

Practice Trends in the Use of Extracorporeal Treatments for Poisoning in Four Countries

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ABSTRACT

Extracorporeal treatments (ECTR) such as hemodialysis (HD), enhance the elimination of a small number of toxins. Changes in overdose trends, prescribing practices, antidotes, and dialysis techniques may alter the indications and rates of ECTR use over time. This study analyzed trends in ECTR for poisonings in four countries. A retrospective study of national poison center databases from the United States, Denmark, United Kingdom, and five regional databases within Canada was performed. All cases of patients receiving an ECTR were included. ECTR cases were totalled annually and reported as annual rates per 100,000 exposures with stratification per types of ECTR and toxins. The data collection varied by countries. United States, 1985–2014; United Kingdom, 2011–2013; Denmark, 2005–2014, and regions of Canada as follows: Alberta, 1991–2015; Saskatchewan, 2001–2015; Nova Scotia-PEI, 2006–2015;

Quebec, 2008–2014; Ontario-Manitoba, 2009–2015; British Columbia, 2012–2015. During the study period, the total number of ECTR and rates per 100,000 exposures, respectively, were: United States, 40,258 and 65.7; United Kingdom, 343 and 232.6; Denmark, 616 and 305.5; Canada, 2709 and 177.5; case rates increased over time for the United States, Denmark, and Canada, but decreased in the United Kingdom. Across the United States and Denmark, HD was the preferred modality used. Toxins for which ECTR was most often used were: United States, ethylene glycol; Canada, methanol; United Kingdom, ethylene glycol; Denmark, salicylates. A high number of ECTR were performed for atypical toxins such as acetaminophen and benzodiazepines. These data demonstrate a growing use of HD for poisoning with significant regional variations in the overall rates and indications.

Extracorporeal treatments (ECTR) such as hemodialysis and hemoperfusion can enhance the elimination of selected poisons. Historically, these techniques were recommended as definitive treat-

ments for severe poisonings caused by salicylates, lithium, ethylene glycol, methanol, and theophylline (1–5). In special circumstances, toxicity from other poisons may warrant extracorporeal removal; examples include carbamazepine, valproic acid, long-acting barbiturates, phenytoin, acetaminophen, metformin, baclofen, methotrexate, paraquat, and others (6–9). The development of new antidotes, improvements in supportive care, better understanding of toxicokinetics and improvement in dialysis techniques have changed the indications for ECTR. A previous study reviewing United States trends in

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ECTR use for poisoned patients from 1985 to 2005 showed that hemodialysis had largely supplanted hemoperfusion and other modalities (10). The purpose of this study was to update trends in ECTR for poisonings in the United States and also present data from three other countries.

Materials and Methods

Study Design

A retrospective study was undertaken of three different centralized national poison center databases (United States, Denmark, United Kingdom) and five regional databases within Canada (British Columbia, Quebec, Ontario-Manitoba, Alberta-Saskatchewan, and Nova Scotia-Prince Edward Island). All information available concerning reported patients receiving an ECTR were included.

Database Description

United States

The National Poison Data System (NPDS) is an electronic national database maintained by the American Association of Poison Control Centers (AAPCC) that captures all exposures from participating poison centers in the United States. NPDS contains more than 60 million exposure case records going back to 1983. Data are collected during normal poison center operations by Specialists in Poison Information (SPI) using electronic health record systems with mandatory common data elements and reporting requirements. Cases are reported both directly from the public and from healthcare providers. This registry contains extensive information on patient demographics, route and estimation of exposure, toxin identification, clinical effects, managements, and outcomes. Recorded therapeutic managements include supportive measures, gastrointestinal decontamination, antidote administration, and elimination enhancement techniques, including ECTRs. This database has undergone several updates and transformations since its inception in 1983, with regard to captured fields, toxins reviewed, and other data. For example, the fields for exchange transfusion (ET) and peritoneal dialysis (PD) were removed and replaced by "Other extracorporeal treatments." Some data (such as symptoms and signs) were not reported prior to 1993. The identification of each toxin is recorded under one of two headings: Pharmaceuticals or non-pharmaceuticals. Product-specific codes are mapped to generic codes which are assigned to Major and Minor categories. Currently NPDS has 1081 active generic codes, 68 major categories, and 172 minor categories. The headings may represent a toxin/drug class (calcium antagonists, organophosphate insecticides) or a specific toxin or drug (e.g., carbamazepine, methanol). Occasionally, the specificity may be lost; for example, amitriptyline is rep-

resented as a class by its own, whereas other tricyclic antidepressants are grouped together. Some toxins are not categorized systematically under a specific subheading (e.g., methotrexate, diethylene glycol). NPDS maintains rigorous coding guidelines and each data element and its options are defined in the NPDS System Information Manual available on the NPDS web portal (<http://www.aapcc.org/data-system/>). The AAPCC annually present limited epidemiological data of selected portions in terms of number of exposure and clinical outcome. The period of time where data were collected was from 1985 to 2014 (although data from 2014 are still considered preliminary at the time of this writing). From 1985 to 2000, cases were derived from a previous sub-database (obtained from an earlier study) (10) while from 2000 to 2014, data were accessed electronically from the NPDS database. In 2014 alone, there were 2,164,831 total exposures.

