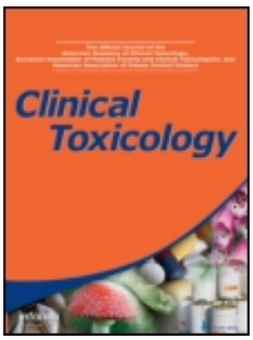

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CRITICAL CARE

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

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Background. The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup presents its systematic review and clinical recommendations on the use of extracorporeal treatment (ECTR) in valproic acid (VPA) poisoning. *Methods.* The lead authors reviewed all of the articles from a systematic literature search, extracted the data, summarized the key findings, and proposed structured voting statements following a predetermined 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 in person. A second vote was conducted to determine the final workgroup recommendations. *Results.* The latest literature search conducted in November 2014 retrieved a total of 79 articles for final qualitative analysis, including one observational study, one uncontrolled cohort study with aggregate analysis, 70 case reports and case series, and 7 pharmacokinetic studies, yielding a very low quality of evidence for all recommendations. Clinical data were reported for 82 overdose patients while pharmaco/toxicokinetic grading was performed in 55 patients. The workgroup concluded that VPA is moderately dialyzable (level of evidence = B) and made the following recommendations: ECTR is recommended in severe VPA poisoning (1D); recommendations for ECTR include a VPA concentration > 1300 mg/L (9000 µmol/L)(1D), the presence of cerebral edema (1D) or shock (1D); suggestions for ECTR include a VPA concentration > 900 mg/L (6250 µmol/L)(2D), coma or respiratory depression requiring mechanical ventilation (2D), acute hyperammonemia (2D), or pH ≤ 7.10 (2D). Cessation of ECTR is indicated when clinical improvement is apparent (1D) or the serum VPA concentration is between 50 and 100 mg/L (350–700 µmol/L)(2D). Intermittent hemodialysis is the preferred ECTR in VPA poisoning (1D). If hemodialysis is not available, then intermittent hemoperfusion (1D) or continuous renal replacement therapy (2D) is an acceptable alternative. *Conclusions*. VPA is moderately dialyzable in the setting of overdose. ECTR is indicated for VPA poisoning if at least one of the above criteria is present. Intermittent hemodialysis is the preferred ECTR modality in VPA poisoning.

Keywords Anticonvulsant; Extracoporeal treatments; Poisoning; Recommendations; Valproic acid

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Introduction

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Table 1) who were assembled to provide recommendations on the use of extracorporeal treatment (ECTR) in poisoning (www.extrip-workgroup.org). The rationale, background, objectives, methodology, and first recommendations were reported previously.[1–10] Here, the workgroup presents a systematic review and recommendations for ECTR in valproic acid (VPA) 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 Toxicologist	Spanish Clinical Toxicology Foundation

Pharmacology and toxicokinetics

VPA is widely used in the treatment of partial and generalized seizure disorders. Given its favorable safety profile and large therapeutic index, VPA is also commonly used for the management of bipolar disorder as well as for migraine prophylaxis. As a result, intentional and unintentional VPA overdoses are common. In 2013, the American Association of Poison Control Centers' National Poison Data System recorded a total of 7776 cases including VPA, of which 2923 were single exposures, including 65 cases of major toxicity and 2 deaths.[11]

VPA has a small molecular mass of 144 Da. The time to reach peak plasma concentrations (Tmax) is 1–4 h during normal therapeutic dosing,[12] but may be prolonged to more than 7 h in overdose.[13] Divalproex sodium is a complex molecule that dissociates to VPA in the gastrointestinal tract with the potential for delayed peak plasma concentrations. VPA has a small volume of distribution (0.1–0.5 L/Kg) and exhibits saturable plasma protein binding; although at therapeutic concentrations (< 100 mg/L), VPA is 94% protein bound, protein binding decreases to as low as 15% as concentrations rise to greater than 1000 mg/L.[14] The corresponding increase in the active fraction of free (unbound) drug likely leads to greater clinical toxicity (Table 2).

Table 2. VPA: Physical and TK properties.

