, USA. Tel: 1.212.447.8153 Email: bobhoffmd@gmail.com

Introduction

The Extracorporeal Treatments In Poisoning (EXTRIP) workgroup is comprised of international experts representing diverse specialties and professional societies (Table 1) to provide recommendations on the use of extracorporeal treatments (ECTRs) in poisoning (www.extrip-workgroup.org). The rationale, background, objectives, complete methodology, and first recommendations have been published.^{1–9} The following describes a systematic review and the ECTR recommendations for theophylline poisoning.

Table 1. Represented Societies.

Acute Dialysis Quality Initiative	European Renal Best Practice
American Academy of Clinical Toxicology	European Society For Emergency Medicine
American College of Emergency Physicians	European Society of Intensive Care Medicine
American College of Medical Toxicology	French Society of Intensive Care
American Society of Nephrology	German Society of Nephrology
American Society of Pediatric Nephrology	Indian Society of Critical Care Medicine
Asia Pacific Association of Medical Toxicology	INDO-US Emergency & Trauma Collaborative
Association of Physicians of India	International Pediatric Nephrology Association
Australian and New Zealand Intensive Care Society	International Society of Nephrology
Australian and New Zealand Society of Nephrology	Latin American Society of Nephrology and Hypertension
Brazilian Association of Information Centres and Toxicologic Assistance	National Kidney Foundation
Brazilian Society of Nephrology	Pediatric Continuous Renal Replacement Therapy
Brazilian Society of Toxicology	Pediatric Critical Care Medicine
Canadian Association of Poison Control Centres	Quebec Association of Emergency Physicians
Canadian Association of Emergency Physicians	Quebec Association of Specialists in Emergency Medicine
Canadian Society of Nephrology	Quebec Society of Nephrology
Chinese College of Emergency Physicians	Renal Association
Chinese Medical Doctor Association	Society of Critical Care Medicine
European Association of Poison Centres and Clinical Toxicologists	Spanish Clinical Toxicology Foundation

Pharmacology and pharmacokinetics

Theophylline (1,3-dimethylxanthine) is a plant-derived methylxanthine compound, similar to caffeine (1,3,7-trimethylxanthine), paraxanthine (1,7-dimethylxanthine), and theobromine (3,7-dimethylxanthine). Theophylline is used for the treatment of bronchospasm from asthma and chronic obstructive pulmonary disease (COPD), neonatal apnea, lethargy, and weight loss. While typically used orally, an intravenous water-soluble salt (aminophylline; 85% of anhydrous theophylline) is also available.

Theophylline is a small molecule (180 Da) and is approximately 40–60% protein-bound, although this is reduced in infants and patients with cirrhosis and uremia.¹⁰ Following ingestion, theophylline is well absorbed with up to 90% oral bioavailability and distributes into an apparent volume of approximately 0.5 L/kg (Table 2). Peak serum concentrations are achieved within 1–2 h following therapeutic dosing, but this is slowed by the presence of food and in modified-release preparations.¹¹ Theophylline undergoes extensive hepatic metabolism, primarily mediated by cytochrome P450 enzymes (CYPs). There is considerable inter-individual variability depending on age and comorbidities, which can be further enhanced by CYP inducers (e.g., smoking,

phenytoin, and phenobarbital) or reduced by CYP inhibitors (e.g., cimetidine and macrolides).^{12,13} Less than 10% of ingested theophylline is excreted unchanged by the kidneys (renal clearance < 10 mL/min).¹⁴ The half-life with therapeutic dosing in adult non-smokers is approximately 8–11 h, with an endogenous total body clearance of 40–60 mL/min,^{15–21} although clearance can be markedly lowered in overdose because of a change to zero-order elimination at high concentrations [typically over 60 mg/L (333 µmol/L)].²² The therapeutic range for theophylline is 5–15 mg/L (28–83 µmol/L). The pharmacokinetics of caffeine and other methylxanthines are similar to theophylline although caffeine has a slightly larger apparent volume of distribution and a shorter elimination half-life.²³ In infants, the half-life of both theophylline and caffeine is substantially prolonged.²⁴

Methylxanthines produce their therapeutic effects by increasing the release of endogenous catecholamines and antagonizing the effects of adenosine. This leads to both an increase in adrenergic tone with stimulation of both β_1 and β_2 adrenergic receptors, as well as a modulation of adenosine's effects on promoting histamine release. At toxic doses, methylxanthines also inhibit phosphodiesterases, thereby preventing the degradation of cyclic AMP.

Table 2. Theophylline: physicochemical and toxicokinetic data.

	Theophylline	Caffeine
Molecular mass	180.2 Da	194 Da
Conversion	1 mg/L = 5.55 µmol/L	1 mg/L = 5.15 µmol/L
Protein binding	50%	35%
Oral bioavailability	> 90% (therapeutic)	> 90%
Volume of distribution	0.5 L/kg	0.7 L/kg
Elimination half-life	Neonates: 30 h Adults: 8–10 h	Neonates: 80 h Adults: 2.5–4.5 h
Therapeutic concentration	5–15 mg/L (28–83 µmol/L)	N/A
Toxic concentration	> 25 mg/L (139 µmol/L)	> 30 mg/L (155 µmol/L)
Toxic dose	> 15 mg/kg	> 15 mg/kg
Lethal dose	> 100 mg/kg	> 150 mg/kg

Overview of theophylline poisoning

Due to the superior therapeutic index of selective β_2 agonists, the use of theophylline has decreased substantially over the past 20 years. Data from the US National Poisoning Data System in 2012 show only 218 exposures and 3 deaths related to theophylline²⁵ compared with 6744 exposures and 38 deaths in 1991.²⁶ Despite this, theophylline is used with higher frequency in some countries outside the US and new indications for its use are emerging,^{27–29} so there remains a potential concern for toxicity.

