Seminars in Dialysis

Blood Purification in Poisoning

Why are we Still Dialyzing Overdoses to Tricyclic Antidepressants? A subanalysis of the NPDS database

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ABSTRACT

A recent analysis of the American Association of Poison Control Centers database, showed that poisonings from toxins not usually considered amenable to extracorporeal purification ("non-classic toxins" such as ethanol and tricyclic antidepressants) continue to be reported. This publication investigates factors that may explain these findings. Our results suggest that: 1) the relatively high absolute number of ECTR performed for non-classic toxins may simply reflect the large number of exposures to these toxins, 2) poisoning from another toxin may have been the reason for ECTR initiation in some exposures to non-classic toxins, 3) poisoning from non-classic toxins may receive ECTR for purposes other than toxin removal, and 4) the decisional threshold to initiate ECTR may be lower for non-classic toxins because of heightened toxicity.

Poisoning from toxic alcohols, salicylates, and lithium are among the most common indications for extracorporeal elimination of toxins in the United States, Canada, United Kingdom, and Denmark (1). Collectively, they represent approximately 50% of all poisoning cases that received an extracorporeal treatment (ECTR) in these countries. Surprisingly, two publications revealed that ECTRs, such as hemodialysis and hemoperfusion, were commonly used during poisonings from toxins that are either not considered dialyzable or not considered common indications for extracorporeal purification (tricyclic antidepressants, benzodiazepines, ethanol, acetaminophen) (1,2). These trends were noted across multiple countries in recent years suggesting that such practice may be widespread.

This paper intends to evaluate hypotheses that were developed to understand these unexpected findings for toxins for which ECTR would not usually be indicated, termed "nonclassic toxins," compared to those for which ECTR would more commonly be indicated termed "classic toxins" (see Box 1, Definitions); 1) Despite the large absolute number of ECTRs performed for nonclassic toxins such as acetaminophen (1), their use may still be relatively rare, especially when compared to the total number of exposures to that toxin; 2) because several of the nonclassic toxins (e.g., ethanol, benzodiazepines, and acetaminophen) are common coingestants, it is possible that another toxin prompted treatment with ECTR; 3) ECTR during nonclassic toxin poisoning may be performed for indications other than removal of that toxin, such as associated metabolic acidosis or impaired kidney function; 4) the threshold for ECTR initiation may be lower in patients poisoned with nonclassic toxins, especially those who are clinically ill for reasons other than listed in the third hypothesis; 5) most of the ECTRs performed for nonclassic toxins may have occurred predominantly during the earlier years of the database, when toxicokinetics, indications and the technical limitations of ECTRs were not as well understood.

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Box 1

Definitions

- A "toxin" is a xenobiotic presumed to be associated with the toxic exposure.
- The "primary toxin" is the first toxin among several listed or the only toxin listed. This ranking of toxins is intended to illustrate their relative importance in the context of the history and clinical presentation.
- A "classic toxin" is a toxin for which ECTR is commonly considered indicated in severe exposures, for example salicylates (3), ethylene glycol, methanol (4) and lithium (5).
- A "non-classic toxin" is a toxin for which ECTR is uncommonly indicated, even in severe exposures. Examples of non-classic toxins include tricyclic antidepressants, acetaminophen, cardiac glycosides and benzodiazepines. Although ECTR is recommended for the treatment of severe acetaminophen exposures (2,6), it was included here because the subset of poisoned patients considered to likely benefit from ECTR is extremely limited.
- An "exposure" is a single patient entry reported to the poison center with an actual or suspected exposure to a toxin.
- A "severe exposure" is when the clinical effect as classified by NPDS is either moderate, major or death.
- An "ECTR" is an extracorporeal treatment designed to remove endogenous or exogenous toxins. ECTRs include hemodialysis (HD), peritoneal dialysis (PD), continuous renal replacement therapy (CRRT), hemoperfusion (HP), exchange transfusion (ET), liver support devices, and therapeutic plasma exchange (TPE).
- A "case" is a patient who received an ECTR.

The objectives of this work are to review and test these hypotheses by performing a subanalysis of a US cohort described in a previous publication (1).

