Special Feature

Extracorporeal Treatment for Thallium Poisoning: Recommendations from the EXTRIP Workgroup

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Summary

Background The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup was formed to provide recommendations on the use of extracorporeal treatment (ECTR) in poisoning. To test and validate its methods, the workgroup reviewed data for thallium (Tl).

Methods After an extensive search, the co-chairs reviewed the articles, extracted the data, summarized findings, and proposed structured voting statements following a predetermined format. A two-round modified Delphi method was chosen to reach a consensus on voting statements and RAND/UCLA Appropriateness Method to quantify disagreement. Blinded votes were compiled, returned, and discussed during a conference call. A second vote determined the final recommendations.

Results Forty-five articles met inclusion criteria. Only case reports and case series were identified, yielding a very low quality of evidence for all recommendations. Data on 74 patients, including 11 who died, were abstracted. The workgroup concluded that Tl is slightly dialyzable and made the following recommendations: ECTR is recommended in severe Tl poisoning (1D). ECTR is indicated if Tl exposure is highly suspected on the basis of history or clinical features (2D) or if the serum Tl concentration is >1.0 mg/L (2D). ECTR should be initiated as soon as possible, ideally within 24–48 hours of Tl exposure (1D), and be continued until the serum Tl concentration is <0.1 mg/L for a minimal duration of 72 hours (2D).

Conclusion Despite Tl's low dialyzability and the limited evidence, the workgroup strongly recommended extracorporeal removal in the case of severe Tl poisoning.

Due to the number of contributing authors, the affiliations are provided in Appendix 1 of the Supplemental Material.

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Introduction

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies. It was assembled to provide recommendations on the use of extracorporeal treatment (ECTR) in poisoning (www.extrip-workgroup.org). Rationale, background, objectives, and complete methods of this endeavor, supported by the Acute Dialysis Quality Initiative, were reported previously (1,2).

To evaluate and validate the methods, the workgroup chose a poison for which the published literature was both limited and potentially complex to interpret. Thallium (Tl) appeared to fit both criteria and was thus selected for review. The list of participating societies is shown in Table 1.

Tl Toxicokinetics

The toxicokinetics of Tl are poorly and inconsistently described. This reflects a lack of controlled experimental data on the effect of dose, salts, type of exposure (acute or chronic), and interindividual variability in toxicokinetics (3). Tl physicochemical and toxicokinetic characteristics are outlined in Table 2.

Tl is extensively absorbed through almost all routes of exposure. Oral bioavailability of hydrophilic Tl salts approaches 90%–100% (4–7). Absorption may be prolonged if there is Tl-associated paralytic ileus (8).

Tl distributes widely throughout the body in a multicompartment fashion; two- and three-compartment kinetic models have been previously fit to Tl concentration-time data (6,8–10). Reported differences in the rate and extent of Tl distribution probably stem from variations in modeling procedures used to characterize its toxicokinetics, particularly regarding timing of assessment (*i.e.*, before or during terminal or steady-state distribution). It is rapidly distributed into the intracellular space, exhibiting an initial apparent half-life of 5 minutes (6,10). Distribution into other peripheral compartments, including the central nervous system (CNS), occurs over 24 hours (6,10,11). Tl has a large apparent volume of distribution (3–10 L/kg) (5,6,8,9). Once distribution is complete, Tl is detectable in nearly all

Table 1. Represented societies	
American Academy of Clinical Toxicology[a]	European Renal Best Practice[a]
American College of Medical Toxicology[a]	European Society for Emergency Medicine[a]
American Society of Nephrology	European Society of Intensive Care Medicine[a]
American Society of Pediatric Nephrology	French Language Society of Resuscitation[a]
Asia Pacific Association of Medical Toxicology[a]	German Society of Nephrology[a]
Australian and New Zealand Intensive Care Society[a]	International Pediatric Nephrology Association
Australian and New Zealand Society of Nephrology[a]	International Society of Nephrology[a]
Brazilian Association of Information Centres and Toxicologic Assistance[a]	Latin American Society of Nephrology and Hypertension[a]
Brazilian Society of Nephrology[a]	National Kidney Foundation[a]
Brazilian Society of Toxicology[a]	Pediatric Continuous Renal Replacement Therapy[a]
Canadian Association of Poison Control Centres[a]	Pediatric Critical Care Medicine
Canadian Association of Emergency Physicians[a]	Quebec Association of Emergency Physicians[a]
Canadian Society of Nephrology[a]	Quebec Association of Specialists in Emergency Medicine[a]
Chinese College of Emergency Physicians[a]	Quebec Society of Nephrology[a]
Chinese Medical Doctor Association[a]	Renal Association[a]
European Association of Poison Centres and Clinical Toxicologists[a]	Society of Critical Care Medicine[a]
	Spanish Clinical Toxicology Foundation[a]

[a]Support/endorsement of these recommendations.

