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Extracorporeal treatments for isoniazid poisoning: systematic review and recommendations from the Extracorporeal Treatments in Poisoning workgroup

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ABSTRACT

BACKGROUND: Isoniazid toxicity from self-poisoning or dosing errors remains common in regions of the world where tuberculosis is prevalent. Although treatment of isoniazid poisoning is centered on supportive care and pyridoxine administration, extracorporeal treatments (ECTRs), such as hemodialysis, have been advocated to enhance elimination of isoniazid. No systematic reviews or evidence-based recommendations currently exist on the benefit of ECTRs for isoniazid poisoning.

OBJECTIVES: The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup systematically collected and rated the available evidence on the effect of and indications for ECTRs in cases of isoniazid poisoning.

METHODS: We conducted a systematic review of the literature, screened studies, extracted data on study characteristics, outcomes, and measurement characteristics, summarized findings, and formulated recommendations following published EXTRIP methods.

RESULTS: Forty-three studies (two animal studies, 34 patient reports or patient series, and 7 pharmacokinetic studies) met inclusion criteria. Toxicokinetic or pharmacokinetic analysis was available for 60 patients, most treated with hemodialysis (n=38). The workgroup assessed isoniazid as “Moderately Dialyzable” by hemodialysis for patients with normal kidney function (quality of evidence = C) and “Dialyzable” by hemodialysis for patients with impaired kidney function (quality of evidence = A). Clinical data for ECTR in isoniazid poisoning were available for 40 patients. Mortality of the cohort was 12.5%. Historical controls who received modern standard care including appropriately dosed pyridoxine generally had excellent outcomes. No benefit could be extrapolated from ECTR, although there was evidence of added costs and harms related to the double lumen catheter insertion, the extracorporeal procedure itself, and extracorporeal removal of pyridoxine.

CONCLUSIONS: The EXTRIP workgroup suggests *against* performing ECTR in addition to standard care (weak recommendation, very low quality of evidence) in patients with isoniazid poisoning. If standard dose pyridoxine cannot be administered, we suggest performing ECTR only in patients with seizures refractory to $GABA_A$ receptor modulators (weak recommendation, very low quality of evidence).

Keywords: isoniazid; poisoning; extracorporeal treatment; dialysis; dialyzability; systematic review; consensus recommendations; EXTRIP

Introduction

Isoniazid is a first-line agent in the treatment of both latent and active tuberculosis. Toxicity from self-poisoning and therapeutic errors remain common, especially where tuberculosis is prevalent.[1, 2] Treatment of isoniazid poisoning is centered towards supportive care and pyridoxine. However, in severe cases, extracorporeal treatments (ECTRs) such as hemodialysis (HD) and hemoperfusion (HP) are occasionally proposed to enhance elimination of isoniazid.[3, 4]

Clinical Pharmacology and Toxicokinetics

Isoniazid is primarily used for treatment of *Mycobacterium tuberculosis* infections but also for rarer nontuberculous mycobacterial infections. Its importance is highlighted by inclusion on the World Health Organization's List of Essential Medicines.[5]

Isoniazid's physicochemical and pharmacokinetic properties are summarized in Table 1. Between 75% and 95% of isoniazid is acetylated by hepatic N-acetyltransferase-2 to acetylisoniazid and then to acetylhydrazine and by hydrolysis to isonicotinic acid and hydrazine.[6] The capacity for acetylation is genetically determined and varies among ethnic groups: 50% of Caucasians and African-Americans and 80 to 90% of Asians and native peoples of Arctic regions are rapid acetylators.[7] This genetic polymorphism results in a two- to three-fold difference in elimination half-lives (Table 1). Isoniazid half-life becomes prolonged in liver disease and kidney impairment.[8] Although a prolonged apparent isoniazid half-life has been reported in overdose [9, 10], most report values comparable to therapeutic use.[11-15]

Overview of Toxicity

Isoniazid and its metabolites inhibit pyridoxine metabolism and conversion of glutamate to gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter, while increasing glutamate concentrations, the major excitatory neurotransmitter in the central nervous system (CNS).[34, 35] Symptoms of isoniazid poisoning manifest within 1-2 hours post ingestion and are characterized by metabolic acidosis, coma, and seizures refractory to benzodiazepines and other anticonvulsants.[36-39] Metabolic alterations include severe metabolic acidosis, hyperglycemia, glycosuria, ketonuria, and mild hyperkalemia.[36, 37, 40] Although isoniazid interferes with conversion of lactate to pyruvate, in animal studies acidosis does not occur without seizures and resolves within 2 hours of seizure termination.[41]

The length and severity of toxicity (especially seizures) is dependent on the isoniazid dose ingested.[38, 42, 43] Early publications report a dose of 40 mg/kg was needed to induce seizures in schizophrenic patients requiring electroconvulsive therapy, [44] although seizures occurred more reliably with doses over 100-150 mg/kg.[45] Serum isoniazid concentrations are imprecise surrogates of potential toxicity. Based on data from 28 patients, in case series containing three or more cases of isoniazid poisonings, the reported median highest isoniazid concentration was 74.5 mg/L (range: 0.5-450 mg/L) in survivors (n=24) and 127.5 mg/L (range: 72-600 mg/L) in fatalities (n=4).[36, 46-49]