Materials and Methods

Database Description

A description of the American Association of Poison Control Centers' National Poison Data System (NPDS) database is presented in depth elsewhere. The NPDS is an electronic database that captures all exposures reported to participating poison centers in the United States. Prior to 2005, NPDS was known as the Toxic Exposure Surveillance System or TESS. For convenience we will refer to the combined database by its current name. NPDS contains more than 60 million exposure case records going back to 1983. Data collected during routine poison center operations are entered in the database by Specialists in Poison Information (SPIs), who are trained and certified health care professionals. NPDS has undergone several updates and transformations since its inception in 1983 with regard to captured fields, toxins reviewed, and a variety of other information. NPDS maintains rigorous coding guidelines, and each data element and its options are defined in the NPDS System Information Manual, which is available on the NPDS web portal (http://www.aapcc.org/data-system/). Each year, the AAPCC publishes limited epidemiological data of selected portions of the larger data set in terms of number of exposures, clinical effect and outcome (7,8). From 1993 to 2000, cases were derived from a previous sub-database (2) while from 2000 to 2014, data were accessed electronically from NPDS. From 1993 to 2014, there were nearly 50 million reported exposures by US poison centers, while in 2014 alone there were 2,165,142 reported toxic exposures. The current sub-analysis was performed on cases collected since January 1, 1993, since clinical manifestations were not coded in earlier years.

Analyses

The influence of coingestants on the initiation of ECTR (hypothesis 2) was explored to remove confounding for the indication for ECTR by coingested toxins. The initial analysis only reviewed the primary (top-listed) toxin (1) (Box 1); to eliminate errors in this attribution, for example, a misleading clinical history or miscoding in toxin ranking by the SPI, we analyzed single toxin exposures separately.

In any poisoning, ECTR may be performed for any number of indications, including to facilitate removal of the toxin(s), support organ function (e.g., acute kidney injury, liver support device for hepatic failure), correct acid-base or electrolyte abnormalities (e.g., hyperkalemia) or any combination of these. The precise clinical indication that prompted the use of ECTR for a specific case is not coded in NPDS; in order to explore hypothesis 3, we further analyzed and stratified all included cases for clinical conditions that could be potential confounders for ECTR initiation (Table 2), such as "elevated creatinine," "renal failure," "electrolyte abnormality," "pulmonary edema," "rhabdomyolysis," "anuria/oliguria," and "acidosis," regardless of whether these conditions were coded by the poison center as related or unrelated to the poisoning.

Comorbid conditions or other markers of critical illness may influence the decision to initiate ECTR (hypothesis 4). We therefore compared the age of cases and the markers of severity of illness including acuity of the poisoning, duration of toxicity, manifestations of severe poisoning (asystole, cardiac arrest, hypotension, coma, supportive treatments,

vasopressors, mechanical ventilation) for classic compared to nonclassic toxins.

In order to review the evolution of ECTR practices for nonclassic toxins (hypothesis 5), all cases of ECTRs with a coingestant or a potential confounding clinical condition (i.e., acidosis, kidney impairment, or electrolyte disturbances) were excluded. Included cases were reviewed longitudinally and assessed for changing trends.

Statistics

Continuous variables were reported as means with 95% confidence intervals or medians with interquartile ranges and compared using Student's *t*-tests or Mann–Whitney *U* tests, as appropriate. Binomial and categorical variables were compared with Fisher's exact tests or Chi-square tests, as appropriate. To evaluate the trends of ECTR use for tricyclic antidepressants, acetaminophen and ethanol, annual rates of ECTR performed per 100,000 total exposures were calculated. Poisson regression models were used to assess the effect of time (period of 1 year) on the rate of ECTR performed. Testing for trends was conducted by fitting time as a continuous variable in the log linear Poisson model with the number of exposures used as offset. Two-tailed *p*-values of <0.05 were considered to be significant. Statistical analyses were performed with IBM SPSS Statistics 22 for Windows (IBM Corp., Armonk, NY, USA).

Results

Toxins for which ECTR was Most Commonly Performed

Table 1 presents the most common toxins for which an ECTR was performed during the study period. Among poisonings to "classic toxins," those where an ECTR was most often performed were ethylene glycol, followed by lithium, salicylates, methanol, valproic acid, theophylline, metformin, isopropanol, phenobarbital, and carbamazepine. Among nonclassic toxins, those for which an ECTR was most often performed were acetaminophen, followed by ethanol, cardiac glycosides, benzodiazepines, calcium channel blockers, cocaine, tricyclic antidepressants, atypical antipsychotics, beta-adrenergic antagonists, and methadone.