United Kingdom

The National Poisons Information Service (NPIS) consists of four poisons units based in Birmingham, Cardiff, Edinburgh, and Newcastle. It handles enquiries only from healthcare professionals via the telephone and also provides information via an online database, TOXBASE[®]. It does not provide advice to the general public. Enquiries are received from all parts of the UK, and also from The Republic of Ireland at night. Data from telephone enquiries are recorded on the United Kingdom Poisons Information Service Database (UKPID). UKPID records data in a structured fashion and includes information about demographics, toxins to which the patient was exposed, doses, route of administration, investigations, and treatment recommended. The severity of features is recorded using the WHO poisoning severity score (11). The period of time where UKPID data were analysed was from 2011 to 2013. In 2013 alone, there were 51,593 reported exposures.

Denmark

The Danish Poison Information Centre (DPIC) provides information as an open 24 hour telephone service to the public and healthcare professionals on acute poisonings. All telephone enquiries are registered in a local database with detailed information about the poisoning and registration of the enquirer and the patient. Registration includes demographic patient data, a description of the exposure (amount, mode of exposure, etc.), clinical status, risk assessment, and management. All DPIC enquiries are classified into subgroups and arranged in main groups (substance categories). ECTRs are not entered as a specific field but rather classified as "other treatment." All hospitalizations are coded with regard to diagnosis and treatment and collected in the National Patient Registry (NPR). Substance exposures presented to the DPIC only

represent part of the total number of poisonings in Denmark during the period—many patients are poisoned and hospitalized with no contact to the DPIC. Coupling diagnosis code of toxicity with treatment code ECTR for the unique patient identification code was used to extract the study patient group (Study approval number FSEID 898). The DPIC covers all exposures reported from Denmark, Greenland, and the Faroe Islands, while the NPR covers reported hospitalizations from Denmark only. The period of time where data were collected was from January 1, 2005 to July 10, 2014. In 2013 alone, there were 23,171 reported exposures to the DPIC and 18,885 exposures reported to the NPR.

Canada

The period of time where data were collected was different for every province: Alberta (1991–2015), Saskatchewan (2001–2015), Nova Scotia-Prince Edward Island (2006–2015), Quebec (2008–2014), Ontario/Manitoba (2009–2015), British Columbia (2012–2015). The full description of regional databases is included in Data S1.

Definitions

- An “exposure” is defined as a single patient entry reported to the poison center and filed as a toxic exposure.
- An “ECTR” is defined as 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), and therapeutic plasma exchange (TPE).
- A “toxin” is defined as a xenobiotic presumed to be associated with the toxic exposure.
- A “toxin indication for ECTR” is defined as an exposure to a toxin when the ECTR was performed, regardless if the ECTR was performed to remove the toxin, to correct complications associated to the poisoning, both, or even if the toxin was a bystander when ECTR was performed.
- A “case” is defined as a patient who received an ECTR.

The ranking of co-ingestants by some poison centers is designed to reflect the relative contribution of the effect of a toxin on the overall clinical condition of the patient, as judged by the SPI or supervising physician; a toxin ranked number 1 is usually assumed to be the one most implicated in the effect. For these reasons, where ranking was undertaken, the toxin ranked first was considered to be the “responsible toxin” and was included for analysis while other co-ingestants were discarded: for example, a patient exposed to lithium (i), codeine (ii), amphetamines (iii) was considered as a lithium exposure. In addition, poisoning to combination

products were counted as a separate individual category (e.g., “salicylate-oxycodone”) but were later regrouped in the appropriate toxin class. For example, an exposure to ‘aspirin with oxycodone’ would be eventually be counted for salicylates.

Inclusion/Exclusion Criteria

All cases where the data entry for ECTR was “performed” were included. Duplicates cases were excluded if age, exposure, sex, and time to presentation were identical. Animal exposures and calls solely made for information requests were also excluded.

Data Extraction

Data from all databases were merged, cannibalized, consolidated, and transferred onto an Excel spreadsheet (Version 2013; Microsoft Corporation, Redmond, WA, USA) for analysis. For statistical analysis purposes, simplified headings for toxin identification were created to permit consistency between databases.

Calculations

Number of toxin exposures and performed ECTR cases were totalled annually for each country and further stratified per types of ECTR and toxins, when available. Annual rates of cases per 100,000 exposures were calculated in order to eliminate a potential confounding effect related to changes in poisoning incidence or reporting to and by PCCs. Poisson regression models were used to assess the effect of time and cases per 100,000 exposures in the four different counties. Testing for trends was conducted by fitting time (annually) as a continuous variable in the log linear Poisson model. Two-sided p-values of less than 0.05 were considered to be significant. Statistical analyses were performed with IBM SPSS Statistics 22 for Windows (IBM Corp., Armonk, NY, USA).