Standard care for acute isoniazid overdose includes seizure abortive therapies with $GABA_A$ receptor allosteric modulators (e.g., benzodiazepines, barbiturates, propofol) and off-label high-dose pyridoxine; endotracheal intubation for airway protection and respiratory support; correction of metabolic acidosis; and minimization of drug absorption with activated charcoal. Pyridoxine restores GABA production so that $GABA_A$ receptor modulators can enhance GABA receptor activity and interrupt seizure activity.[50] Animal models show pyridoxine is superior to conventional anticonvulsants for termination of convulsions and preventing mortality.[51, 52] Compared to 41 isoniazid poisoned patients receiving no or inadequate pyridoxine, five patients with similar isoniazid toxicity receiving one gram of pyridoxine per gram of isoniazid ingested had a shorter duration of coma (7 h with pyridoxine vs 24 h with no or inadequate pyridoxine, $p<0.1$) and prompt resolution of metabolic acidosis; a statistically significant dose-dependent effect of pyridoxine on seizure recurrence was noted.[48]

Intravenous pyridoxine is dosed at one gram of pyridoxine for each gram of isoniazid ingested.[36, 37, 50] If an unknown amount of isoniazid is ingested, pyridoxine 70 mg/kg in children or five grams in adults is usually given.[36, 37] Pyridoxine and $GABA_A$ receptor modulators can be re-administered if seizures persist or recur.[37, 51] Pyridoxine is well tolerated at doses up to 350 mg/kg in poisoned patients but permanent and debilitating sensory neuropathies have been reported at doses of 2,000 mg/kg.[48, 53]

Prior to the use of pyridoxine, isoniazid poisoning mortality in large cohorts often exceeded 20% [54-56], which decreased when pyridoxine was used more systematically.[36, 48, 57] With appropriate doses of pyridoxine, mortality from isoniazid poisoning is rare, unless patients present late to care.[38, 39, 42, 43, 58, 59] The last four years of data from the American Association of Poison Control Centers' National

Poison Data System lists 497 single substance isoniazid exposures of which 135 were moderately or severely toxic, but no fatalities.[60-63]

Although injectable pyridoxine is easily manufactured, supplies may be difficult to obtain in resource poor settings and a single isoniazid poisoning can exhaust a hospital's stores of pyridoxine.[64-67] Recent data shows only 30% of Italian emergency departments stocked pyridoxine[59] and there are few manufacturers of injectable pyridoxine, which increases risk of supply chain interruptions. In 2018 and 2019, there were shortages of injectable pyridoxine due to manufacturing problems.[68, 69] Oral pyridoxine, crushed and given via nasogastric tube, has also been used successfully[42, 58, 64, 70, 71] for treating isoniazid poisoning, although not preferred as absorption may be impaired in critically ill patients.[72] If pyridoxine is unavailable, $GABA_A$ receptor modulators are used, but their effectiveness may be limited. No systematic reviews or evidence-based recommendations currently exist on the benefit of ECTRs for isoniazid poisoning.

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Supplementary Table 1). Its mission is to provide recommendations on the use of ECTRs in poisoning (http://www.extrip-workgroup.org). The rationale, background, objectives, methodology, and initial recommendations from the EXTRIP workgroup are published.[73-89] Our objective is to present EXTRIP's systematic review of the literature and recommendations for ECTR use in isoniazid poisoned patients.

Methods

The workgroup developed recommendations on the use of ECTR following published EXTRIP methodology with modifications, updates, and clarifications.[75] The full methods and a glossary are presented in the Supplemental Material.

In brief, the effect of extracorporeal (ECTR) was measured against standard care and alternative treatments. Clinical questions were formulated following the standard "Patient, Intervention, Comparison, Outcome" PICO model.

Search Strategy

The following electronic databases were searched: PubMed/Medline, EMBASE, and Cochrane Database for systematic reviews. Searches were not limited to English language or year of publication. Titles were screened for appropriateness by two workgroup members independently and full text papers were obtained and abstracted by the same two members into a standardized data extraction tool. To supplement the electronic searches, workgroup members had the option of contacting experts and manually searching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles.

The following search strategy was used regarding the use of ECTR: (dialysis or hemodialysis or haemodialysis or hemoperfusion or haemoperfusion or plasmapheresis or plasmaphaerisis or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or plasma exchange or CRRT or CKRT or CVV* or exchange transfusion or MARS) and (isoniazid or INH).

To identify cases of isoniazid-poisoned patients that were not treated with ECTR as historical controls, the following search strategy was used: ([Toxicity OR poison* OR intoxication OR overdos*] AND [Isoniazid OR INH]) AND Human. Only articles with patient-level data on more than three cases were included to minimize publication bias. Cohorts with lack of granularity around dose, symptoms, and treatments were excluded.