Hypothesis #1: Absolute Versus Relative ECTR Cases Per Total Toxin Exposures

Table 1 presents the number of cases where an ECTR was performed during the management of the most common classic and nonclassic toxins, in relation to the total number of exposures and the number of severe exposures (i.e., clinical effect

TABLE 1. ECTR cases in the most common toxins (NPDS 1993–2014)

	For primary toxin exposure*			For single toxin exposure	
Toxins	Total ECTR cases (n)	ECTR cases per severe exposures (%)	ECTR cases per total exposures (%)	ECTR cases (n)	ECTR cases with single toxin exposure per total ECTR cases (%)
Classic toxins					
Ethylene glycol	7351	50.9%	5.5%	5472	74.4%
Lithium	6695	23.5%	5.4%	4413	65.9%
Salicylates	4150	6.4%	0.5%	2863	69.0%
Methanol	1411	36.1%	2.8%	1043	73.9%
Valproic acid	691	3.3%	0.4%	351	50.8%
Theophylline	663	9.9%	2.2%	501	75.6%
Metformin	632	14.6%	0.7%	379	60.0%
Isopropanol	299	2.0%	0.1%	195	65.2%
Phenobarbital	251	2.6%	0.4%	149	59.4%
Carbamazepine	189	0.9%	0.2%	115	60.8%
Median (Q1; Q3)		8.1% (2.8%; 21.2%)	0.6% (0.4%; 2.7%)		65.6% (60.2%; 72.7%)
Nonclassic toxins					
Acetaminophen	2676	1.4%	0.1%	940	35.1%
Ethanol	719	0.5%	0.0%	314	43.7%
Cardiac glycosides	658	4.6%	0.6%	592	90.0%
Benzodiazepines	525	0.4%	0.0%	94	17.9%
Calcium channel blockers	485	2.1%	0.2%	147	30.6%
Cocaine	320	1.0%	0.3%	167	52.2%
Tricyclic antidepressants	305	0.4%	0.1%	97	31.8%
Atypical antipsychotics	304	0.3%	0.1%	59	19.4%
Beta-adrenergic antagonists	286	1.0%	0.1%	103	36.0%
Methadone	208	1.4%	0.3%	78	37.5%
Median (Q1; Q3)		1.0% (0.4%; 1.4%)	0.1% (0.1%; 0.3%)		35.6% (30.9%; 42.2%)
p-value (classic vs. nonclassic toxins)		0.001	0.005		0.003

*The primary toxin is defined either as the first toxin out of multiple listed or as the only toxin listed.
Q1: lower quartile; Q3: upper quartile.

classified as moderate, major, or death) in the NPDS annual reports. ECTR was performed in more than 5% of all lithium and ethylene glycol exposures; moreover, an ECTR was performed in approximately 50% of severe ethylene glycol exposures and 25% of severe lithium exposures. Although the high absolute number of ECTRs performed for toxins like acetaminophen (2676 cases) and ethanol (719 cases) rank them among the most common, ECTRs were used infrequently when compared to the number of total exposures and severe exposures for these toxins, that is, approximately 0.1% and 1%, respectively. The frequency of ECTR cases relative to the total of toxin exposures and of severe toxin exposures were statistically greater for classic than nonclassic toxins (p-value = 0.005 and 0.001, respectively).

Hypothesis #2: ECTR Cases in Single vs. Multiple Toxin Exposures

As demonstrated in Table 1, for classic toxins, two-thirds of ECTRs were performed in the context of single toxin exposure. This percentage for toxic alcohols (methanol and ethylene glycol) was even higher at approximately 75%. For nonclassic toxins, only one-third of cases were performed in a context of single toxin exposure (as low as 18% for benzodiazepines). This difference between classic and nonclassic toxins in the proportion of single exposures receiving ECTR was statistically different (p-value = 0.003).

Hypothesis #3: Confounding Indications for ECTR

Among classic toxins, less than half of all cases had at least one potential indication for ECTR other than toxin removal, while this proportion rose to over three quarters for nonclassic toxins (Table 2). In fact, when ECTR was performed, at least one potential indication for ECTR other than toxin removal was present for methadone (91%), cocaine (89%), atypical antipsychotics (88%), and acetaminophen (86%). For example, rhabdomyolysis was present in more than 33% of cocaine and methadone overdoses that received an ECTR. Kidney impairment was present in more than 75% of all acetaminophen cases. Electrolyte disturbances were present in more than half of cardiac glycoside cases. The difference in the presence of any of the above clinical conditions between classic and nonclassic toxins was statistically significant (p-value = 0.02).