Results

Use of ECTR

ECTR Cases Performed By Countries

United States. From 1985 to 2014, there were 45,253 distinct poisoned patients in whom an ECTR was either recommended and/or performed: there were 1413 ECTRs “recommended but not performed”, 3583 ECTRs that were “recommended but unknown if performed”, and 40,258 patients for whom at least 1 ECTR was performed, for an overall rate of 65.7 ECTRs performed per 100,000 exposures.

United Kingdom. From 2011 to 2013, there were 343 cases where ECTR had been undertaken prior to the enquiry or recommended by the NPIS (232.6 ECTRs per 100,000 exposures).

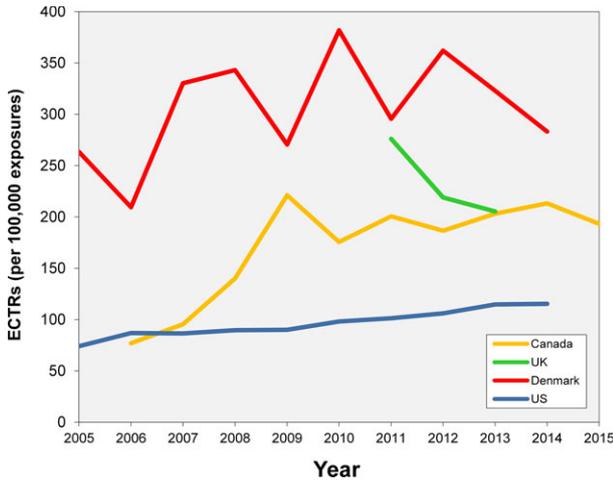


FIG. 1. Reported annual rate of ECTRs per 100,000 exposures. Rates were significantly increasing in the United States, Denmark, and Canada and significantly decreasing in the UK.

Denmark. There were 481 ECTRs recommended by the DPIC (398.7 ECTRs per 100,000 exposures) and 616 ECTRs reported performed to the NPR (305.5 ECTRs per 100,000 registered exposures).

Canada. a total of 2709 ECTRs were performed in Canada during the study period, of which 799 cases were reported in Alberta, 107 in Saskatchewan, 122 in Nova Scotia-PEI, 809 in Quebec, 736 in Ontario and Manitoba, and 136 in BC. Recognizing that there was considerable heterogeneity of study periods across provinces, the overall rate was 177.5 ECTRs performed per 100,000 exposures.

Longitudinal Variations in the Use of ECTRs in four Countries (2005–2014)

The annual case rates of ECTR has steadily and significantly increased in the United States from

2005 to 2014 (from 74.1 to 115.3 cases per 100,000 exposures, $p < 0.0001$). This increase was also documented in Denmark ($p = 0.001$) and Canada ($p < 0.0001$), while the rate decreased in the United Kingdom over a 3-year period ($p = 0.001$; Fig. 1).

Types of ECTR Used

United States. Overall, the ECTR consisted of HD in approximately 95% of cases. PD and ET were performed in 8.5% and 4.2% of all reported cases respectively prior to 1993 (these were no longer reported afterward). Overall, HP was performed in 5% of all ECTRs performed; the case rates of HP rose from 1985 to 1987 and then progressively decreased to below 2 cases per 100,000 exposures by 1997 and remained approximately stable thereafter. By 2014, HD had remained the overwhelming choice of ECTR for poisonings (Fig. 2). The absolute number of performed HDs increased every year.

Denmark. HD remained the overall preferred ECTR but CRRT actually surpassed HD in 2013 and 2014. Approximately, 10% of all ECTRs were a combination of HD and CRRT (Fig. 2). The use of PD in Denmark throughout the 10 year study period was inconsequential (three cases in total, not shown in figure).

No specific data on the type of ECTR available were available for the United Kingdom or Canada, although preliminary data for the latter suggest that intermittent HD is predominantly used while HP has all but disappeared.

Toxin Indication For ECTR

Per Country

The toxins for which ECTR was most often performed per country is presented in Table 1. The same table also shows how often (in %) an ECTR

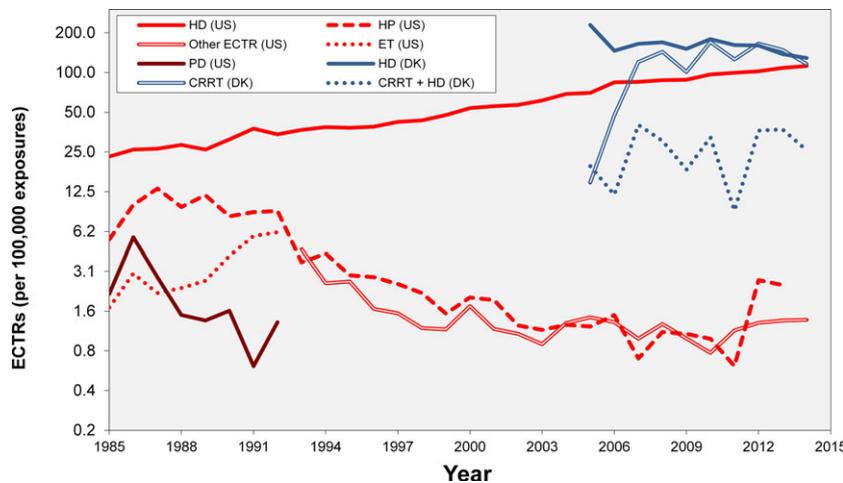


FIG. 2. Annual rates of different ECTRs in the United States and Denmark (logarithmic scale). *PD rates in Denmark not shown. DK, Denmark; HD, hemodialysis; CRRT, continuous renal replacement therapies; ET, exchange transfusion; HP, hemoperfusion; PD, peritoneal dialysis.