Methylxanthine poisoning affects multiple organ systems. Early signs and symptoms of acute overdose include anorexia, nausea, and vomiting. As concentrations rise, severe and protracted vomiting can occur. Cardiovascular effects include hypotension, sinus tachycardia, and various atrial and ventricular dysrhythmias. Supraventricular tachycardia, atrial fibrillation, multifocal atrial tachycardia, premature ventricular contractions, and, finally, ventricular tachycardia may occur. Hyperventilation can result in respiratory alkalosis and respiratory fatigue. Methylxanthine concentrations in the cerebrospinal fluid correlate with those in plasma.^{30,31} Central nervous system stimulation is a hallmark of methylxanthine toxicity with headache, anxiety, tremor, irritability, agitation, and seizures occurring as concentrations increase. Theophylline is one of the few causes of true toxin-induced status epilepticus, due to adenosine antagonism.³² In chronic toxicity, cardiovascular and neurological manifestations predominate over gastrointestinal findings.^{33,34} Hypokalemia is caused by β -adrenergic receptor-mediated intracellular shift and can contribute, when severe, to both cardiac and neuromuscular complications. Metabolic acidosis with lactate accumulation and excessive metabolic activity is common in overdose. Hyperglycemia and leukocytosis are common presenting findings as well.^{35,36}

The relationship between the serum theophylline concentration ([theophylline]) and symptoms is controversial. Although most studies have suggested a relationship especially in acute poisoning,^{34,36–45} others have either failed to identify a correlation or observed toxicity at lower concentrations.^{33,44,46–48}

General supportive therapies are the mainstay of theophylline poisoning as no specific antidote exists. After attention to airway, breathing, and circulation, care should be aimed at maintaining normal hemodynamics and preventing clinical decompensation in patients at risk for severe toxicity. The treatment of specific complications such as ventricular dysrhythmias, hypotension, intractable vomiting, and seizures are reviewed in depth elsewhere.^{49,50} Judicious potassium replacement may be required to prevent worsening cardiac conduction defects, although rebound hyperkalemia has been described once the theophylline concentration normalizes.⁵¹ Decontamination, with activated charcoal, has both theoretical and clinical utility.⁵² Multi-dose activated charcoal (MDAC) enhances elimination of theophylline through “gut dialysis.”^{53–55} Unfortunately, its administration is often limited by intractable vomiting^{37,51,56} in particular when the [theophylline] is > 50 mg/L (278 μ mol/L).⁵⁷

More definite theophylline elimination may be provided by extracorporeal purification, although the exact indications remain imprecise. Some recommendations are based on an elevated [theophylline] regardless of symptoms, that is, > 80 – 100 mg/L (444–555 μ mol/L),^{49,50,58–60} although others have suggested different cut-offs such as 150 mg/L (833 μ mol/L),⁶¹ > 40 – 60 mg/L (222–333 μ mol/L) in chronic overdose,^{50,58–61} and a lower threshold for extremes of age.^{58,59} ECTR has also been suggested in the presence of significant dysrhythmias, seizures, mental status changes, or hypotension, irrespective of the [theophylline] or chronicity of exposure.^{50,58–60} Some recommendations include a combined approach based on both the [theophylline] and the presence of either severe symptoms (seizures, sustained hypotension and ventricular dysrhythmias),⁴⁹ failure to administer MDAC,^{50,61} serious comorbidities or coexisting conditions [COPD, end-stage renal disease (ESRD), and liver failure], or any extremes in age.⁵⁰ Additionally, the choice of ECTR is also debated, with some sources preferring hemoperfusion^{49,58,60,61} and others preferring hemodialysis.^{50,59}

Methodology

A predetermined methodology, incorporating guidelines from the Appraisal of Guidelines for Research and Evaluation⁶² and Grades of Recommendation Assessment, Development and Evaluation (GRADE),⁶³ was used and is described in detail elsewhere.² The primary literature search was first conducted on July 12th, 2012 in MEDLINE, Embase, and Cochrane library (Review and Central) and updated prior to the final vote on November 15th, 2014 using the same search strategy.

The search strategy was

[(theophylline OR aminophylline OR caffeine OR methylxanthine) AND (dialysis OR hemodialysis OR haemodialysis OR hemoperfusion OR haemoperfusion OR plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR extracorporeal therapy OR continuous renal replacement therapy {CRRT})].

A manual search of conference proceedings of the EAPCCT and 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 the EXTRIP workgroup completed the literature search, reviewed each article, extracted data, and summarized findings. The level of evidence assigned to each clinical recommendation was determined by the subgroup and the epidemiologist (Table 3). Dialyzability was determined based on criteria listed in Table 4. The potential benefit of the procedure was 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.

Table 3. Strength of recommendations and level of evidence scaling on clinical outcomes.