Evidence Review

Dialyzability was defined a priori (Supplementary Table 2). The quality of individual studies reporting on toxicokinetic outcomes was assessed according to a pre-defined set of criteria (Supplementary Table 3) and then summarized into a quality of the overall evidence (Supplementary Table 4). All clinical outcomes of interest were identified a priori and rated for relative importance for decision making (Table 5). Risk of bias was assessed using Cochrane risk of bias tools. Quality of the evidence (Supplementary Figure 1) was assessed for each critical and important outcome, and then for each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[90, 91]

Development of Clinical Recommendations

For all recommendations, the workgroup members voted to reach agreement for final recommendations. The anonymous online voting process consisted of a two-round modified Delphi with each statement voted on a 9-point Likert scale and final results interpreted according to EXTRIP voting rules based on median, lower or upper quartile (LQ or UQ) as appropriate, and disagreement index (DI) as calculated using RAND/UCLA Appropriateness Method (Supplementary Figure 2) and was performed using SimpleSurvey software. All recommendations were labelled as either "strong" or "weak/conditional" according to the GRADE approach. The words "we recommend" indicate strong recommendations and "we suggest" indicate weak recommendations and can be interpreted using Supplementary Figure 1

Results

Results of the literature search (first performed on March 1, 2019 and last updated October 23, 2020) are presented in Figure 1. No new articles were identified after recommendations were finalized.

A total of 949 articles were identified after removal of duplicates. Forty-three articles were included for qualitative analysis: 2 animal experiments [92, 93], 7 pharmacokinetic studies [21, 30, 94-98], and 34 case reports or case series.[9-14, 29, 36, 40, 99-123] No randomized controlled trials or observational studies were identified.

In the search for historical controls, a total of 6,294 articles were identified after removal of duplicates. After exclusions, 36 articles reporting on three or more patients were identified with full text available for 35 articles. Twenty-six articles had information on 192 individual patients with isoniazid poisoning in which ECTR was not performed (Supplementary Figure 3).[2, 36, 40, 45-49, 58, 70, 124-139]

Summary of Evidence

Dialyzability

Isoniazid is a small molecule with negligible protein binding. This suggests that isoniazid passes seamlessly through diffusive and convective ECTR membranes and would be adsorbed by charcoal cartridges. This is confirmed by *in vitro* experiments with HD and HP [92, 93], and by high extraction ratios and clearances in human subjects.[14, 21, 96, 116]

Despite a small volume of distribution, isoniazid's high endogenous clearance and short endogenous half-life limits the utility of ECTR for enhanced elimination. Pharmacokinetic studies show that when intravenous isoniazid is given at the onset of HD, three quarters of administered dose is recovered from the dialysate in 4-5 hours.[21] However, if HD is started 2 hours after ingestion of isoniazid, only 2.4-18% of an oral dose is recovered in 3.5 hours.[96] This can be explained by significant metabolism and elimination prior to dialysis in the latter study (perhaps by incomplete absorption as well). Toxicokinetic modeling suggests ECTR would be most beneficial within 2 hours of isoniazid ingestion.[121]

Table 2 presents the half-life and clearances of isoniazid observed during ECTR. Hemoperfusion appears more efficient than HD at eliminating isoniazid. This can be attributed to older and less efficient HD technology used for assessment of dialyzability (only 2 publications published after 1990). Data spanning over 50 years confirms major improvement in technology, filters, and catheters: HD clearance of isoniazid was less than 25 mL/min in 1967 [94], approximately 80 mL/min in the 1970s [14, 21], and surpassed 100 mL/min in 1999.[96]

Peritoneal dialysis (PD) was inefficient at removing isoniazid. A pharmacokinetic study of 9 patients showed mean isoniazid clearance of 2.7+6.6 mL/min.[30] Recovery of isoniazid from dialysate was low: 1.1 g in 36 hours from 5 g ingested [105], 0.2 g in 7 hours from 6 g ingested [10], and 3.1 g in 14 hours from 15 g ingested.[107] Although the data are very limited, continuous kidney replacement therapy (CKRT) and exchange transfusion (ET) appeared less efficient than both HP and HD.[9, 99, 121] In one case, ECTR accelerated isoniazid elimination from the CNS compartment.[14] The kinetics of isoniazid metabolites during ECTR are not described.

The workgroup acknowledged that specific patient conditions would render ECTRs more efficient relative to isoniazid metabolism and elimination. For example, endogenous clearance of isoniazid would be expected to be less (and apparent half-life longer) in cases of kidney impairment, ileus, slow acetylator status, and perhaps overdose. For these reasons, contribution of extracorporeal clearance to total clearance (i.e., extracorporeal clearance + endogenous clearance) and dialyzability is greater in patients with impaired kidney function. The workgroup assessed isoniazid as "Dialyzable" with HD in patients with impaired kidney function (level of evidence: A) and as "Moderately dialyzable" with HD in those with normal kidney function (level of evidence: C) (Table 3).

Dialyzability of pyridoxine: Because of its high water solubility, small size, and small volume of distribution (0.6 L/kg)[140], removal of pyridoxine is substantial during HD (mean *in vivo* clearance 173 ± 90.2 mL/min with a cellulose dialyzer and blood flow of 375 mL/min)[141] but negligible during PD (0.5 mL/min).[142]

Clinical Data

Evidence for a clinical effect of ECTR on isoniazid poisoning consists of case reports and case series, all of which are anecdotal, lack controls, and are susceptible to publication bias. Forty cases were described, 34 published prior to 1990, reflecting standards of care different than from today. Most publications were of low methodological quality and lacked critical information [78]. Demographics, clinical findings, management, and outcomes are listed in Table 4**.** There were five fatalities (12.5%) [36, 102, 105, 106] and two patients suffered anoxic brain injury from prolonged seizure activity.[9, 36] These patients either received no pyridoxine or a dose regarded today as inadequate (less than 10% of the recommended dose). In a small number of patients, improvement was noted after initiation of ECTR.[11, 13, 40, 99, 101, 103, 108-110, 113, 118, 120] In others, no improvement could be inferred.[9, 12, 105]