Molecular mass	144 D
Volume of distribution	0.1–0.5 L/kg
Protein binding	Variable 94% at therapeutic concentration 15% when [VPA] > 1000 mg/L
Oral bioavailability	68–100%
Elimination half-life (therapeutic)	12 h
Endogenous clearance	5–10 mL/min
Conversion factor	1 mg/L = 6.94 μmol/L
Therapeutic range	50–100 mg/L (347–694 μmol/L)
Toxic exposure	> 200 mg/kg
Lethal exposure	> 1000 mg/kg

The drug is primarily metabolized in the liver by glucuronide conjugation and to a lesser extent by mitochondrial β-oxidation and cytosolic ω-oxidation. Cytosolic ω-oxidation of VPA may lead to the production of toxic metabolites such as 4-en-valproate.[15] Only a small proportion (< 3% of an administered dose) of VPA is excreted unchanged in the urine.[16] The endogenous plasma clearance of VPA is 5–10 mL/min,[12] and its elimination half-life is approximately 12 h at therapeutic concentrations, but increases to more than 30 h in overdose.[17,18]

Valproic acid poisoning

Careful clinical assessment and objective evaluation of the severity of poisoning are necessary in considering whether patients with VPA poisoning may benefit from therapeutic interventions such as ECTR.

Serum VPA concentrations can be useful in establishing the severity of poisoning. Concentrations between 50 and 100 mg/L (350–700 μmol/L) are considered therapeutic. In overdose, central nervous system depression is the most common clinical manifestation of VPA poisoning. Ataxia, sedation, and lethargy commonly occur in mild poisoning with ingestions around 200 mg/kg.[19] At ingestions of 400 mg/kg or more, severe VPA poisoning is associated with coma and respiratory depression requiring mechanical ventilation, cerebral edema, hemodynamic instability, and shock that may lead to a fatal outcome.[19] Laboratory abnormalities reported during severe poisoning include hypernatremia, hypocalcemia, thrombocytopenia, evidence of impaired mitochondrial function (i.e., metabolic acidosis and hyperlactatemia), and hyperammonemia which is thought to play a role in the pathogenesis of cerebral edema.[15] In a prospective, multicenter case series, a serum VPA concentration of more than 450 mg/L (3125 μmol/L) was more likely to be associated with a moderate or major adverse outcome and a hospital stay of more than 48 h; a concentration of more than

Table 3. Strength of recommendation and level of evidence scale 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*

850 mg/L (5900 μmol/L) was more likely to be associated with coma and metabolic acidosis.[13]

Cases of VPA poisoning can often be managed with proactive care alone. Initial attention should be directed to the need for airway protection and cardiovascular stabilization. Patients presenting with a recent VPA ingestion may benefit from gastrointestinal decontamination with single-dose activated charcoal. The use of multiple-dose activated charcoal (MDAC) in the treatment of VPA poisoning is not currently recommended.[20]

L-carnitine is proposed as an antidote for VPA poisoning. It is postulated that L-carnitine depletion may impair the mitochondrial transportation and β-oxidation of VPA, favor the production of toxic metabolites, and contribute to the development of hyperammonemia. L-carnitine supplementation may increase mitochondrial β-oxidation and thus limit cytosolic ω-oxidation and the production of toxic metabolites.[21] L-carnitine is commonly recommended in patients with VPA toxicity and hyperammonemic encephalopathy.[22] However, evidence supporting the use of L-carnitine as an antidote for VPA poisoning is limited.[23,24]

Acute VPA toxicity should be differentiated from valproate-induced hyperammonemic encephalopathy, which may exhibit clinical characteristics similar to mild VPA overdose but is characterized by elevated ammonia concentrations in the setting of VPA concentrations within or near the therapeutic range.[25]

Although reports of ECTR for severe VPA poisoning are published, there is no current consensus on the indications for ECTR and on the most effective modality for VPA removal.[16] References suggest ECTR for severe VPA toxicity manifesting with seizures or refractory hypotension,[26] or with massive ingestions of 1 g/kg or more, rapid deterioration, hemodynamic instability, hepatic dysfunction, cerebral edema, and high serum concentrations of 850 mg/L (5450 μmol/L).[27,28]

Methods

A predetermined methodology, incorporating guidelines from the Appraisal of Guidelines for Research and Evaluation (AGREE)[29] and Grading of Recommendations Assessment, Development and Evaluation (GRADE),[30] was used and 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 as follows:

[(valpro*) AND (dialysis OR hemodialysis OR haemodialysis OR hemoperfusion OR haemoperfusion OR

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

[A]Applicable to all modalities of ECTR, including hemodialysis, hemoperfusion, and hemofiltration.
[B]Corresponds to % removal of ingested dose or total body burden in a 6-hour ECTR period.
[C]Measured during the same period of time.
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 not clinically relevant). Furthermore, the primary criteria are preferred for poisons having a large Vd (> 5 L/Kg).
Reproduced with permission from Lavergne V, Nolin TD, Hoffman RS, et al. The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: Guideline methodology. Clin Toxicol 2012; 50:403–413.