Strength of recommendation (consensus-based)	Level of evidence (based on GRADE system)
Level 1 = Strong recommendation = “We recommend...” <i>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.</i>	Grade A = High level of evidence <i>The true effect lies close to our estimate of the effect.</i>
Level 2 = Weak recommendation = “We suggest...” <i>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.</i>	Grade B = Moderate level of evidence <i>The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.</i>
Level 3 = Neutral recommendation = “It would be reasonable...” <i>The course of action could be considered appropriate in the right context.</i>	Grade C = Low level of evidence <i>The true effect may be substantially different from our estimate of the effect.</i>
No recommendation <i>No agreement was reached by the group of experts.</i>	Grade D = Very low level of evidence <i>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.</i>

The strength of recommendations was evaluated by a two-round modified Delphi method for each proposed voting statement (Fig. 1) and a RAND/UCLA Appropriateness Method was used to quantify disagreement between voters.⁶⁴ 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.

Results

The results of the literature search are shown in Fig. 2. A total of 436 articles were identified after duplicates were removed, of which 290 full-text articles were retrieved, and 141 studies were finally included for qualitative analysis: 4 observational studies,^{37,65–67} 7 descriptive cohorts,^{36,44,46,48,56,68,69} 101 case reports/case series,^{22,30,31,40,51,57,70–164} 19 pharmacokinetic studies in ESRD patients,^{10,165–182} 1 animal study with clinical comparison,¹⁸³ 3 animal toxicokinetic studies,^{184–186} and 6 in vitro studies.^{187–192} No randomized controlled trials were identified.

Clinical outcomes

The clinical benefit of ECTR in theophylline toxicity was analyzed from 4 observational studies.^{37,65–67} One retrospective cohort of acute overdose patients with a [theophylline] > 20 mg/L (111 μmol/L) compared 8 patients who received supportive care and ECTR (hemoperfusion or hemodialysis) with 18 who received supportive care alone.⁶⁵ The group treated with ECTR appeared more clinically ill at baseline (the ECTR group had a statistically higher admission and peak [theophylline], a lower mean arterial blood pressure, and a greater incidence of dysrhythmias). Yet, the length of toxicity (i.e., time from ingestion to normalization of toxic symptoms) was significantly shorter in the ECTR group (13.5 vs. 21.6 h, $p < 0.05$) although survival was comparable. These results suggest a significant clinical benefit of ECTR for acutely poisoned patients.

One prospective study included patients with a [theophylline] > 30 mg/L (167 μmol/L). Criterion for ECTR was a [theophylline] > 80 mg/L (444 μmol/L) after an acute ingestion, > 40–50 mg/L (222–278 μmol/L) in chronic toxicity, or the presence of intractable seizures or dysrhythmias.³⁷ The group who received ECTR prophylactically (i.e., prior to the development of symptoms) was compared with another who

Table 4. Criteria for dialyzability*.

Dialyzability ^a	Primary criteria % Removed ^b	Alternative criteria 1 CL _{ECTR} /CL _{TOT} (%)	Alternative criteria 2 T _{1/2 ECTR} /T _{1/2} (%)	Alternative criteria 3 RE _{ECTR} /RE _{TOT} (%) ^c
D, Dialyzable	> 30	> 75	< 25	> 75
M, Moderately dialyzable	> 10–30	> 50–75	> 25–50	> 50–75
S, Slightly dialyzable	≥ 3–10	≥ 25–50	≥ 50–75	≥ 25–50
N, Not dialyzable	< 3	< 25	> 75	< 25

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Legend: ECTR = Extracorporeal treatment, CL_{ECTR} = Extracorporeal clearance, CL_{TOT} = Total clearance, RE_{ECTR} = Extracorporeal removal, RE_{TOT} = Total removal, T_{1/2 ECTR} = Half-life on ECTR, T_{1/2} = Half-life off ECTR.

*These criteria should only be applied if measured or calculated (not reported) endogenous half-life is > 4 h (otherwise, ECTR is considered to be not clinically relevant). Furthermore, the primary criteria are preferred for poisons having a large Vd (> 5L/Kg).

^aApplicable to all modalities of ECTR, including hemodialysis, hemoperfusion, and hemofiltration.

^bCorresponds to % removal of ingested dose or total body burden in a 6-h ECTR period.

^cMeasured during the same period of time.

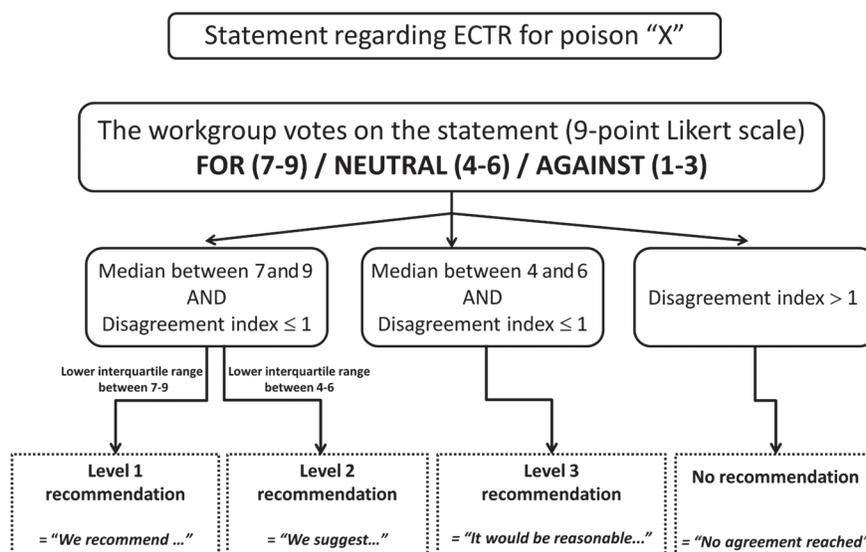


Fig. 1. Strength of recommendation algorithm.