ECTR complications included one patient with thrombocytopenia-associated pharyngeal bleeding following HP [113] and another developed hypotension during PD.[105] A concern with ECTR is removal of pyridoxine[141]: five patients experienced seizures after initiation of ECTR, although in four, the pyridoxine dose administered prior to ECTR was inadequate.[9, 100, 105, 107] Several publications also report ESKD patients receiving therapeutic doses of isoniazid, who developed toxicity despite a therapeutic serum isoniazid concentration, including ototoxicity[143], optic neuritis[144, 145], and encephalopathy.[10, 111, 123, 146-161] Although the etiology of toxicity in these cases is likely multifactorial (malnutrition, uremia-induced impairment of phosphorylation), the chronology supports the hypothesis of an ECTR-induced reduction in concentrations of pyridoxine and pyridoxal 5'-phosphate (the active form of pyridoxine).[141, 162, 163]

In the absence of comparative studies, the panel estimated the overall effect of ECTR by comparing the cohort of patients receiving ECTR identified from our systematic review to similar cohorts of patients not receiving ECTR (Table 5). Analysis limitations include the heterogeneous nature of our

cohort, spanning 60 years, during which the standards of care have evolved: only 42% of patients received a pyridoxine dose considered appropriate by modern standards and many $GABA_A$ receptor modulators like benzodiazepines or propofol were not available in earlier reports. Mortality of patients treated with modern standard care including appropriately dosed pyridoxine, without ECTR, approaches 0%[2, 38, 39, 42, 43, 58-60] (Tables 4 and 5) and occurs in patients who did not receive an appropriate pyridoxine dose or presented with severe toxicity.[38, 42] Recurrence of seizures after appropriate pyridoxine is rare in historical cohorts.[38, 58] In patients identified from our systematic review of controls; 31 of 41 patients had no further seizures, one remained asymptomatic, and in 11 patients recurrence could not be determined.[36, 47-49, 58, 70, 124, 126, 128, 129, 133, 134, 137] Only one case had ECTR performed for ongoing seizures after an appropriate pyridoxine dose.[120] Outcomes comparing patients treated with ECTR to those treated with neither ECTR nor pyridoxine would be useful to assess the impact of ECTR in situations where pyridoxine is unavailable: in one recent case series, all eight patients with isoniazid overdose who were treated without pyridoxine survived without sequelae, although these patients had fewer indices of severity than our cohort (median isoniazid ingestion 2.7 g (75 mg/kg) versus 10.3 g (183 mg/kg) in our cohort).[2] As mentioned above, older cohorts receiving no or inappropriate pyridoxine report mortality rates often exceeding 20% although this could be attributed to variable standard care including unavailability of $GABA_A$ receptor modulators and ventilatory support.[36, 48, 54-57]

In summary, although the panel judged that formal comparisons between the ECTR cohort and historical controls were inherently flawed, the indirect evidence from these outcome data suggests no added benefit from ECTR in patients with isoniazid poisoning receiving appropriately dosed pyridoxine. The quality of the evidence for all reported patient-important outcomes assessing the potential beneficial effect of ECTR was graded as very low (Table 5). There is, however, evidence of added harms and costs related to the insertion of a double lumen catheter and the procedure itself.[164] The potential for these harms varies by local practices, methods of catheter placement, and type of ECTR used. There is also significant concern for harm from removing pyridoxine with ECTR.

Recommendations

Final Recommendation

In patients severely poisoned with isoniazid, we *suggest against* performing ECTR in addition to standard care rather than standard care alone (weak recommendation, very low quality of evidence).

In the rare circumstance in which standard dose pyridoxine cannot be administered, we suggest performing ECTR only in patients with seizures refractory to $GABA_A$ receptor modulators (weak recommendation, very low quality of evidence).

Rationale

In the usual scenario in which standard dose pyridoxine can be administered, the workgroup agreed that the risks and costs associated with ECTR likely surpass potential benefits in isoniazid poisoning (result of votes: median = 2, upper quartile = 4, disagreement index = 0.33). This was based on the observation that mortality and sequelae of isoniazid poisoned patients treated with modern standard care including appropriate dose pyridoxine, without ECTR, are rare. Recurrence of seizures after appropriate pyridoxine is unusual and would likely respond to supplementary pyridoxine and additional anticonvulsants with $GABA_A$ receptor activity. Coma is expected to improve with pyridoxine unless caused by a post-ictal condition, anoxic brain injury, or other diagnoses. No clear benefit can be observed from ECTR. Additionally, the panel recognized the increase in cost and potential harm from catheter insertion and ECTR itself. The risk of harm from ECTR appears heightened in isoniazid poisoning due to the removal of pyridoxine by ECTR.