TABLE 1. Top 10 toxins present when ECTR was performed in four countries during the study period

	United States	Canada	Denmark	United Kingdom
1	Ethylene glycol ($n = 7831$; 3.9%)	Methanol ($n = 413$; 5.7%)	Salicylates ($n = 140$)	Ethylene glycol ^a ($n = 150$; 24.0%)
2	Lithium ($n = 7315$; 4.1%)	Ethylene glycol ($n = 315$; 5.9%)	Lithium ($n = 109$)	Acetaminophen ($n = 30$; 0.2%)
3	Salicylates ($n = 4551$; 0.4%)	Salicylates ($n = 254$; 1.8%)	Barbiturates ($n = 48$)	Ethanol ($n = 23$; 0.3%)
4	Acetaminophen ($n = 2868$; 0.1%)	Lithium ($n = 251$; 7.6%)	Valproic acid ($n = 39$)	CCBs ($n = 23$; 1.4%)
5	Methanol ($n = 1749$; 2.2%)	Acetaminophen ($n = 96$; 0.1%)	Ethanol ($n = 36$)	Valproic acid ($n = 20$; 2.1%)
6	Theophylline ($n = 1235$; 1.6%)	Valproic acid ($n = 68$; 1.5%)	Metformin ($n = 26$)	Salicylates ($n = 18$; 0.7%)
7	Ethanol ($n = 770$; 0.0%)	Ethanol ($n = 51$; 0.3%)	Carbamazepine ($n = 16$)	Benzodiazepines ($n = 22$; 0.6%)
8	Valproic acid ($n = 701$; 0.3%)	Benzodiazepines ($n = 44$; 0.2%)	Pregabalin ($n = 16$)	Lithium ($n = 15$; 2.7%)
9	Cardiac glycosides ($n = 690$; 0.5%)	Metformin ($n = 41$; 1.2%)	Lamotrigine ($n = 13$)	Metformin ($n = 15$; 1.3%)
10	Metformin ($n = 633$; 0.5%)	Carbamazepine ($n = 21$; 0.6%)	Magnesium ($n = 12$)	Methanol ($n = 15$; 2.8%)

In parenthesis, the number of ECTRs performed and % of toxin-specific exposures treated with ECTR (when the number of exposure was unavailable, the % was not presented). CCBs, calcium channel blockers.

^aIncludes "Antifreeze".

is used when accounting for all exposures for a specific toxin. For example, in the United States, 3.9% of all reported exposures to ethylene glycol were treated with an ECTR. Fig. 3 shows which toxins proportionally account for the most number of ECTRs per country from 2005 to 2014.

United States. Ethylene glycol, lithium, and salicylates accounted for nearly half of all toxin indications for ECTR. Toxins for which ECTR is considered either unnecessary or not amenable to removal, such as ethanol, benzodiazepines, and calcium antagonists were also ranked high on the list. For 2014, the 10 toxins most often implicated in order of decreasing frequency were: ethylene glycol (353 cases), lithium (311 cases), salicylates (284 cases), ethanol (235 cases), benzodiazepines (200), acetaminophen (160 cases), methanol (53 cases), metformin (51 cases), cardiac glycosides (48 cases), and antihistamines (27 cases). Fig. 4 shows the absolute number of ECTRs performed yearly for major toxins, while Fig. 5 shows these by 5-year period.

United Kingdom. Ethylene glycol was by far the most common toxin indication for ECTR, representing nearly half of all cases. The next most common toxins were acetaminophen, ethanol, calcium channel blockers, and valproic acid.

Denmark. Salicylates represented the most common indication for ECTR, followed by lithium, barbiturates, valproic acid, and ethanol.

Canada. Methanol, ethylene glycol, lithium, and salicylates represented approximately 50% of all toxins indications for ECTR. In contrast to the United States, methanol was the most common toxin indication for ECTR.

Longitudinal Variations in Toxins Treated with ECTR (1985–2014)

There were longitudinal variations in how many ECTRs were performed for specific toxins in the United States: for example, in 2006, 535 ECTRs were performed for ethylene glycol, compared to only 353 in 2014. There were 112 ECTRs performed for theophylline in 1991, while there were only two

in 2014. There was 1 ECTR performed for metformin in 1992, but 86 in 2013.

Although there were yearly fluctuations in the absolute number of ECTRs performed for specific toxins, the case rate of ECTR per 5-year period for toxin-specific exposures increased for every toxin ($p < 0.0001$) from 1985 to 2014, except for barbiturates ($p = 0.4$) which remained stable over time (Fig. 6).