underwent ECTR when symptoms had already developed. Only 1 patient out of 21 from the prophylactic ECTR group (5%) developed seizures during the procedure, whereas 71% of patients who received ECTR after clinical toxicity apparently continued to have ongoing toxic manifestations. This suggests a benefit for ECTR in asymptomatic patients who have an elevated [theophylline], but it is impossible to confirm this hypothesis since no formal group comparison was presented in the study in order to evaluate the presence of potential confounders and the presence of potential selection bias (confounding-by-indication) in the decision to perform ECTR.

One retrospective cohort included patients presenting with a [theophylline] ≥ 30 mg/L (167 $\mu\text{mol/L}$).⁶⁶ Patients with no theophylline-related toxicity ($n = 22$) (defined as an absence of dysrhythmias, seizures, cardiovascular instability, or death) were compared with those presenting with severe toxicity and/or who underwent hemoperfusion after

a voluntary overdose or after iatrogenic overdose ($n = 14$). The primary intent of the study was not to evaluate a clinical effect of ECTR. Despite hypothesizing that the use of hemoperfusion prevented the development of severe toxicity, the clinical impact of ECTR is rather difficult to evaluate in this study since the ECTR-treated patients ($n = 6$) had a higher [theophylline] and less clinical toxicity than those not receiving ECTR ($n = 8$). The mortality rate observed between these two subgroups was comparable (16.7% vs. 37.5%, respectively; $p = 0.6$) although this comparison is likely underpowered.

Finally, one prospective study compared poisoned patients treated with hemoperfusion ($n = 17$) to those treated with hemodialysis ($n = 39$).⁶⁷ Both groups were comparable at baseline in regard to age, interval time from ingestion to presentation, admission and peak [theophylline], time to peak [theophylline], type of poisoning, symptoms at initiation of ECTR, incidence of vomiting, and interval time from

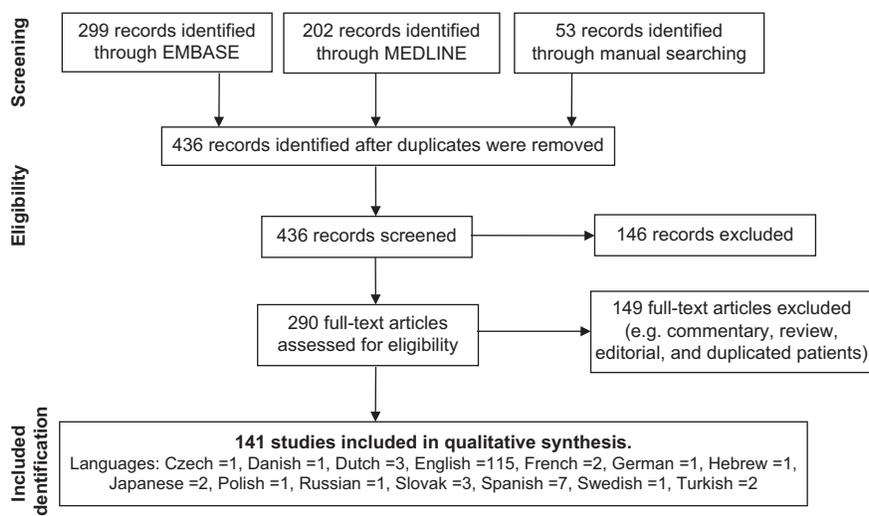


Fig. 2. Flow diagram for literature Search (November 15th 2014).

presentation to ECTR. Although the reason for preference for either hemoperfusion or hemodialysis was not stated, there was no statistical difference in outcome: the rate of major toxicity during or after ECTR as well as mortality was comparable in both groups. However, there was significantly more procedure-related complications in the hemoperfusion group (18% vs. 0%, $p = 0.007$). Other comparative studies did not evaluate ECTR as a factor associated with outcome, so they were only included in the analysis for patient-level data if the information was available.⁴⁴

In one animal study, no clinical benefit was observed in aminophylline-poisoned rats treated with peritoneal dialysis compared with that in controls.¹⁸³ However, the authors attributed the lack of benefit to concomitant anesthesia, which may have clouded evaluation of clinical improvement. The remainder of the clinical evidence is composed of case reports and uncontrolled descriptive cohorts. Although the observational studies had limitations, the evidence

does suggest a clinical benefit for ECTR. The quality of the evidence was considered to be low or very low for all recommendations.

In total, 143 patients were described in sufficient detail (i.e., data containing patients' demographics, exposure, clinical manifestation, treatment including ECTR, and/or outcome) in either case reports or observational studies to be included in the clinical review (Table 5). The large majority of reported cases were following an acute ingestion (86%), mostly involving the use of modified-release formulations. The mean peak [theophylline] was 119.4 mg/L (663 $\mu\text{mol/L}$). The most frequently encountered sign of toxicity was hypokalemia (82%), the incidence and extent of which were comparable with those of other reported cohorts.^{36,193} Sinus tachycardia (74%), nausea/vomiting (58%), seizures (49%, most being multiple), and hypotension (41%) were also common. Because of the older nature of the literature, hemoperfusion was the predominantly used ECTR modality.