In the rare circumstance in which a standard dose of intravenous or oral pyridoxine cannot be administered (e.g., mass poisoning or insufficient supplies), but ECTR is available, the workgroup suggested use of ECTR only in patients with seizures refractory to $GABA_A$ receptor modulators (result of votes: median = 7, lower quartile = 1, disagreement index= 0.79). The additional elimination of isoniazid by efficient ECTRs appears to outweigh the potential risk for harm from ongoing isoniazid toxicity when appropriate dose pyridoxine cannot be given, especially if other factors that alter isoniazid pharmacokinetics are present (e.g., ileus, impaired kidney function). The high mortality and morbidity reported in historical cohorts not treated with appropriate dose pyridoxine, added with the incremental addition of clearance from ECTR, support this recommendation, although the risk of removing pyridoxine was again noted. If appropriate pyridoxine cannot be administered and the patient is seizing despite administration of other $GABA_A$ receptor modulators, the panel preferred the use of high-efficiency hemodialysis as data suggest it to be efficient, most available, and comparatively inexpensive.[164] Unavailability of pyridoxine in a patient with ongoing isoniazid-induced seizures was, for most of the panel, the only indication for ECTR. The use of ECTR for correction of

metabolic acidosis is not recommended as acidosis is unlikely to occur without seizures and resolves with seizure termination.[41]

Serum isoniazid concentrations should not be used as a criterion for ECTR as the concentration-toxicity response is not well defined and isoniazid assays typically are not available in a time-frame necessary to influence clinical decisions (only two out of 38 panelists had isoniazid assays with results available within 6 hours of admission). The panel acknowledged that an undetectable isoniazid concentration with ongoing seizures or prolonged coma would force reconsideration of the diagnosis of isoniazid toxicity. Similarly, the panel acknowledged that a patient showing CNS signs more than 24 hours after ingestion warrants consideration of alternative diagnoses given the short elimination half-life of isoniazid. If ECTR is performed, and assuming that isoniazid assays are not available, clinical end points (sustained seizure resolution, improvement in consciousness, normalization of acid-base status) or availability of pyridoxine seemed appropriate to justify stopping ECTR. If no improvement is observed after 8 hours of high-efficiency techniques, alternate diagnoses such as brain injury should be excluded; otherwise, below the lower range of isoniazid therapeutic concentration (3-5 mg/L) was considered an acceptable objective and no benefit would be expected by targeting lower concentrations.

Research Gaps

Additional data is needed on outcomes of patients with isoniazid poisoning where pyridoxine availability is an issue (especially those treated with ECTR). More information on the dialyzability of pyridoxine is also warranted. Case reports presenting toxicokinetic data should include the patient's acetylator status.

Conclusion

This article presents the EXTRIP workgroup's systematic review and recommendations of ECTR for isoniazid poisoning. The workgroup suggests against ECTR in addition to standard care and appropriate dose pyridoxine in isoniazid poisoning. In circumstances where pyridoxine cannot be administered, the workgroup suggested ECTR in addition to standard care.

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Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature search.

TABLE 1. Physicochemical and pharmacokinetic properties of isoniazid

Characteristic			**References**
Molecular weight		137 g/mol	
Protein binding		0-15%	16, 17
Volume of distribution	*Adults (including CKD)*	0.6-0.8 L/kg	8, 18-21
	Children	0.8-1.2 L/kg	
Fractional oral bioavailability		100%	18
Half-life	*Rapid acetylator*	1.1-1.8 h	8, 18, 19, 21-29
	Slow acetylator	2.8-4.0 h	
	CKD and ESKD	1.5-3.0 h (rapid acetylator) 3.5-6.5 h (slow acetylator)	
Total body clearance	*Rapid acetylator*	350-600 mL/min	8, 18-20, 30
	Slow acetylator	130-260 mL/min	
	CKD and ESKD	100-300 mL/min	
Renal clearance (normal kidney function)		40-50 mL/min	6, 8, 23, 31
Serum therapeutic range		3-6 mg/L (300 mg daily) 9-18 mg/L (900 mg 3x weekly)	32, 33

CKD: Chronic kidney disease, ESKD: End stage kidney disease

Table 2: Isoniazid half-life and clearance data during ECTR

ECTR	**$T_{1/2}$ (hours)**				**Clearance (mL/min)**				**References**
	During ECTR			*Endogenous*	ECTR			*Endogenous*	
	Value	Range	n		Value	Range	n		
CKRT	4.1		1	*1.1-4.0*	No data			*130-600*	121
ET	3.9	3.8-4.0	2		No data				9, 99
HD	2.7	1.1-4.5	38		71.7	29.2-110	3		11-14, 21, 29, 94-96, 98, 101, 103, 109, 117

HP	1.2	0.8-1.8	3		148.5	143-154	2		14, 113, 116
PD	7.7	3.5-16.6	16		5.3	1.5-11.1	5		10, 30, 36, 40, 100, 105, 107, 108, 115

ECTR: Extracorporeal treatment, CKRT: Continuous kidney replacement therapy, ET: Exchange transfusion; HD: Hemodialysis, HP: Hemoperfusion, PD: Peritoneal dialysis; $T_{1/2}$: Elimination half-life