Table 2. Thallium physicochemical and toxicokinetic data	
Variable	Level
Molecular weight (g/mol)	204.4
Volume of distribution (L/kg)	3–10
Protein binding (%)	0
Oral bioavailability (%)	90–100
Therapeutic range	NA
Toxic blood concentrations (mg/L)	>0.1
Intervention blood concentration (mg/L)	≥1.0
Lethal dose (mg/kg)	>6–8

organs, with highest concentrations in kidney and liver, followed by bone, stomach, intestine, spleen, muscle, lung, testes, and brain (4,8,10).

Tl is primarily eliminated unchanged from the body via the bile and feces (51%) and urine (26%), but it is also excreted in sweat, saliva, tears, and breast milk and appears in hair and nails (7,11). Although Tl appears in urine within an hour of exposure (6), its large apparent volume of distribution and extensive enterohepatic recirculation result in a long terminal elimination half-life, commonly reported to be between 2 and 4 days (7–10). More prolonged half-lives of 10–15 days have been reported (6,10).

Overview of Tl Poisoning

Thallium salts were formerly used as medicinal agents (for ringworm) (12,13) and rodenticides (14). Today Tl is used in the manufacture of optical lenses, extreme cold thermometers, and electric lighting. Poisonings are reported from countries where Tl rodenticide use continues (15), in homicides (16), and from contaminated herbal products and drugs of abuse (17,18). Recent data from Poison Control Centers in the United States document approximately 20 cases each year (19–21). Human dose-response data are lacking, but epidemiologic investigations estimate that the potentially fatal oral dose is >6–8 mg/kg (13,22). The small amounts used for radioactive contrast (<10 μg) pose no threat to human health (9).

Tl toxicity stems from its ability to mimic potassium because of similar charge and ionic radii. Once inside the cell, Tl replaces potassium and can stimulate or inhibit electrochemical and enzymatic processes. Inhibition of critical enzymes, such as pyruvate kinase and succinate dehydrogenase, impairs ATP generation and leads to mitochondrial injury (23,24). Additionally, Tl binds to sulfhydryl groups and interferes with cross-linking of keratin, accounting for changes occurring in hair, skin, and nails (15,25).

Gastrointestinal manifestations of Tl poisoning include abdominal pain associated with diarrhea or constipation (14–16,25). Characteristic findings include alopecia and a painful ascending peripheral neuropathy (12,26). In one large series, alopecia was present in all cases; ataxia, weakness, somnolence, and tremor were present in two thirds of cases; and neuropathy was present in one fourth of cases (13). Other manifestations of Tl exposure may include autonomic instability, involvement of cranial nerves, and AKI. Severe cases develop altered mental status, coma with loss of airway-protective reflexes, respiratory muscle paralysis, and cardiac arrest. The timing of signs and symptoms varies and partially depends on dose. Gastrointestinal symptoms typically begin within minutes to hours and are followed rapidly by the onset of a painful peripheral neuropathy. Alopecia is delayed by approximately 5 days. Although altered mental status is highly variable in onset, early occurrence suggests a significant exposure and, therefore, a poor prognosis.

Tl concentrations are measured by atomic absorption spectroscopy, which is present in only a small number of reference laboratories. Thus, confirmation of exposure is usually not rapidly available to clinicians. Moreover, results on most standard laboratory tests (biochemistry, hematology) are normal or nonspecific. The urine Tl concentration (normal, <5 μg/L) may confirm exposure but does not correlate well with blood concentrations or symptoms. Tl

has been found in hair, nails, stool, and blood; only the latter has any clear relationship to clinical poisoning.