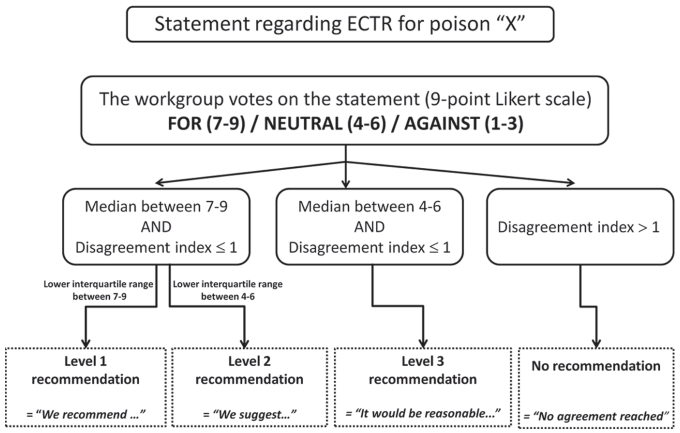

Fig. 1. Delphi method (2 rounds) for each recommendation.

plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR extracorporeal therapy OR CRRT)]. As mentioned, cases of valproate-induced hyperammonemia with a VPA concentration within the therapeutic range (< 100 mg/L) were excluded from the clinical analysis (as ECTR is performed to remove excess ammonia rather than VPA) but could be included in the pharmacokinetic/toxicokinetic (PK/TK) analysis.

A manual search of conference proceedings of the European Association of Poison 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 subgroup and epidemiologist determined the level of evidence assigned to each clinical recommendation (Table 3). Dialyzability was determined based on criteria listed in Table 4. The potential benefit of the procedure was weighed against its cost, availability, alternative treatments, and its related complications. All of this information was submitted to the entire workgroup for consideration, along with structured voting statements based on a predetermined format.

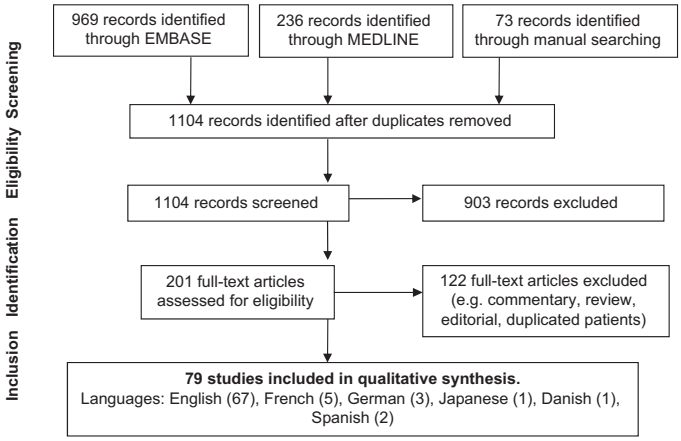

Fig. 2. Flow diagram for literature search (November 15, 2014).

The strength of recommendations was evaluated by a two-round modified Delphi method for each proposed voting statement (Fig. 1) and RAND/UCLA Appropriateness Method was used to quantify disagreement between participants.[31] Anonymous votes with comments were sent to the epidemiologist who then compiled and returned them to each participant. The workgroup met in person to exchange ideas and debate statements. A second vote was subsequently submitted and these results were used in developing the core EXTRIP recommendations. The literature search was updated on November 15, 2014 following the above-mentioned methodology; the new articles and summarized data were submitted to every participant who then updated their votes.

Results

The search strategy performed on November 15, 2014 retrieved 1104 citations. After duplicates and articles without original data were removed 79 articles were accepted in the final analysis, including 1 observational study,[32] 1 uncontrolled cohort with aggregate results,[13] 70 case reports or case series,[14,17,18,33–99] and 7 pharmacokinetic studies (i.e., when VPA concentration is therapeutic) (Fig. 2).[100–106] Patient-level data were available for clinical analysis in 82 patients (Supplementary Table 1 to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1035441) and for PK/TK grading in 55 patients. (Supplementary Table 2 to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1035441).