TABLE 3: Dialyzability of isoniazid

PK/TK grading	NUMBER OF PATIENTS SATISFYING A CRITERION FOR DIALYZABILITY						FINAL GRADING AND QUALITY OF THE EVIDENCE
	IMPAIRED KIDNEY FUNCTION (Mostly ESKD)		NORMAL KIDNEY FUNCTION				
	HD	PD	HD	HP	PD	ET	IMPAIRED KIDNEY FUNCTION: HD: Dialyzable, A PD: Not Dialyzable, A NORMAL KIDNEY FUNCTION* HD: Moderately Dialyzable, C HP: Dialyzable, D ET: Moderately dialyzable, D PD: Slightly Dialyzable, C
Dialyzable	19		1	1			
Moderately dialyzable	7**		2		1	2	
Slightly dialyzable	3**	2			3		
Not dialyzable		9					

*One study performed modeling for CKRT removal of isoniazid [121] which suggests that CVVHD would provide 4 times the endogenous clearance of isoniazid, but that appears improbable considering a conservative estimate of isoniazid's endogenous clearance equal to 100 mL/min and a maximal CVVHD clearance of 100 mL/min.

** Includes 1 pharmacokinetic study where hemodialysis was given 2.2h after administration of an oral isoniazid dose

PK: Pharmacokinetics TK: Toxicokinetics, HD: Hemodialysis, HP: Hemoperfusion, PD: Peritoneal dialysis, ET: Exchange transfusion, ESKD: End-stage kidney disease, CKRT: Continuous kidney replacement therapy, CVVHD: Continuous veno-venous hemodialysis

TABLE 4: Clinical summary of patients severely poisoned with isoniazid identified from our systematic reviews

Parameters		ECTR Cases 34 articles, N=40	Standard Care Case Series 26 articles, N=192
Patient characteristics	**Age (years)**	20 [16,29.5], range 0.9-59	20 [15,27], range 1.5-67
	Male (%)	53.7%	31.3%
Poisoning info	**Isoniazid ingestion (g)**	10.3 [5-21.3], range 0.9-50	6.0 [3,10] range 0.3-27
	Isoniazid ingestion (mg/kg)	183 [117,197], range 82-469	109 [76,200], range 14.3-417
	Peak isoniazid concentration (mg/L)	68 [30.5,144], range 13.3-1500†	7 [34.2,125.5], range 0.5-600
	Intentional ingestions with coingestants (%)	37%	9.5%
	Delay between exposure and admission (h)	2.0 [1.3,4.0], range 0.3-36	2.0 [1.0,3.0], range 0.5-24
	Onset between ingestion and symptoms (h)	2.0 [1.0,3.3], range 0.5-6.5	1.5 [1.0,2.8], range 0.25-48
Symptoms/ Signs / Labs	**Coma (%)**	88.6%	33.3%
	Seizure (any, %)	97.2% Onset = 2.0h [1.1, 2.8], range 0.5-6.5	65.1% Onset = 1.5h [1.0,2.6], range 0.25-24
	Seizures (multiple, %)	97.2% Onset = 2.0h, [1.1,2.8], range 0.5-6.5	53.1% Onset =1.5h [1.0,2.1], range 0.25-24
	Seizures (single, %)	0%	12.0% Onset = 3.0h [2.0-4.0], range 0.5-6.0
	Acute kidney injury (%)	23.3%	1.5%
	Vomiting (%)	78.6%	49.2%
	Metabolic acidosis (%)	93.3%	37.5%
	Lowest serum bicarbonate (mEq/L)	12 [8,18], range 5-20	13.0 [8.8,18.0], range 6.0-26.0
	Highest serum lactate (mEq/L)	4.2 [3,11.8], range 1-39.2	15.3 [9.5,16.0], range 3.7-16.6
	Lowest serum pH	7.18 [6.88,7.30], range 6.63-7.42	7.10 [6.99,7.14], range 6.71-7.38
	Highest serum glucose (mg/dL)	126 [108,218], range 81-396	220 [169,286], range 86-465
	Highest white blood cell count (x10^9/L)	18.5 [15.2,22], range 10-39	16.7 [11.8,21.6], range 9.2-30
Treatments	**Gastric lavage (%)**	57.1%	14.6%
	Activated charcoal (%)	20.7%	8.9%
	IV Bicarbonate (%)	48.0%	20.3%
	Benzodiazepines (%)	61.8%	17.2%
	Phenytoin (%)	32.1%	8.3%
	Barbiturate (%)	53.6%	10.9%
	Mechanical ventilation (%)	64.3%	0.5%
	Pyridoxine (%)	89.7%	65.6%

	Pyridoxine dose (g)	2.5, [0.6,11.0], range 0.1-22	4.0 [0.9-6.0], range 0.01-25
	Patients receiving at least 1g:1g pyridoxine dose or 5g if ingestion unknown (%)	41.7%	37.8%
ECTR	**Time from admission to ECTR initiation (hours)**	4.0, [2.5,15.0], range 0.8-72	NOT APPLICABLE
	Hemodialysis (%)	50%	
	Charcoal hemoperfusion (%)	7.5%	
	Continuous kidney replacement therapy (%)	2.5%	
	Peritoneal dialysis (%)	30%	
	Exchange transfusion (%)	5%	
	More than 1 ECTR (%)	5%	
Outcome	**Length of stay (days)**	6 [3,9], range 0.8-121	4.5 [2.0,6.8], range 1-72
	ICU stay (days)	3.5 [2.5,4.3], range 1-5	6.0 [4.0,8.0], range 2-10
	Death (%)	5/40 = 12.5%	21/192 = 10.9%‡
	Recurrence of seizure after initiation of treatment (%)	5/33 = 15.2% (after ECTR initiated)	0/32 = 0% (after standard dose pyridoxine)
	Permanent sequelae (%)	2/27 = 7.4%	6/192 = 3.1%

Value presented as medians and quartiles, unless otherwise indicated.