Patient Demographics and Mortality Rates

Demographics of Patients in Whom ECTR was Performed (Table 2)

In the United States, the mean age of patients was 42.8 years. Approximately, two-thirds of all cases were single toxin exposures. The majority of exposures were acute and suicidal intent was the reason for poisoning in over half the cases. Over 75% of patients were treated in a critical care unit. Symptoms and signs confirm the severity of poisoning: coma was present in 30%, hypotension in 25%, and respiratory failure in 11%. Over 75% of patients experienced at least a moderate effect from poisoning and 8.9% of them died. Approximately, one-third of patients required mechanical ventilation and 18% vasopressors. Data from other countries were irregularly reported, but when available, was comparable to that of the United States.

Deaths

Among patients who received an ECTR, there were 3295 deaths reported to the United States, representing 8.9% of all cases. Toxins most related to fatalities were acetaminophen (675), ethylene glycol (432), salicylate (251), methanol (245), and metformin (122). There were 123 deaths in Denmark representing 20% of all patients receiving an ECTR who were reported to the NPR with salicylates (35), acetaminophen (18), "other analgesic" (23), and drugs of abuse (5) the most commonly reported toxins. There were 76 reported deaths in Canada,

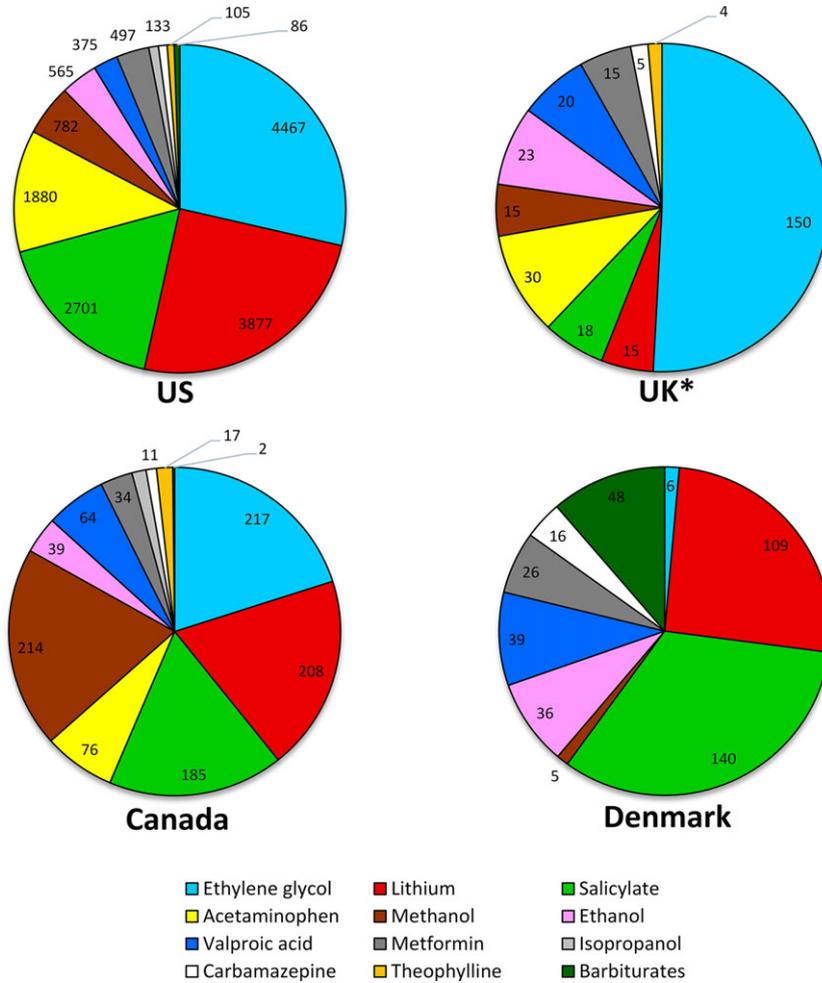


Fig. 3. Toxin indication for ECTR in four countries 2005–2014. *Ethylene glycol in the United Kingdom includes “Antifreeze”.