Table 5. Clinical data related to the reported 143 patients who received ECTR for theophylline toxicity.*

Demographics	Average age (years) % Male	31.7 (range 0–83) 42.4%
Poisoning exposure	Acute exposure**	86.0%
	Form	
	<i>Oral caffeine</i>	7.0%
	<i>Rectal theophylline</i>	2.6%
	<i>Immediate-release oral theophylline</i>	26.3%
	<i>Modified-release oral theophylline</i>	53.5%
	<i>Intravenous theophylline (aminophylline)</i>	10.5%
	Mean theophylline exposure (grams)	13.3 (range 0.1–106)
	Mean peak concentration (mg/L)	Theophylline: 119.4 (range 25–330) Caffeine: 212.7 (72–405)
Symptoms and signs***	Delay between acute exposure and admission (hours)	7.9 (0–66)
	Altered consciousness	46.2%
	Seizure (one)	9.8%
	Seizures (> 1)	39.2%
	Hyperthermia	9.1%
	Metabolic acidosis	31.5%
	Hypokalemia (< 3.5 mEq/L)	81.7%
	Mean potassium (mEq/L)	2.9 (range 1.8–7.2)
	Leukocytosis	10.5%
	Nausea/Vomiting	58.1%
	Tachycardia	74.1%
	Cardiac arrest	11.2%
	Hypotension	40.6%
	Dysrhythmias	28.0%
Other treatments administered	MDAC	21.7%
	Mechanical ventilation	27.3%
Extracorporeal treatments	Mean time from admission to ECTR initiation (hours)	13.9 (range 1.5–168)
	Hemodialysis	12.6%
	Charcoal hemoperfusion	35.7%
	Resin hemoperfusion	10.5%
	Hemoperfusion (not specified)	3.5%
	CRRT	6.3%
	Peritoneal dialysis	4.2%
	Hemoperfusion–hemodialysis	14.7%
	Exchange transfusion	3.5%
	Liver support therapy	0.7%
	More than 1 ECTR	8.4%
Outcome	Death	7.0%
	Permanent sequelae	8.4%

*These only include cases in which patient-level data could be extracted.

**Acute exposures include intravenous therapeutic errors, subacute exposures, and acute voluntary overdose.

***Symptoms and other treatments were often underreported in case reports, so the real incidence is likely higher.

More than three-fourths of patients improved during the procedure; in some cases, this was prompt and spectacular, as manifested by either a normalization of mental status, correction of hypotension, or an abrupt termination of seizures or dysrhythmias during ECTR.^{65,74,77,91,111,127,138,143,151,169} There were 10 deaths among the 143 patients included,^{30,40,57,65,66,96,135,136,140,150} many of which occurred from complications of anoxic brain injury that likely preceded ECTR.^{30,65,96,136,140}

Complications

Reported complications from ECTR were almost exclusively attributed to hemoperfusion: several studies reported a drop in platelet concentration (approximately 50–60%), which was usually transient and reversible.^{57,65,75,77,82,84,87,101,111,115,118,124,134,135,137,138,152,154,158,162} Occasionally, hemoperfusion also produced a fall in hemoglobin concentration^{57,124,137,140} or serious bleeding necessitating transfusion.^{22,77,84,89,135,150} In two cases receiving hemoperfusion, massive hemolysis was reported.^{90,131} Mild asymptomatic hypocalcemia was also noted.^{57,87,137,140,152} Complications during other procedures were rare. This supports the findings from the prospective study described above, which showed that procedural complications during hemoperfusion statistically exceeded those during hemodialysis.⁶⁷

Dialyzability

Theophylline's low molecular weight, low volume of distribution, and modest protein binding would predict that it is highly dialyzable. This is indeed confirmed by the literature review (Table 6); mean clearance with charcoal hemoperfusion, for example, exceeds 100 mL/min. Averaged clearance for intermittent hemodialysis is lower but this result is

skewed by the inclusion of older articles using obsolete technology. This is readily apparent when comparing the dialytic theophylline clearance over time: it was approximately 35 mL/min in reports from the 1970s,^{10,176} doubled with more permeable membranes in the 1980s,^{170,174,180} and increased further to 150 mL/min in the 1990s with high-surface area filters and maximization of blood flow and dialysate flow.^{96,103,127} This compares favorably to an endogenous clearance (for therapeutic dose) of 40–60 mL/min,¹⁹⁴ which may be reduced by half in overdose.²² It is therefore expected that a high-efficiency ECTR can increase total clearance in poisoning by up to 400% (from 30 to 150 mL/min).

The combination of hemoperfusion and hemodialysis in series appears to provide the best clearance.^{97,136} As expected by their lower blood and/or effluent flow, clearances for less efficient techniques like CRRT and sustained low-efficiency dialysis are inferior to those obtainable with hemodialysis or hemoperfusion.^{103,156} Clearances with exchange transfusion and peritoneal dialysis seldom surpass 15 mL/min, a value that is clinically insignificant for any patient except newborns.^{129,195} As expected, hemodialysis was significantly better than peritoneal dialysis at removing theophylline in one pharmacokinetic study.¹⁷⁵

The evidence for dialyzability is provided by several studies that quantified removal via the effluent^{83,85,103,121,127,156,166,174,175} or the extruded column.⁷⁷ This is further supported by cases in which there was an iatrogenic intravenous methylxanthine exposure, which both removes the uncertainty attributable to exposure quantity and the unclear impact of ongoing absorption.^{82,121,125} According to the dialyzability criteria in Table 4, in most of the cases that underwent an ECTR (especially hemoperfusion or hemodialysis) theophylline would qualify as “dialyzable” (Table 7). For these reasons, the workgroup agreed that theophylline is DIALYZABLE (Level of evidence = A).