Hypothesis #4: Clinical Severity and Comorbid Conditions

When comparing characteristics of patients who received ECTR for classic vs. nonclassic toxins, the latter patients were significantly older, were more

TABLE 2. Clinical conditions present when ECTR performed in single toxin exposures.

	Clinical conditions present when ECTR was performed					
Toxins	Rhabdomyolysis	Acidosis	Electrolyte abnormality	Pulmonary edema	Kidney impairment*	Any condition present
Classic toxins						
Ethylene glycol	50 (0.9%)	3686 (67.4%)	1478 (27.0%)	37 (0.7%)	2670 (48.8%)	4282 (78.3%)
Lithium	26 (0.6%)	124 (2.8%)	768 (17.4%)	19 (0.4%)	1337 (30.3%)	1713 (38.8%)
Salicylates	62 (2.2%)	1378 (48.1%)	980 (34.2%)	175 (6.1%)	532 (18.6%)	1914 (66.9%)
Methanol	7 (0.7%)	595 (57.0%)	237 (22.7%)	6 (0.6%)	145 (13.9%)	636 (61.0%)
Valproic acid	7 (2.0%)	88 (25.1%)	70 (19.9%)	3 (0.9%)	34 (9.7%)	138 (39.3%)
Theophylline	7 (1.4%)	39 (7.8%)	112 (22.4%)	6 (1.2%)	45 (9.0%)	159 (31.7%)
Metformin	6 (1.6%)	349 (92.1%)	143 (37.7%)	2 (0.5%)	233 (61.5%)	367 (96.8%)
Isopropanol	13 (6.7%)	58 (29.7%)	32 (16.4%)	1 (0.5%)	52 (26.7%)	95 (48.7%
Phenobarbital	3 (2.0%)	9 (6.0%)	11 (7.4%)	1 (0.7%)	9 (6.0%)	26 (17.4%)
Carbamazepine	2 (1.7%)	8 (7.0%)	15 (13.0%)	1 (0.9%)	24 (20.9%)	35 (30.4%)
Median (Q1; Q3)						44.0% (33.5%; 5.4%)
Nonclassic toxins						
Acetaminophen	47 (5.0%)	431 (45.9%)	272 (28.9%)	21 (2.2%)	720 (76.6%)	804 (85.5%)
Ethanol	16 (5.1%)	211 (67.2%)	101 (32.2%)	3 (1.0%)	147 (46.8%)	236 (75.2%)
Cardiac glycosides	0 (0.0%)	38 (6.4%)	339 (57.3%)	13 (2.2%)	368 (62.2%)	454 (76.7%)
Benzodiazepines	15 (16.0%)	24 (25.5%)	27 (28.7%)	0 (0.0%)	54 (57.4%)	63 (67.0%)
Calcium channel blockers	4 (2.7%)	42 (28.6%)	61 (41.5%)	23 (15.6%)	90 (61.2%)	111 (75.5%)
Cocaine	60 (35.9%)	67 (40.1%)	53 (31.7%)	8 (4.8%)	145 (86.8%)	149 (89.2%)
Tricyclic antidepressants	16 (16.5%)	21 (21.6%)	26 (26.8%)	3 (3.1%)	51 (52.6%)	61 (62.9%)
Atypical antipsychotics	21 (35.6%)	22 (37.3%)	22 (37.3%)	1 (1.7%)	46 (78.0%)	52 (88.1%)
Beta-adrenergic antagonists	1 (1.0%)	11 (10.7%)	32 (31.1%)	2 (1.9%)	47 (45.6%)	57 (55.3%)
Methadone	27 (34.6%)	30 (38.5%)	30 (38.5%)	3 (3.8%)	68 (87.2%)	71 (91.0%)
Median (Q1; Q3)						76.1% (69.1%; 7.5%)
p-value (classic vs. nonclassic toxins)						0.02

*Kidney impairment includes "Creatinine increase," "Renal failure," and "Oligo/anuria" categories of NPDS.
Q1: lower quartile, Q3: upper quartile.

likely to have severe effects from the poisoning, had evidence of greater morbidity (coma, hypotension, life-threatening dysrhythmia), and were sick for a longer period of time (Table 3).