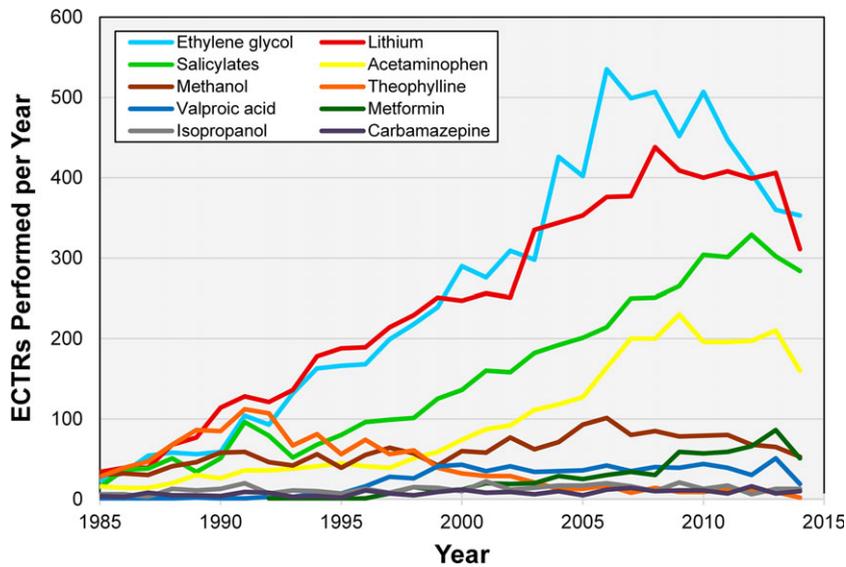


Fig. 4. Absolute yearly number of ECTRs performed for major toxins in the United States.

representing 4.6% of ECTR patients in whom the outcome was reported. Methanol (20), acetaminophen (8), ethylene glycol (6), and salicylates (5) were the toxins most commonly associated with fatalities.

Discussion

This analysis reviews how ECTRs are used for poisoning in four distinct countries over the last

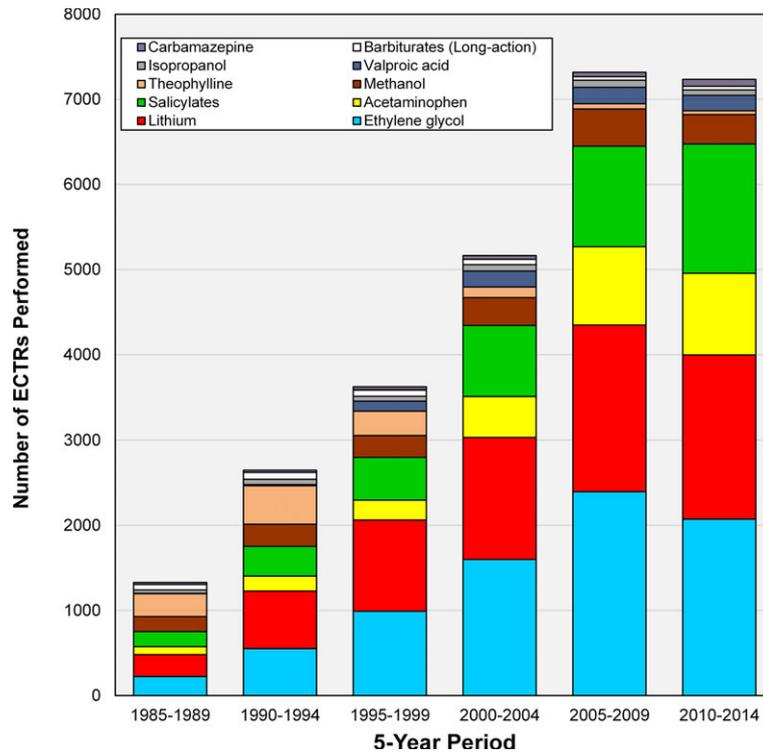


Fig. 5. Absolute number of ECTRs performed for major toxins (stacked columns) per 5-year period in the United States.

decade. With regard to the US data, this paper follows a previous publication that reviewed the NPDS data from 1985 to 2005, but extends the analysis to 2014 (10).

The ECTRs rates were different in every country, likely a reflection of the heterogeneity in the denominator rather than major variations in the indications and applications of ECTRs. For example, the ECTR rates in Denmark were much higher than those reported elsewhere. In the United States and Canada, a substantial proportion of exposures are

derived from calls from the public, few of which will eventually receive ECTR. In Denmark, exposures reported to the National Patient Registry are all derived from cases treated in a health care facility, and therefore are likely to be more clinically ill following consequential exposures. Similarly, in the United Kingdom, calls are made exclusively from healthcare professionals, which also restrict the denominator in favor of a sicker population and therefore a proportionally greater ratio of ECTRs performed. For example, using a denominator solely

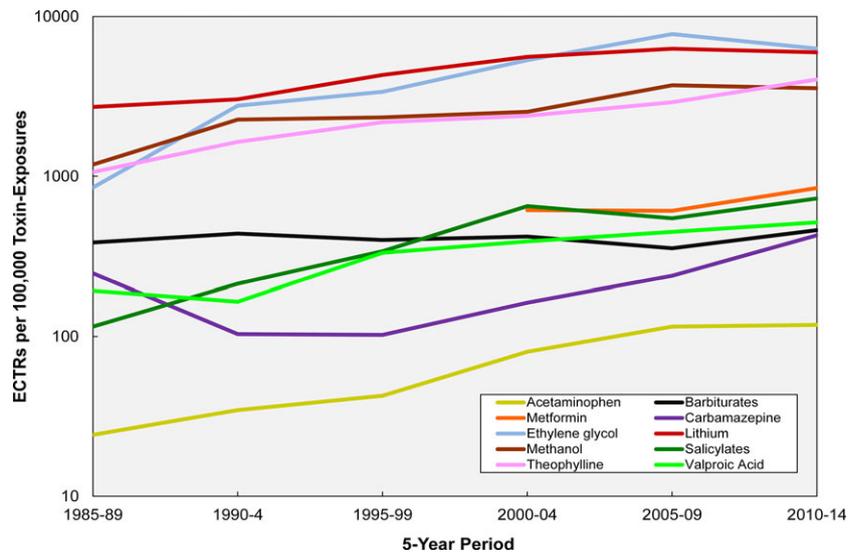


Fig. 6. Longitudinal variations of case rates of ECTRs performed per toxin-specific exposures in the United States per 5-year time periods. *Rates significantly increased for every toxin ($p < 0.0001$) except barbiturates.