Clinical analysis

One observational study was identified which included patients admitted with a VPA concentration over 100 mg/L (694 μmol/L);[32] the group that received ECTR ($n = 6$) was compared with the one that did not ($n = 26$). Although all patients survived with complete neurological recovery, the ECTR group appeared to be more severely ill (i.e., significantly higher peak VPA concentration, treated more often with activated charcoal, and requiring intensive care admission, mechanical ventilation, and vasopressors more frequently) which suggests the presence of confounding-by-indication. The conclusion could be either inferred as a benefit of ECTR or an absence of effect, an interpretation which is further limited by a lack of power. Since the remainder of the clinical evidence is solely composed of case reports, the level of evidence can be considered very low.

Individual patient-level data were extracted from 82 patients (excluding 7 patients presented from an uncontrolled observational cohort where data could not be extracted) and presented in Supplementary Table 1 to be found at online http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1035441. Aggregate data from all reported cases are presented in Table 5. Most reported poisonings involved regular-release VPA. The mean reported ingestion and VPA concentration were 39.8 g and 975 mg/L, respectively, both over the thresholds accepted to cause severe toxicity.[13,19] The most commonly reported signs and symptoms were a decrease in consciousness followed by respiratory depression, hypoten-

Table 5. Clinical data related to the 82 reported patients that received ECTR for VPA toxicity.*

Demographics	Average age (years)	27.9 (range: 0.2–62)
	% Male	36.5%
Poisoning exposure	Form	
	Modified-release VPA	25.6%
	Regular-release VPA	74.4%
	Mean number of co-ingestants	0.6 (range: 0–6)
	Mean acute VPA ingestion (grams)	39.8 (range: 4–160)
	Mean VPA peak concentration (mg/L)	974.5 (range: 132–2493)
	Delay between acute exposure and admission (hours)	5.0 (1–24)
Symptoms and signs**	Decreased consciousness	96.3%
	Seizure(s)	11.0%
	Metabolic acidosis	28.0%
	Elevated lactate	23.2%
	Respiratory depression	65.9%
	Peak ammonia concentration (μmol/L)	319.4 (range: 30–1052)
	Cerebral edema	7.3%
	Thrombocytopenia	14.6%
	Hypotension	39.0%
	Hypernatremia	4.9%
Other treatments administered	AC	58.5%
	MDAC	11.0%
	Mechanical ventilation	62.2%
	L-carnitine	25.6%
	Vasopressors	23.2%
Extracorporeal treatments	Mean time from admission to ECTR initiation (hours)	13.3 (range: 2–48)
	Hemodialysis	45.1%
	Hemoperfusion	12.2%
	CRRT	14.6%
	Hemoperfusion–hemodialysis in series	7.3%
	Therapeutic plasma exchange	1.2%
	Liver support therapy	2.4%
	Other	3.7%
	More than 1 ECTR	10.9%
Outcome	Death	0%***

VPA, valproic acid; ECTR, extracorporeal treatments; AC, activated charcoal; MDAC, multiple-dose activated charcoal.
*These only include cases in which patient data could be extracted.
**Symptoms and other treatments were often underreported in case reports, so the real incidence is likely higher.
***2 deaths were reported in the cohort from Spiller et al, but there were none from reported cases.

sion, and metabolic acidosis. When reported, ammonia was almost always over the accepted normal range (> 30 μmol/L). Most patients required mechanical ventilation. Hemodialysis was by far the most commonly reported ECTR. The use of ECTR was associated with clinical improvement in the majority of cases with regard to mental status, respiratory depression, and hemodynamics; in some cases, especially when hemoperfusion or hemodialysis was used, this improvement was dramatic.[38,44,47,56,57,61,64,71,82,83,89,90,95,97,99] The use of continuous renal replacement therapy (CRRT) was often associated with slower clinical improvement over a period of days.[34,48,62] The timing of ECTR may also play an important role; clinical improvement was noted to occur faster when ECTR was used within 24 h of admission. Two fatalities were described, both in the cohort reported by Spiller et al.[13] VPA concentrations were over 1200 mg/L in both cases and hemodialysis was began more than 24 h after the onset of serious toxicity.