Table 6. Averaged toxicokinetic and pharmacokinetic parameters for all techniques.

Type of ECTR	Mean ECTR theophylline clearance with range (mL/min)	Mean apparent theophylline T _{1/2} with range (hours)
<i>Endogenous (from cohort)</i>	49.5 (n = 21; 16.1–154)	10.6 (n = 69; 2.1–57.9)
Charcoal hemoperfusion	114.9 (n = 25; 24.7–231)	2.1 (n = 64; 0.7–6)* Caffeine: 1.9 (n = 1)
Resin hemoperfusion	81.5 (n = 4; 30–133)	2.8 (n = 10; 0.8–6.3) Caffeine: 4.3 (n = 1)
CRRT	64.2 (n = 13; 35–66.6)	7.6 (n = 5; 4.6–15)
Hemodialysis	82.8 (n = 44; 5.9–156)	2.5 (n = 80; 0.6–7)*
Hemoperfusion–hemodialysis in series	200.0 (n = 4; 149–244.7)	2.5 (n = 6; 1.3–4.5)
Sustained low-efficiency dialysis	42 (n = 1)	7.1 (n = 1)
Therapeutic plasma exchange		1.7 (n = 1)
Exchange transfusion	3.8 (n = 1)	10.3 (n = 2; 6.6–14)
Peritoneal dialysis	7.7 (n = 13; 0.3–17.5)	7.8 (n = 8; 4.6–14.8) Caffeine: 11.4 (n = 2; 9.1–13.6)
Liver support therapy		1.8 (n = 1)

PK, Pharmacokinetics; TK, Toxicokinetics; CRRT, Continuous renal replacement therapy.

Some clearances include neonates which skew the means, as maximal blood flow is usually < 50 mL/min.

Some clearances were erroneously calculated in some papers and were therefore not included.

*Includes results from the cohort described by Shannon (Shannon M. Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. *Acad Emerg Med* 1997; 4(7):674–8.).

Table 7. Kinetic grading for individual patients*.

PK/TK grading	HD	CHP	RHP	PD	CRRT	ET	HD-CHP in series	LST	SLED
Dialyzable	33	22	5	2	1	1	2	1	0
Moderately dialyzable	6	10	1	0	1	0	1	0	0
Slightly dialyzable	2	3	1	9	1	1	0	0	0
Not dialyzable	1	1	1	2	0	1	0	0	1

PK, Pharmacokinetics; TK, Toxicokinetics; HD, Hemodialysis; CHP, Charcoal hemoperfusion; RHP, Resin Hemoperfusion; PD, Peritoneal dialysis; CRRT, Continuous renal replacement therapy; ET, Exchange transfusion; LST, Liver support therapy; SLED, Sustained low-efficiency dialysis.

*Patients who received more than 1 ECTR may appear at more than 1 place.

The data for other methylxanthines also appear to support a “dialyzable” grading: over 30% of administered dyphylline (dihydroxypropyltheophylline) is removed over 6 h during hemodialysis, doubling the body’s endogenous clearance.¹⁷³ In 2 cases of caffeine poisoning, hemoperfusion reduced caffeine half-life by approximately 50%.^{162,164} Metabolites of theophylline such as 1,3-dimethyluric acid, 3-methylxanthine, and 1-methyluric acid also appear to be readily removable by hemoperfusion.^{93,181}

MDAC versus ECTR

Some authors have suggested that ECTR offers little to no benefit over MDAC as a therapeutic intervention.¹⁹⁴ MDAC can enhance elimination of theophylline in therapeutic and overdose conditions,^{54,55,57,196,197} in one study of eight healthy volunteers, MDAC increased total body clearance from 36 to 73 mL/kg/hr.⁵⁴ In comparison, both hemodialysis and hemoperfusion achieve clearances that surpass 150 mL/min.

In one cohort study that was only presented in abstract form, hemoperfusion was superior to MDAC at reducing [theophylline] during the same time period.¹⁰⁸ In every study where half-life comparison was possible in the same patient, hemoperfusion or hemodialysis reduced apparent half-life more readily than during MDAC.^{73,75,89,90,94,96,114,141,147,149} In one poisoning case, theophylline clearance during hemoperfusion was at least four-fold superior than that during MDAC.¹⁴⁷ Whereas hemoperfusion and hemodialysis always reduced [theophylline] in reported patients, up to 25% of patients receiving MDAC had rising concentrations.^{51,96,141,149} When less efficient techniques were used, the contrast between MDAC and ECTR was less apparent; in one report, therapeutic plasma exchange showed a non-significant increase in elimination rate compared with that in MDAC.¹¹¹ In one caffeine-poisoned patient, the apparent half-life without treatment was 76 h, compared with 14.5 h during MDAC, and 9.1 h when both MDAC and peritoneal dialysis were administered.¹⁶³

Recommendations (Table 8)