TABLE 2. Demographics of ECTR cases performed

	United States (<i>n</i> = 40,258) ^a	Canada (<i>n</i> = 1837) ^b	Denmark (<i>n</i> = 463)	United Kingdom (<i>n</i> = 353)
Demographics				
Mean age (years)	42.8	44.6	44	
Gender (% male)	53.9%	50.7%	35.2%	
Mean weight (kg)	79.7			
Poisoning				
1 toxin exposure	65.8%	66.0%	57.8%	
2 toxins exposure	19.4%	14.8%	28.3%	
>2 toxins exposure	14.7%	19.2%	13.9%	
Acute exposures	67.3%			
Suicidal intent	57.2%	67.2%	70.4%	
Ingestion route	87.5%			
Home as exposure site	92.2%	76.2%		
Treated in the intensive care unit	78.5%	84.4%		
Symptoms and signs (related or not)				
Acidosis	40.9%			
Asystole	2.3%			
Cardiac arrest	7.4%			
Coma	25.8%			
Creatinine increased	33.3%			
Electrolyte abnormality	29.2%			
Hypotension	25.3%			
Oligo/anuria	14.4%			
Pulmonary edema	2.3%			
Renal failure	25.2%			
Respiratory arrest	6.1%			
Respiratory failure	11.4%			
Rhabdomyolysis	5.8%			
Seizure (>1)	3.7%			
Other treatment performed				
Alkalinization	33.9%			
SDAC	18.5%			
MDAC	4.3%			
Ventilation	33.4%			
Vasopressors	18.0%			
Severity of clinical effects				
Moderate effect	31.8%	12.6%		15.6%
Major effect	44.2%	52.1%		68.3%
Death	8.9%	4.6%	20.0% ^c	

^aData were derived from 1985 to 2014, except for symptoms and signs where data was derived from 1993 to 2014 (*n* = 35,827).

^bDemographic data for Canada do not include British Columbia and Ontario.

^cFrom NPR data.

composed of hospitalized patients in the United States in 2014, the case rate for ECTR becomes 454 per 100,000 exposures instead of 115 per 100,000 exposures for all cases reported to the AAPCC.

The results show a significant increase in the reported annual number of ECTRs performed per 100,000 exposures in both the United States and Canada. This is in contrast to that of several popular techniques, including decontamination procedures like single-dose activated charcoal, whole-bowel irrigation, gastric lavage as well as elimination enhancement techniques such as multiple-dose activated charcoal (MDAC) which have all decreased over time in the United States (Fig. S1) (19). This growing popularity of ECTR may reflect the greater availability of dialysis centers as well as the development of more efficient dialyzers and higher blood flows, which have now permitted removal of toxins that were previously not considered “dialyzable”. Better understanding of toxicokinetics may also have encouraged wider applications of ECTR to newer drugs (dabigatran, pregabalin). This increase in ECTR use in North America and

Denmark was not paralleled in the United Kingdom perhaps due to the limited time frame during which these data were compiled (3 years).

This study confirms the major preference for HD over other ECTRs in poisoning situations, especially in the United States, where it is now practically the only ECTR used. Unfortunately, these data are likely misinterpreted; in the United States, the only codes that allow tracking for an ECTR are “Hemodialysis”, “Hemoperfusion”, and “Extracorporeal Procedure, Other”. Technically, ECTRs such as TPE, PD, CRRTs, and other ECTRs are coded as “Extracorporeal Procedure, Other”, although it is unknown to what extent this is done accurately. Considering that there are numerous case reports of toxins treated with CRRTs and very few cases reported to the NPDS as “Extracorporeal Procedure, Other”, it is suspected that CRRTs are often miscoded as “Hemodialysis”, artificially inflating the numbers for HD. When CRRT and hemodialysis are entered distinctly, such as in Denmark, a growing use for CRRT in poisoning cases is indeed reported. Although toxin clearance achievable with

CRRTs is lower than that achievable by intermittent hemodialysis, there may be obstacles to perform acute intermittent hemodialysis because of constraints in beds or personnel; in some institutions, ECTR is performed exclusively in the intensive care unit, where continuous techniques are often favored over intermittent ones. In Canada and the United Kingdom, there is no coding distinction between ECTRs. Ideally, CRRTs, TPE, and other emerging ECTRs should be coded as distinct data entries.