Complications associated with ECTR

Although rare, both procedural hypotension[32,56,82] and hemoperfusion-associated thrombocytopenia[32,33,47,53,81,85] were reported; however, it is difficult to determine if these were related to the ECTR or VPA toxicity itself. In one case, thrombocytopenia contributed to a hematoma from the insertion of a vascular access, which required platelet transfusion.[47] In another report, massive hemolysis and acute kidney injury (AKI) were reported during hemoperfusion when the prescribed blood flow exceeded the recommended flow.[85] Other complications specific to VPA may include withdrawal seizures in an epileptic patient if the VPA concentration falls below the therapeutic range[104] and possibly increasing intracranial pressure during ECTR in a patient with or at risk of cerebral edema.[107–110] There is also a theoretical concern of potential dialyzability of L-carnitine. No data were found to quantify the removal of L-carnitine that is administered during ECTR for poisoning; however, L-carnitine is reported to be extensively cleared during hemodialysis sessions when given in supplementation doses.[111–113]

Dialyzability

The elimination of VPA is neither enhanced by urine alkalinization nor by MDAC in animals,[114] human volunteers,[115] or poisoned patients,[116] and is not currently supported by the latest position statements.[20] Because of its small molecular mass, low endogenous clearance, and small volume of

distribution, VPA would appear to be readily removable by most ECTRs were it not for its high protein binding at therapeutic concentration. This is confirmed by a low sieving coefficient[117] and a relatively low extraction ratio through filters and columns at low VPA concentrations.[17] However, in situations such as uremia and overdose, the protein binding sites for VPA decrease[103] or saturate, thereby increasing the fraction of unbound drug, rendering it more amenable to extracorporeal removal; despite using outdated dialysis parameters, approximately 20% of a therapeutic VPA dose was recovered in four uremic patients during a 4-hour hemodialysis, when protein binding was 70%.[102]

In overdose, the extent of protein binding decreases further so the magnitude of the ECTR effect becomes greater, as is confirmed by the literature review; VPA clearance during dialysis is greater in overdose than at therapeutic dose (median: 87 vs. 22 mL/min, respectively). After intentional poisoning, three different reports quantified that over 10 g were recovered during a standard dialysis session.[18,61,67]

Although the data are limited, intermittent convective techniques (online hemodiafiltration) appear equally efficient to diffusive techniques (Table 6); median VPA clearances for both intermittent hemodialysis and hemodiafiltration reach 90 mL/min with identical apparent half-lives.[44,76] These are both superior to adsorptive-based hemoperfusion, which is often limited by extensive cartridge saturation[17,53] and vastly superior to native endogenous clearance (5–10 mL/min).[12,61,76]

As expected by their lower blood flow and/or effluent flow, low-efficiency techniques such as CRRT therapies provide clearances (≅10–15 mL/min) that are considerably lower than high-flux dialysis. This is also the case for peritoneal dialysis. In every reported patient who received more than 1 type of ECTR, hemodialysis always resulted in a higher VPA clearance and/or a shorter apparent VPA half-life than other ECTRs.[17,33,36,62,67,69,95]

While the addition of albumin in the dialysate may enhance clearance of VPA,[118] it remains unclear if it would show any superiority to traditional hemodialysis in overdose. Both liver support therapies and therapeutic plasma exchange are specifically suited for protein-bound poisons, so they would not be particularly useful in VPA overdose, during which most of the drug is not protein bound. Even at therapeutic concentration, removal of VPA was inconsequential during therapeutic plasma exchange.[101]

In the majority of cases, the evidence for dialyzability is based on half-life comparison during and off ECTR. This evidence is further strengthened by articles that quantified removal via effluent or extruded column.[18,58,61,64,67,96] According to the dialyzability criteria in Table 4, most of the cases that underwent an ECTR session (especially hemoperfusion or hemodialysis) would qualify as either "dialyzable" or "moderately dialyzable" (Table 7). The workgroup agreed with the conservative assessment that VPA was MODERATELY DIALYZABLE (Level of evidence = B). The dialyzability of VPA metabolites requires confirmation by further studies but appears to be substantial.[105]

Dialyzability of ammonia

Hyperammonemia often complicates VPA poisoning and may contribute to cerebral edema. Because ammonia distributes in total body water, hemodialysis appears to be the most efficient way to remove ammonia,[119,120] and is superior to continuous techniques or peritoneal dialysis in this regard.[121,122] The addition of convection to diffusion is promising to facilitate ammonia removal, but requires further study.[123] Because of its similar molecular size and distribution, ammonia clearance would likely approach that of urea.[124] Similar to urea, the optimization of blood flow, dialysate flow, and increasing the surface area of the filter will provide improved dialytic clearance,[125] as will increasing ultrafiltration flow during convection.[124]

Table 6. Kinetic aggregates of clearance and half-life for ECTR.