(1) General Statement: ECTR is recommended in severe theophylline poisoning (1C)

Rationale: Theophylline poisoning is a medical emergency and is potentially life-threatening. Multiple cases of chronic sequelae and fatalities are described following or associated with seizures, dysrhythmias, hypotension, rhabdomyolysis,

or severe electrolyte disturbances. At higher concentrations, theophylline kinetics follows zero-order elimination, thereby prolonging toxicity.²² There are no antidotes to reverse toxic effects. Enhanced elimination with MDAC is often limited by intractable vomiting or ineffective at reducing the [theophylline].^{51,96} Current evidence suggests that either hemoperfusion or hemodialysis can augment total body clearance several fold^{37,66} and can also promote removal of methylxanthines from the central nervous system.³¹ The observational clinical data, albeit limited by confounders, suggest a benefit for ECTR.⁶⁵ ECTR (hemodialysis in particular) can also help correct severe metabolic derangements (acidemia and hypokalemia) and hyperthermia. With these considerations, all 28 members of the workgroup supported the use of ECTR in patients with severe theophylline poisoning (median vote = 9) and concluded that the potential clinical benefits of ECTR far outweighed its cost, complications, and uncertainties.

(2) Indications of ECTR

ECTR is recommended if

- [Theophylline] > 100 mg/L (555 μmol/L) in acute exposure (1C)
- Seizures are present (1D)
- Life-threatening dysrhythmias are present (1D)
- Shock is present (1D)
- There is a rising serum [theophylline] despite optimal therapy (1D)
- There is clinical deterioration despite optimal therapy (1D)

ECTR is suggested if

- [Theophylline] > 60 mg/L (333 μmol/L) in chronic exposure (2D)
- The patient is less than 6 months or over 60 years old and the [theophylline] > 50 mg/L (278 μmol/L) in chronic exposure (2D)
- Gastrointestinal decontamination cannot be administered (2D)

Rationale: The workgroup proposed a unified strategy for ECTR in asymptomatic patients at high risk of developing toxicity (*prophylactic ECTR*) as well as those exhibiting established complications that have high impact on morbidity (*therapeutic ECTR*).

Table 8. Executive summary of recommendations.

- 1) General Statement: ECTR is recommended in severe theophylline poisoning (1C)
- 2) Indications of ECTR
ECTR is recommended if
 - [Theophylline] > 100 mg/L (555 μ mol/L) in acute exposure (1C)
 - Seizures are present (1D)
 - Life-threatening dysrhythmias are present (1D)
 - Shock is present (1D)
 - There is a rising serum [theophylline] despite optimal therapy (1D)
 - There is clinical deterioration despite optimal therapy (1D)
 ECTR is suggested if
 - [Theophylline] > 60 mg/L (333 μ mol/L) in chronic exposure (2D)
 - The patient is < 6 months or > 60 years old and the [theophylline] > 50 mg/L (278 μ mol/L) in chronic exposure (2D)
 - Gastrointestinal decontamination cannot be administered (2D)
- 3) Cessation of ECTR:
 - Cessation of ECTR is recommended when clinical improvement is apparent OR the [theophylline] < 15 mg/L (83 μ mol/L) (1D)
- 4) Choice of ECTR:
 - Intermittent hemodialysis is the preferred recommended ECTR (1C)
 - The following are acceptable alternatives if hemodialysis is not available
 - Hemoperfusion (1C)
 - CRRT (3D)
 - Exchange transfusion is an alternative to hemodialysis in neonates (2D)
- 5) Miscellaneous: MDAC should be continued during ECTR (1D)

Despite some uncertainties, a high [theophylline], independent of symptoms, is a recognized marker of toxicity, especially after an acute exposure;^{34,36–45,51,147,198–201} in this setting, a concentration over 80–100 mg/L (444–555 μ mol/L) appears highly predictive of morbidity and identifies the patients who might most benefit from ECTR.^{36,37,40,44,65,199,200} Above this, severe dysrhythmias,^{37,40,199} seizures,^{37,40,65,199,200} and hypotension⁴⁰ are likely, although there are rare reports of patients surviving with a [theophylline] as high as 300 mg/L (1665 μ mol/L) with supportive care alone.¹⁸²

At a given [theophylline], higher morbidity is observed in chronic toxicity than in acute poisoning,^{33,37} although concentrations are less prognostic in chronic toxicity: some studies have found a correlation,^{39,40} while others have not.^{33,44,46–48} Although further study is needed to identify who might most benefit from ECTR with chronic poisoning, it was deemed reasonable to suggest ECTR with the understanding that some patients might be overtreated and that this criteria will not identify all patients at risk. The workgroup agreed for a cut-off of 60 mg/L (333 μ mol/L) in chronic toxicity.⁴⁰ Because of the poorer correlation with outcome, this only achieved a 2D suggestion.