The waning popularity of HP is apparent in this study; this may be explained by a ten-fold higher cost of charcoal cartridges over dialysis filters (12), a higher rate of complications associated with HP (13), the phenomenon of cartridge saturation necessitating its replacement every 2–4 hours (14), the lesser availability of these cartridges (15), and its inefficiency at correcting acid-base and metabolic derangements (14). These factors, added to the greater efficacy of dialysis filters, have rendered HP an anecdotal technique for poisonings in Europe and North America (15). Elsewhere, such as in China and India, charcoal and resin hemoperfusion remain in use (16). In the United States, resin hemoperfusion is unavailable and charcoal cartridges are relatively scarce (15). Peritoneal dialysis clearance is much inferior to that achieved by HD (17,18), so its marginal use is expected.

This study confirms that toxic alcohols, salicylates, lithium, and acetaminophen account, in absolute numbers, for the majority of toxin indications for ECTR. This is true for the United States, United Kingdom, and Canada although methanol appears a major toxin indication for ECTR in the latter, perhaps because of easy access to industrial and commercial methanol products, especially during winter months. Severe toxic alcohol exposures are uncommon in Denmark, because the availability of methanol is strictly regulated to industrial or laboratory use only.

There was a significant increase in ECTR case rates for all reviewed toxins in the United States aside from barbiturates. This may reflect both greater awareness among clinicians and greater availability of hemodialysis across the country. Considering that hemodialysis is more-efficient, safer, and less expensive than ever before, this lower risk-benefit ratio of HD may explain its greater use for poisoning. There was also an increase in ECTR rates for both methanol and ethylene glycol over time, although these rates decreased in 2010–2014; this finding is consistent with a previous publication showing that the wider availability of fomepizole may obviate the necessity of ECTRs in early ethylene glycol and possibly also in methanol poisoning (20).

The demographics of poisoned patients treated by ECTR are not surprising: in most cases, poisonings treated with ECTR follow an acute exposure. This is expected, as by definition, toxin concentration in the blood is often much higher in acute than chronic poi-

soning. This condition is more conducive to extracorporeal elimination, which relies on the presence of toxin in the blood compartment although there are many circumstances where chronic exposure to a toxin may warrant ECTR (e.g., salicylates, lithium, metformin). Patients who received an ECTR, as a whole, were sick and had a high number of life-threatening symptoms and signs: more than a third of patients were either receiving vasopressors or were intubated for airway protection or hypoventilation. Despite ECTR, about 9% of patients treated in the United States expired. The death rate was twice as high in Denmark, which again may be related to regional variations in care, with a potential bias to only request ECTR support in Denmark for more severely poisoned patient; it is unknown if this increased death rate also relates to a greater relative number of salicylate cases. Unfortunately, the databases do not allow for a more formal case-matching evaluation of this hypothesis.

Our analysis has several limitations. None of the national databases provide quantitative data to express severity, such as pH, serum concentration, or osmolal gap. The amount of clinical detail supplied from Canada and especially from Denmark and the United Kingdom is far less comprehensive than that available from the United States. Poison coding differs from country to country (in Denmark, e.g., lithium is coded to the NPR as “antidepressants”). The toxins rank in a multi-toxin exposure may have not been coded correctly, leading to inaccuracies in the identification of the exact indication for ECTR. The study periods for the various regional poison centers in Canada were heterogeneous, although this effect is dampened by the preferential use of rates (per 100,000 exposures) instead of absolute numbers.

The retrospective nature and subjective interpretation of the charts by the SPIs and poison center medical directors add more uncertainty to the value of the data. Only cases in which ECTR was known to be “performed” were kept. It is possible that the number of ECTRs is misestimated; in the United Kingdom, ECTR cases included those that were either performed prior to the call or recommended by the poison center; in the United States, the “recommended” and “recommended, unknown if performed” fields represent approximately 15% of the data, leading to an underestimation of the actual number of ECTRs performed. In all countries, follow-up information was not always available to assess if the ECTR was performed according to the recommendation of the PCC.

A surprising finding in this publication, also observed in a prior publication (10), was the high number of ECTRs performed in exposures to acetaminophen, benzodiazepines or ethanol. In many of these cases, it is recognized that the ECTR may not have been performed for toxin removal, but rather for treatment of secondary complications, such as acidosis or acute kidney injury. In a subsequent paper, we will analyze hypotheses for this finding.

In conclusion, this study is the first to study multiple national databases over a period of time, permitting longitudinal analysis of what type of ECTRs are used for poisoning and for which toxins ECTR is most often performed. These results suggest that intermittent hemodialysis remains the preferred ECTR, that its use is increasing for poisonings (although not in the UK), and that toxic alcohols, lithium, and salicylates remain the toxins for which an ECTR is most often performed.

Disclaimer

The American Association of Poison Control Centers (AAPCC; <http://www.aapcc.org/>) maintains the national database of information logged by the country's poison centers (PCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure, etc.), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCs and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1 Database description.

Fig. S1 Case rates of ECTRs compared to common poisoning treatments in the United States.