Hypothesis #5: Evolving Practice Trends for ECTR

Figure 1 shows the longitudinal evolution of annual rate of these ECTR cases per 100,000 exposures for tricyclic antidepressants, acetaminophen, and ethanol. ECTR practice trends remained statistically stable for acetaminophen and tricyclic antidepressants while they decreased for ethanol ($p = 0.007$) over the study time period (Figure 1).

TABLE 3. Characteristics of patients who received an ECTR in a context of severe poisoning

	Classic toxins (N = 21,979)	Nonclassic toxins (N = 6478)	p-value
Patient demographic			
Mean age (years, 95%CI)	43.2 (43.0; 43.4)	45.2 (44.8; 45.6)	<0.0001
Poisoning characteristics			
Type of poisoning (acute)	12772 (57.5%)	2804 (43.3%)	<0.0001
Duration of toxicity (> 3 days)	6932 (31.2%)	2423 (37.4%)	<0.0001
Clinical presentation			
Severity (at least a moderate effect)	10621 (47.8%)	4622 (71.3%)	<0.0001
Asystole	234 (1.1%)	349 (5.4%)	<0.0001
Cardiac arrest	922 (4.2%)	888 (13.7%)	<0.0001
Hypotension	4021 (18.1%)	2732 (42.2%)	<0.0001
Coma	4743 (21.4%)	2281 (35.2%)	<0.0001
Supportive treatments			
Vasopressors	2722 (12.3%)	2453 (37.9%)	<0.0001
Mechanical ventilation	6678 (30.1%)	3405 (52.6%)	<0.0001

Discussion

Previous studies demonstrated that ECTR was performed during the management of poisonings from many toxins not considered to be routinely amenable to enhanced clearance by such treatments (1,2). The present subanalysis addressed five hypotheses to account for this observation.

Our results suggest the following: 1) the relatively high absolute number of ECTR performed for nonclassic toxins may simply reflect the large number of exposures to these toxins, 2) poisoning by another toxin may have been the reason for ECTR initiation in some exposures to nonclassic toxins, 3) poisoning from nonclassic toxins may receive ECTR for purposes other than toxin removal, 4) the decisional threshold to initiate ECTR may be lower for nonclassic toxins because of heightened toxicity, and 5) new knowledge translation did not appear to influence the proportion of patients with nonclassic toxins that received ECTR.

The number of ECTRs performed for nonclassic toxins is exceedingly low after accounting for all exposures reported for that specific toxin. While this is also true for classic toxins (e.g., ECTR was performed in only 5% of all lithium and ethylene glycol exposures), this percentage was statistically lower for nonclassic toxins. Instead, the apparent high number of ECTRs for nonclassic toxins seems to reflect the relatively higher frequency of these poisonings. Even if only considering severe cases, thus removing the low-risk exposures that are unlikely to be candidates for ECTR, the proportion of cases that received an ECTR is greater in classic toxins.

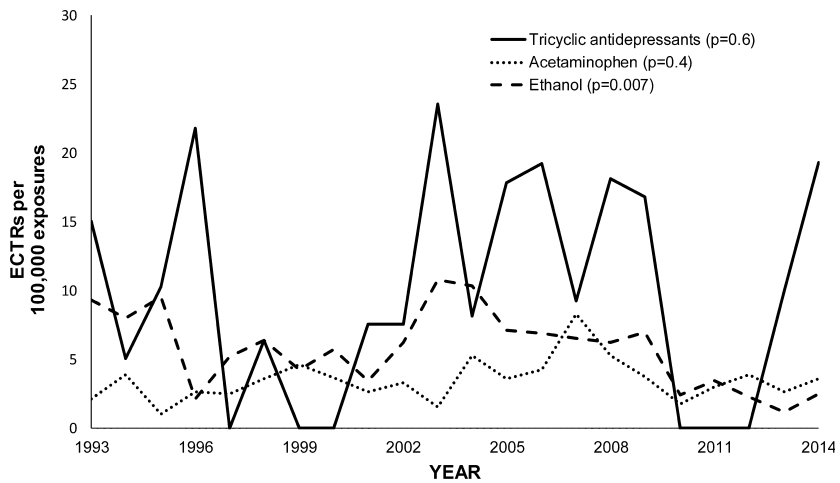

FIG. 1. Annual rate of ECTR performed per total exposures for acetaminophen, tricyclic antidepressants, and ethanol (NPDS 1993–2014).