	ECTR clearance (mL/min)			$T_{1/2}$ (hours)		
Type of ECTR	Median	Range	*N*	Median	Range	*N*
Endogenous (therapeutic)	*5–10*			*12*		
CRRT*	11.0	1.8–23.9	3	9.6	3.2–16.1	14
HD (therapeutic)	22.4	17.7–29.6	4	9.1	5–19.9	5
HD (overdose)	87.5	51.4–140	7	2.5	1.3–8.2	32
PD (therapeutic)	0.7		1	17.8	8.4–27.2	2
PD (overdose)				21.9		1
SLEDD-f				6.2		1
TPE (therapeutic)	18.3	17.1–19.4	2	3.2	2.1–4.2	2
LST	88.3		1	4.9		1
HD–HP	60.5	28.5–80.1	5	3.7	1.7–24.5	8
HDF	93.0		1	2.2	2.2–4.6	3
HP	29.2		1	3.4	0.7–9.2	9
HP–CRRT				3.9		1

PK, Pharmacokinetics; TK, Toxicokinetics; HD, Hemodialysis; CRRT, Continuous renal replacement therapy; HP, Hemoperfusion; TPE, Therapeutic plasma exchange; HP–HD, Hemoperfusion and hemodialysis in series; PD, Peritoneal dialysis; HDF, Intermittent hemodiafiltration; LST, Liver support therapy; SLEDD-f, Sustained low-efficiency daily dialysis and filtration; CAVH, continuous arterio-venous hemofiltration; CAVHD, continuous arterio-venous hemodialysis; CAVHDF, continuous arterio-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemofiltration with dialysis; CVVHDF, continuous veno-venous hemodiafiltration.
*CRRT includes CAVH, CAVHD, CAVHDF, CVVH, CVVHD, and CVVHDF.

Recommendations: A summary of recommendations is presented in Table 8

(1) General Statement: ECTR is recommended in severe VPA poisoning (1D)

Rationale: Although most patients presenting with a voluntary VPA overdose will have a relatively benign clinical course and a good outcome, some will develop life-threatening conditions that may be associated with prolonged coma, respiratory depression requiring mechanical ventilation, cerebral edema, hemodynamic instability, and severe metabolic acidosis. Limited published clinical evidence exists supporting the clinical efficacy of L-carnitine as an antidote, and there is no benefit to either MDAC or urinary alkalinization.

Table 7. Summary of the kinetic grading for individual patients.

GRADING	HD	CRRT*	HP	TPE	HP–HD	PD	HDF	LST	SLEDD-f
TK articles									
D = Dialyzable	14	2	3		4		2	1	
MD = Moderately dialyzable	9	4	2						1
SD = Slightly dialyzable	1	2	2		1				
ND = Not dialyzable		3				1			
PK articles									
D = Dialyzable	2								
MD = Moderately dialyzable	2			1		1			
SD = Slightly dialyzable				1					
ND = Not dialyzable					1	1			

PK, Pharmacokinetics; TK, Toxicokinetics; HD, Hemodialysis; CRRT, Continuous renal replacement therapy; HP, Hemoperfusion; TPE, Therapeutic plasma exchange; HP–HD, Hemoperfusion and hemodialysis in series; PD, Peritoneal dialysis; HDF, Intermittent hemodiafiltration; LST, Liver support therapy; SLEDD-f, Sustained low-efficiency daily dialysis and filtration; CAVH, continuous arterio-venous hemofiltration; CAVHD, continuous arterio-venous hemodialysis; CAVHDF, continuous arterio-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemofiltration with dialysis; CVVHDF, continuous veno-venous hemodiafiltration.
*CRRT includes CAVH, CAVHD, CAVHDF, CVVH, CVVHD, and CVVHDF.

The evidence supporting ECTR in VPA poisoning is composed of one observational study with major limitations and case reports and case series, with absent control groups and possible publication bias. The workgroup considered the following issues in evaluating the potential benefit of ECTR in VPA poisoning: both hemodialysis and hemoperfusion significantly enhance endogenous elimination of VPA and the use of high-efficiency ECTR is associated with rapid clinical improvement in the majority of published cases. ECTR may reduce the duration of coma and the requirement for mechanical ventilation, and prevent the development of cerebral edema. ECTR (especially hemodialysis) corrects acidemia and readily eliminates ammonia. The reported complications associated with hemodialysis are uncommon and the cost of performing ECTR may be balanced by a reduction in duration of coma and length of stay in an intensive care unit. Based on these arguments, the workgroup reached a consensus that the balance of risk versus benefit supports the use of ECTR in severe VPA poisoning and was strongly supported by the workgroup (27/28 participants voted between 7 and 9, median vote = 8).