Some studies that were not able to show any correlation between [theophylline] and outcome were either underpowered, did not distinguish acute from chronic poisonings, or included patients with lower [theophylline].^{22,46–48,201} For example, the highest [theophylline] reported by Aitken et al. was only 76 mg/L (422 μ mol/L).⁴⁷ In one pediatric cohort, no mortality or sequelae were observed; however, the mean [theophylline] was only 62 mg/L (344 μ mol/L), and the 2 patients having the highest concentration actually received ECTR.⁴⁸

Although a high [theophylline] seems to correlate with acute toxicity, this alone cannot always identify the sickest patients who might have a protracted or a dire prognosis.⁴⁷ For example, seizures may occur at a wide range of [theophylline].^{43,47,198} The workgroup also considered that the presence of certain symptoms was either life-threatening by itself or prognostic of a poor outcome, irrespective of [theophylline], and necessitated the use of ECTR as part of the general management. Of these, intractable seizures,^{13,40} life-threatening dysrhythmias,⁴⁰ and shock¹³ were all recommended indications for ECTR. Theophylline-induced seizures were associated with higher mortality in certain cohorts, sometimes up to 50%,^{13,43,44,200} although the outcome after seizures appears better in children and healthy adults.^{198,199,202}

Similarly, because in chronic exposures patients with extremes of age (< 6 months or > 60 years) are more susceptible to toxicity,^{33,37,198} age should lower the decision threshold for ECTR to > 50 mg/L (278 μ mol/L). In those less than 6 months of age, increased toxicity is likely due to a prolonged half-life because of reduced biotransformation. Not surprisingly, patients who deteriorate or have rising concentrations despite maximal supportive therapy require ECTR; several patients in the literature had an increasing [theophylline] despite MDAC.^{51,96} In patients who cannot tolerate MDAC, especially those after an acute ingestion of long-acting theophylline preparation, ECTR is recommended.

The workgroup acknowledged that the decision to institute ECTR should not be based on an ingestion quantity alone, as this criterion was too unreliable. However, a suspected history of massive theophylline ingestion warrants recognition

that ECTR may become needed and early communication with a center that can perform ECTR is encouraged.²⁰³

(3) Cessation of ECTR:

- Cessation of ECTR is recommended when clinical improvement is apparent OR the [theophylline] is < 15 mg/L (83 μ mol/L) (1D)

Rationale: The workgroup felt that once the [theophylline] fell to within the therapeutic range, most if not all of toxic symptoms would have disappeared; in several studies, no toxicity was observed when the [theophylline] was < 15 mg/L (83 μ mol/L).^{39,42,43,45} It was also considered safe to discontinue ECTR when clinical improvement is apparent. Following ECTR, the [theophylline] may rebound due to redistribution from red blood cells and deeper compartments. Although the extent of this rebound can reach 30%, this rarely causes clinical concern,⁶⁶ unless it is caused by ongoing absorption in which case either a prolonged or a repeat treatment with ECTR may be needed.²⁰⁴ Close observation of patients following ECTR is indicated.

(4) Choice of ECTR:

- Intermittent hemodialysis is the preferred ECTR (1C)
- The following are acceptable alternatives if hemodialysis is not available:
 - Hemoperfusion (1C)
 - CRRT (3D)
 - Exchange transfusion is an adequate alternative to hemodialysis in neonates (2D)

Rationale: As shown in Table 6, the greatest theophylline clearance is obtained via charcoal hemoperfusion. Theophylline poisoning was once the most common reason for hemoperfusion use in the US.²⁰⁵ With the advent of new high-efficiency filters, better performing catheters, and higher achievable blood flow rates, the clearances achievable with hemodialysis now rival those with hemoperfusion.^{206,207} In one comparative cohort study published in 1997 (when most of the latest improvements in hemodialysis technology were not implemented),⁶⁷ both the theophylline clearance and half-life statistically favored hemoperfusion over hemodialysis. However, this did not translate into a clinical benefit and was compounded by a statistically significant higher complication rate during hemoperfusion.

The marginal kinetic benefit of charcoal hemoperfusion, which remains debatable with more recent data, is outweighed by its higher incidence of complications (which were occasionally severe),⁶⁷ higher cost,^{201,208} lower availability,²⁰⁹ and presence of column saturation which can be rapid with either resin or charcoal adsorbents.^{97,126,136,138,145,201}

The data are more limited for CRRT, but in general CRRT is associated with a lower clearance rate than hemodialysis¹⁵⁶ and should only be offered if hemodialysis is not available or feasible. Other ECTRs such as peritoneal dialysis, liver support therapies and therapeutic plasma exchange do not offer any specific advantage over hemodialysis or hemoperfusion²¹⁰

and were not recommended by the workgroup. Because of the low V_D of theophylline, exchange transfusion was recognized as a useful alternative to hemodialysis in newborns as this technique is relatively simpler to perform in this population.

(5) Miscellaneous: MDAC should be continued during ECTR (1D)

Rationale: MDAC may enhance elimination of theophylline,⁵⁴ may prevent on-going absorption from modified-release preparations, and thereby may reduce overall toxicity in theophylline-poisoned patients. MDAC is currently recommended for these indications by various toxicology societies.⁵³ The workgroup supported MDAC during ECTR in patients with no contraindications to its use. Its toxicokinetic effect would likely be additive to ECTR.

Conclusion

Here, the EXTRIP workgroup presents its recommendations for ECTRs in theophylline poisoning. Evidence suggests that theophylline is readily dialyzable and that enhancing elimination with hemodialysis or hemoperfusion is superior to MDAC. In severe cases, the group unanimously supported the use of ECTR and felt that the advantages largely outweighed costs and risks associated with the use of ECTR, despite the paucity of robust clinical studies.

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Declaration of interest

The authors declare that they have no conflict of interest financial or otherwise related to this work. Complete financial disclosure for each EXTRIP member can be found on www.extrip-workgroup.org.

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