Other potential contributors for the use of ECTRs in patients with poisoning to nonclassic toxins include the presence of other coingestants, greater severity of poisoning or concomitant clinical conditions that might have prompted ECTR. Although toxin removal could have been an important and even the primary reason for ECTR in these cases, our data also suggest that ECTR may have been performed for other indications altogether. For example, as demonstrated in Table 3, nearly 97% of metformin poisonings treated with ECTR had other concomitant indications for ECTR. This is consistent with findings from a recent systematic review showing that ECTR for metformin toxicity is often performed to correct severe metabolic disturbances (9). This is also consistent with another publication showing that kidney complications (AKI, oliguria) occurred proportionally more frequently after poisoning to cardiac drugs and acetaminophen than ethylene glycol or lithium, yet ECTR was used less frequently. This further strengthens the idea that ECTR is more often used for poison removal in "classical toxins" (10).

In acetaminophen poisoning specifically, the safety, wide availability, and efficacy of acetylcysteine makes ECTR unnecessary for almost all cases (6). However, severe acetaminophen poisoning can be complicated by acute kidney injury or severe metabolic acidosis which could necessitate dialysis (11). A review of individual cases from US poison centers from 1993 to 2005 presented in abstract form confirmed that only 7.6% of ECTRs were interpreted as being initiated for acetaminophen removal, while 26.9% were performed for removal of a coingestant and 61.4% and 54.4% of ECTRs were performed, respectively, for kidney failure or acidosis (12). Alternately, it is possible that ECTR may be clinically beneficial in very specific situations. As mentioned, most toxic acetaminophen exposures, even those that progress to liver injury, do not require hemodialysis unless severe acute kidney injury develops. However, in the subset of patients who present following a massive ingestion with signs of mitochondrial toxicity (profound acidemia with an elevated lactate concentration), hemodialysis may improve clinical outcomes (6,13). Similarly, treatment of ethanol overdose is largely supportive even after a massive ingestion, because its elimination half-life is short and because it rarely causes life-threatening effects. Hemodialysis is seldom necessary, but there are reports of its use in infants who may be more vulnerable to ethanol's effects, or for example, after iatrogenic ethanol intoxication (14–16).

It does appear from the above results that ECTR performed during poisonings from benzodiazepines, cardiac glycosides, and tricyclic antidepressants is less commonly performed for the intended benefit of toxin removal than was suggested by earlier reports. ECTR is unlikely to be useful for such toxins because of their large volume of distribution, which limits their extracorporeal removal, and availability of alternative treatments. However, some clinicians still consider that ECTR may be indicated for some nonclassic toxins like tricyclic antidepressants (17–19).

Hemoperfusion and hemodialysis were often used liberally in the 1980s and 1990s to promote elimination of a large number of poisons (20). However, with better understanding of poison toxicokinetics and technical limitations of ECTRs, we suspected that the use of ECTR to enhance elimination of nonclassic toxins would decrease. However, this hypothesis was only supported for ethanol but not for other toxins. These findings do not imply that ECTR was used inappropriately, as individual case charts were not available for in-depth review to evaluate the reason for ECTR. It is also impossible to discount regional practice differences. Indications for ECTR may vary according to the incidence of poisoning and regional expertise; for example, in the United States, hemodialysis and hemoperfusion are not considered typically useful for poisonings to organophosphate pesticides, while in parts of Asia, these techniques are often part of the standard of care (21–23).

Unfortunately, one limitation of the data is the inability to distinguish between different types of ECTR (other than hemodialysis and hemoperfusion) and the timing of the ECTR with regard to the course of poisoning. This may be especially relevant with acetaminophen where the code entry classified as "ECTR, other" may both include CRRT and liver support devices. The first may be done for poison removal or for AKI while the latter may be used as a bridge to liver transplant in the later phases of toxicity (24).

In conclusion, although ECTRs continue to be performed in the United States for toxins not usually considered amenable to extracorporeal removal, this analysis suggests that it is rarely for enhanced elimination, but more likely for other clinical indications.

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