(2) Indications for ECTR

ECTR is recommended for VPA poisoning if ANY of the following is present:

- Serum VPA concentration > 1300 mg/L (9000 µmol/L) (1D)
- Cerebral edema (1D) or shock (1D), attributed to VPA toxicity

ECTR is suggested for VPA poisoning if ANY of the following is present:

- Serum VPA concentration > 900 mg/L (6250 µmol/L) (2D)
- Coma or respiratory depression requiring mechanical ventilation (2D)
- Acute hyperammonemia (2D)
- pH is ≤ 7.10 (2D)

Rationale: Serum VPA concentrations may be helpful in evaluating the severity of poisoning. As concentration increases, protein binding becomes saturated, increasing the amount of free drug entering the central nervous system. A serum concentration of > 450 mg/L (3125 µmol/L) is associated with a moderate or major adverse outcome and > 850 mg/L (5900 µmol/L) is associated with coma and metabolic acidosis.[13] This cutoff is reflected by the conclusions reached by the workgroup, and ECTR is suggested with a serum concentration > 900 mg/L (6250 µmol/L) (2D) and recommended when > 1300 mg/L (9000 µmol/L) (1D).

Coma, respiratory depression requiring mechanical ventilation, hemodynamic instability and metabolic acidosis are considered manifestations of severe VPA poisoning and may be associated with a higher risk of complications and morbidity. Severe VPA poisoning can lead to cerebral edema, which can be fatal. The etiology of cerebral edema related to VPA poisoning is controversial. It may be attributed to VPA, to one of its metabolites (such as 2-en-VPA and 4-en-VPA), or to hyperammonemia.[126] Given the potential consequences of cerebral edema, the workgroup recommended the use of ECTR in the presence of cerebral edema associated with VPA poisoning. Although shock is often quoted as a contraindication to ECTR, it was acknowledged that this was likely induced by VPA and its metabolites and might therefore be corrected by prompt initiation of extracorporeal removal. It was considered unlikely that hypotension would be exacerbated by ECTR if no net ultrafiltration was prescribed.

Acute hyperammonemia plays an important role in the pathogenesis of encephalopathy and brain edema that occurs in fulminant liver failure of many etiologies. Ammonia crosses the blood–brain barrier and increases extracellular concentrations of glutamate in the brain, which leads to N-methyl-D-aspartate (NMDA) receptor activation.[23] Hyperammonemia is efficiently corrected by hemodialysis, and rapid lowering of serum ammonia may help reverse encephalopathy.[125] VPA-associated hyperammonemia and encephalopathy can occur both chronically with therapeutic use and acutely in overdose, which may lead in the latter

Table 8. Executive summary of recommendations.

General Recommendation
ECTR is recommended in severe VPA poisoning (1D)
Indications
ECTR is recommended if any of the following is present:
If the [VPA] is > 1300 mg/L (9000 µmol/L) (1D)
If shock is present (1D)
If cerebral edema is present (1D)
ECTR is suggested if any of the following is present:
If the [VPA] is > 900 mg/L (6250 µmol/L) (2D)
If coma or respiratory depression requiring mechanical ventilation is present (2D)
If acute hyperammonemia is present (2D)
If pH is ≤ 7.10 (2D)
Cessation of ECTR is indicated if any of the following is present:
Clinical improvement is apparent (1D)
[VPA] is between 50 and 100 mg/L (350–700 µmol/L) (2D)
Choice of ECTR
Intermittent hemodialysis is the preferred ECTR in VPA poisoning (1D)
If hemodialysis is not available, both intermittent hemoperfusion (1D) and CRRT (2D) are acceptable alternatives

VPA, valproic acid; ECTRs, extracorporeal treatments; CRRTs, continuous renal replacements therapies.

case to cerebral edema and a fatal outcome. The best therapeutic approach for acute hyperammonemia associated with severe VPA poisoning remains unknown. The workgroup concluded that ECTR is indicated with acute hyperammonemia in the context of severe VPA poisoning, although it declined to set a specific value for ECTR initiation. It is also acknowledged that, in this context, the entire spectrum of clinical manifestations will usually be considered. Since the focus of EXTRIP is on toxin removal, the workgroup did not specifically consider the question of the best treatment for patients with hyperammonemia in the setting of therapeutic VPA concentrations.