† The reported serum concentration in 1 case was clearly incorrect. It is suspected that the units should have been mg/dL (15.3 mg/dL or 153 mg/L) instead of 15.3 mg/mL.[116] This was corrected.

‡All but two deaths were reported before 1987.

Abbreviations: ECTR= extracorporeal treatment,

TABLE 5: ECTR and standard care compared to standard care in patients severely poisoned with isoniazid (*Evidence profile table*)

Quality assessment						Summary of findings				Importance
Study design (number of studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ECTR + standard care**	**Standard care**	**Effect**	**Quality**	
Mortality†										
Observational studies (N=10) ‡	Very serious§	Not serious	Serious¶	Serious#	Publication bias strongly suspected‖	5/40 = 12.5%	**MODERN COHORTS** 5/47 = 10.6% [42] 0/33 = 0% [43] 2/49 = 4.1% [38] 0/16 = 0% [39] 0/20 = 0% [58] 0/21 = 0% [59] 0/135 = 0% [60-63] **MODERN CASE SERIES (No pyridoxine)** 0/8 = 0% [2] **SYSTEMATIC REVIEW - CASE SERIES** 21/192 = 10.9%	Groups not comparable	⊕◯◯◯ VERY LOW	CRITICAL
Permanent sequelae										
Observational studies (N=2) ††	Very serious§	Not serious	Serious¶	Serious#	Publication bias strongly suspected‖	2/27 = 7.4%	**SYSTEMATIC REVIEW - CASE SERIES** 3.1%	Groups not comparable	⊕◯◯◯ VERY LOW	CRITICAL
Recurrence of seizures after initiation of treatment										
Observational studies (N=4) ‡‡	Very serious§	Not serious	Serious¶	Serious#	Publication bias strongly	5/33 = 15.2% once ECTR	**COHORTS receiving standard pyridoxine**	Groups not comparable	⊕◯◯◯	CRITICAL

					suspected[‖]	started	0% [38] 0% [58] **SYSTEMATIC REVIEW - CASE SERIES** 0%		VERY LOW	
Length of hospital stay										
Observational studies (N=5)[§§]	Very serious[§]	Not serious	Serious[¶]	Serious[#]	Publication bias strongly suspected[‖]	Median = 6.0d	**COHORTS receiving pyridoxine** Mean = 1.9d [39] Mean = 3.3d [43] Mean = 3.3d [42] **SYSTEMATIC REVIEW - CASE SERIES** Median = 4.5d	Groups not comparable	⊕◯◯◯ VERY LOW	IMPORTANT
Length of ICU stay										
Observational studies (N=3)[¶¶]	Very serious[b]	Not serious	Serious[¶]	Serious[#]	Publication bias strongly suspected[‖]	Median = 3.5d	**COHORTS receiving pyridoxine** Mean = 1.4d [42] **SYSTEMATIC REVIEW - CASE SERIES** Median = 6.0d	Groups not comparable	⊕◯◯◯ VERY LOW	IMPORTANT
Serious complications of catheter insertion[##]										
Observational studies (N=5)[‖‖]	Not serious	Not serious[†††]	Not serious[‡‡‡]	Not serious[§§§]	Strong association[¶¶¶]	Rate of serious complications of catheter insertion varies from	≈ 0%	Absolute effect is estimated to be between 1 to 21 more serious complications per 1000	⊕⊕⊕◯ MODERATE	CRITICAL

						0.1% to 2.1%		patients in the ECTR group		
Serious complications of ECTR[###]										
Observational studies (N=6)[‖‖‖]	Not serious	Not serious	Not serious	Not serious	Strong association[††††]	Rate of serious complications of ECTR varies according to the ECTR performed from 0.005% (IHD and CKRT), and up to 1.9% (HP)	≈ 0%	Absolute effect is estimated to be varying from >0 to 19 more serious complications per 1000 patients in the ECTR group depending on the type of ECTR performed	⊕⊕⊕◯ MODERATE	CRITICAL

ECTR: Extracorporeal treatments, IHD: Intermittent hemodialysis, CKRT: Continuous kidney replacement therapy, HP: Hemoperfusion

Explanations

†Although considered relevant patient-important outcomes, “length of coma” and “length of status epilepticus” could not be reliably estimated in the ECTR cohort so no comparison with controls was performed.

‡ Includes our systematic review of the literature on ECTR (40 patients from 34 case reports) as well as 8 cohort studies and our systematic review of case series treated with standard care alone (“SYSTEMATIC REVIEW -CASE SERIES”, 192 patients from 26 case series)

§ Case reports published on effect of ECTR. Uncontrolled and unadjusted for confounders such as severity of poisoning, co-ingestions, supportive and standard care, and co-interventions. Confounding-by-indication is inevitable since ECTR was usually attempted when other therapies have failed.

¶ ECTR and standard care performed may not be generalizable to current practice (older technology, non-standardized dose of pyridoxine)

Few events in small sample size, optimal information size criteria not met.