L-carnitine is commonly recommended initially for the treatment of VPA-associated hyperammonemia, but clinical evidence supporting this indication is limited and it is unclear if L-carnitine has any impact on the clinical manifestations of severe VPA poisoning.[22–24] The benefits of intravenous L-carnitine administration during HD are unknown, especially when considering that L-carnitine is dialyzable.[112]

The reported amount of VPA ingested was not considered a reliable indicator by the workgroup since estimates of the ingested dose may be inaccurate and would not alone justify the potential risks associated with ECTR or the costs associated with transferring a patient to an ECTR center. Therefore, the decision to perform ECTR should not be based on history of ingestion alone but would warrant close monitoring when massive, as indications for ECTR may develop.

(3) Cessation of ECTR

ECTR should be continued until clinical improvement is apparent (1D) OR until the serum VPA concentration is between 50 and 100 mg/L (350–700 µmol/L) (2D).

Rationale: Cessation of ECTR should be based on appropriate correction of the manifestations of severe poisoning such as coma, acidemia, respiratory depression, and hemodynamic instability. This approach may not be applicable to patients with mixed ingestions of sedative drugs not removed by ECTR. Alternatively, ECTR should be continued until serum VPA concentration reaches the therapeutic range (between 50 and 100 mg/L (350 and 700 µmol/L)). This approach may prevent further toxicity, and minimize the risk of withdrawal seizures in a patient requiring VPA.[104] The concentration of VPA may increase ("rebound") after high-efficiency ECTRs, a phenomenon most often caused by redistribution from deeper compartments into the plasma. Although this was often reported,[18,32–34,56,61,62,64,76] the extent of the rebound was invariably minimal and not associated with clinical deterioration. If concerning, rebound could be simply addressed with a second ECTR session.

(4) Choice of ECTR

- Intermittent hemodialysis is the preferred ECTR in VPA poisoning (1D)
- If hemodialysis is not available, both intermittent hemoperfusion (1D) and CRRT (2D) are acceptable alternatives.

Rationale: Several ECTRs have been performed in patients with severe VPA poisoning, in most cases either intermittent hemodialysis, hemoperfusion, CRRTs, or a combination of these. Although the analysis may be skewed by the inclusion of obsolete ECTR parameters (low blood flow and low-flux/low-efficiency membranes), the VPA clearance appears to be most favorable for intermittent hemodialysis, with a median ECTR clearance of 88 mL/min and reaching up to 140 mL/min with modern technology and optimization of operational parameters.[69,127]

The preference of hemodialysis over other ECTR modalities is based on its higher apparent removal of VPA (Tables 6 and 7), its capacity to correct acidemia (a common finding at presentation), and its superior clearance of ammonia.[119–122] Hemodialysis is also more available worldwide, which would likely limit the transfer time for its initiation. Hemoperfusion is more costly,[128] is limited by saturation of both resin and charcoal cartridges,[129] and is fraught with a higher incidence of complications,[130] some of which may

be life-threatening.[85] Hypocalcemia or thrombocytopenia may also complicate hemoperfusion,[33,47,53,81] which may be a concern as thrombocytopenia sometimes complicates VPA toxicity.[13,131]

The workgroup agreed that hemoperfusion may be a convincing alternative in the situation where hemodialysis would not be available. The efficiency of CRRT is noticeably inferior to high-efficiency intermittent dialysis but may be considered when technical or logistic reasons for performing it preclude its use.[132] CRRT has also theoretically less impact on patients with increased intracranial pressure and may therefore be a consideration with patients with documented cerebral edema.[133] Online hemodiafiltration appears promising but requires further study. Both therapeutic plasma exchange and liver support therapies are more costly, less available, and do not appear to offer any advantage over dialysis. As in most cases of poisoning, the benefit of peritoneal dialysis is insignificant and does not justify its cost and potential for complications.[134,135] No data are currently available to evaluate the efficacy of exchange transfusion but, based on the low distribution volume of VPA, may be a consideration in neonates when other ECTRs may be technically complicated to perform.

Conclusion

Intentional overdose with VPA is a common toxicological problem. The majority of patients with VPA ingestions will have a relatively benign clinical course and a good outcome. The use of ECTR should be reserved for patients with severe VPA poisoning such as coma, respiratory depression requiring mechanical ventilation, pronounced acidemia, and high serum concentrations at which complications such as cerebral edema are expected to occur. Intermittent hemodialysis is the preferred ECTR in VPA poisoning. Hemoperfusion may represent an alternative to hemodialysis. CRRTs are associated with lower clearance rates and may be used when hemodialysis is not available. VPA is moderately dialyzable in overdose.

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Declaration of interests

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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Supplementary material available online

Supplementary Tables 1 and 2.