‖ Publication bias is strongly suspected due to the study design (case reports published in toxicology often report very severe poisonings with successful outcomes)

†† Includes our systematic review of the literature on ECTR (40 patients from 34 case reports) as well as our systematic review of case series treated with standard care alone ("SYSTEMATIC REVIEW -CASE SERIES", 192 patients from 26 case series)

‡‡ Includes our systematic review of the literature on ECTR (40 patients from 34 case reports) as well as 1 cohort study and our systematic review of case series treated with standard care alone ("SYSTEMATIC REVIEW -CASE SERIES", 192 patients from 26 case series)

§§ Includes our systematic review of the literature on ECTR (40 patients from 34 case reports) as well as 3 cohort studies and our systematic review of case series treated with standard care alone ("SYSTEMATIC REVIEW -CASE SERIES", 192 patients from 26 case series)

¶¶ Includes our systematic review of the literature on ECTR (40 patients from 34 case reports) as well as 1 cohort studies and our systematic review of case series treated with standard care alone ("SYSTEMATIC REVIEW -CASE SERIES", 192 patients from 26 case series)

For venous catheter insertion, serious complications include hemothorax, pneumothorax, hemomediastinum, hydromediastinum, hydrothorax, subcutaneous emphysema retroperitoneal hemorrhage, embolism, nerve injury, arteriovenous fistula, tamponade, and death. Hematoma and arterial puncture were judged not serious and thus excluded from this composite outcome. Deep vein thrombosis and infection complications were not included considering the short duration of catheter use.

ǁǁ Five single-arm observational studies: two meta-analyses comparing serious mechanical complications associated with catheterization using or not an ultrasound, which included six RCTs in subclavian veins[165] and 11 in internal jugular veins[166]; two RCTs comparing major mechanical complications of different sites of catheterization[167, 168]; and one large multicenter cohort study reporting all mechanical complications associated with catheterization.[169] Rare events were reported from patient series and patient reports.

††† Not rated down for inconsistency because heterogeneity was mainly explained by variation in the site of insertion, use of ultrasound, experience of the operator, populations (adults and pediatric), urgency of catheter insertion, practice patterns and methodological quality of studies.

‡‡‡ Not rated down for indirectness because risks of cannulation and catheter insertion were judged comparable to reported risks when performed for other indications.

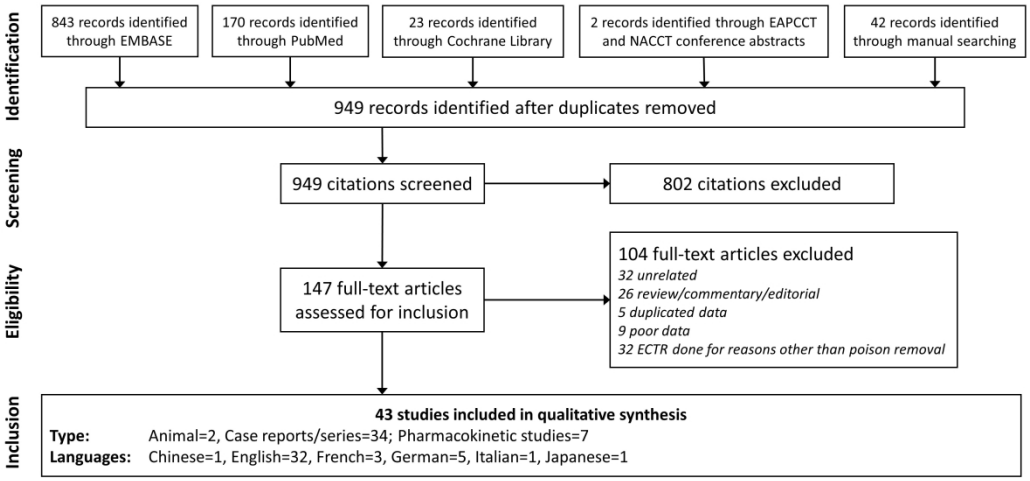
§§§ Not rated down for imprecision because the wide range reported was explained by inconsistency.

¶¶¶ The events in the control group are assumed to be zero (because no catheter is installed for ECTR), therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short timeframe (i.e., few hours).

For IHD and CKRT, serious complications (air emboli, shock, and death) are exceedingly rare. Minor bleeding from heparin, transient hypotension, and electrolytes imbalance were judged not serious. For HP, serious complications include severe thrombocytopenia, major bleeding, and hemolysis. Transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged not serious. For TPE, serious complications include citrate toxicity, severe allergic reaction, arrhythmia, and vasovagal reaction. Hypotension, hypocalcemia, and urticaria were judged as not serious. All non-serious complications were excluded from this composite outcome.

ǁǁǁ IHD/CKRT: two single-arm studies describing severe adverse events per 1000 treatments in large cohorts of patients.[170, 171] TPE: two recent one-arm studies reporting potential life-threatening adverse events.[172, 173] HP: two small single-arm studies in poisoned patients.[174, 175] Rare events were reported in patient series and patient reports.

†††† Assuming that patients in the control group would not receive any form of ECTR, the events in the control group would be zero; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95%CI which included the null value and all observed complications occurred in a very short timeframe (i.e., few hours).



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