Treatment consists of removal from exposure, supportive care, and enhanced elimination. Orogastric lavage is reasonable after early massive exposure in the absence of substantial vomiting. Thereafter, the use of activated charcoal in single or repeated doses is indicated given its high adsorptive capacity for Tl salts (27–29) and survival advantage in animal models (30). Although previously used, forced potassium diuresis and traditional chelators may facilitate Tl redistribution into neurologic tissues in humans (12,31–33) and increase lethality (34,35). Prussian blue is an orally administered ion exchanger that effectively increases fecal elimination of Tl and improves survival in animal models (5). However, availability of Prussian blue is limited in many locations.

Materials and Methods

The methods are described in detail elsewhere (2).

Literature Search

Articles were obtained *via* the preliminary search database. Thereafter, a specific search, last accessed on January 10, 2012, retrieved other articles from MEDLINE, Embase, the Cochrane Library (Review and Central), conference proceedings and meeting abstracts of the European Association of Poisons Centres and Clinical Toxicologists and North American Congress of Clinical Toxicology annual meetings, and Google Scholar. Finally, the bibliographies of all articles obtained were manually reviewed for completeness.

The search strategy was as follows:

[(thall* OR thallium) AND (poison* OR overdos* OR toxicity OR intoxication) AND (dialysis OR hemodialysis OR hemodialysis OR hemoperfusion OR haemoperfusion OR plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR hemofiltration OR hemodiafiltration OR hemodiafiltration OR extracorporeal therapy OR CRRT)]

Voting Process

The co-chairs completed the literature search, reviewed articles, extracted data, summarized findings, and proposed structured voting statements after a predetermined format, all of which were submitted to the workgroup. A two-round modified Delphi method was chosen to reach a formal consensus on proposed voting statements, and the RAND/UCLA Appropriateness Method was used to quantify disagreement between voters (Figure 1) (36). Blinded votes with comments were sent to the statistician, who then compiled and returned them to each participant. A conference call permitted every member to exchange ideas and debate statements. A second vote was submitted 48 hours later, and results reflect the core of EXTRIP recommendations (Supplemental Appendix 2).

Results

Results of the literature search are presented in Figure 2.

Dialyzability

Tl exhibits no protein binding and has a molecular weight well below the cutoff of any ECTR in use today (9).

Thus, excellent plasma Tl clearances (>100 ml/min) are attained with hemodialysis (HD) or hemoperfusion (37–43). However, the limiting factor of Tl removal by ECTR remains its large volume of distribution and intercompartmental transfer rates that appear to be relatively slow given the frequency of rebound in serum Tl concentrations after ECTR (37,40,44–47).

The determination of Tl dialyzability is supported by a large number of case reports. One prospective article of Tl toxicokinetics in healthy persons, using tracer amounts of radioisotopes, was identified, although no actual ECTR measurement was made (9). Most case reports have reasonable toxicokinetics methods (*i.e.*, serial measurements, appropriate calculations in dialysate, correct interpretation) but used older ECTR technology. The level of the evidence for dialyzability of Tl was therefore deemed to be of low-moderate quality.

The workgroup acknowledged, following the primary criteria (2), that ECTR removes only approximately 3% of total body stores over 6 hours. Hemoperfusion seems to be the most efficient ECTR at removing Tl, although the reported toxicokinetic data with HD are outdated. There is an assumption that modern ECTR techniques with optimal dialytic measures would yield enhanced Tl removal. However, because of the large volume of Tl distribution, any ECTR is not likely to remove a substantial proportion of the total body burden of Tl if initiated once distribution is complete. Conversely, if ECTR can be instituted early after ingestion (before tissue Tl distribution is complete), it is likely that more Tl could be removed. Peritoneal dialysis and plasmapheresis do not appear to clear significant amounts of Tl (8,48,49).

ECTR appears more efficient than endogenous elimination pathways in clearing Tl. In most published articles, hourly Tl removal with ECTR largely exceeded renal excretion (38,41,42,45,50,51). Furthermore, there is some evidence that hourly removal by HD or hemoperfusion is at least equivalent to fecal elimination *via* Prussian blue (37,39,47,52–54).

On the basis of the evidence, Tl would be considered "slightly dialyzable" with HD according to criteria 1 but as "dialyzable" according to the alternative criteria (Table 3) (2). The workgroup strongly agreed with the following statement: *Thallium is slightly dialyzable, low evidence (C).*

Executive Summary

An executive summary of the recommendations is presented in Table 4.

Recommendations

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

Rationale. Thallium is a highly toxic xenobiotic that can cause serious and long-term morbidity. Mortality can occur with ingestion as low as 6 mg/kg.

The literature review was composed solely of case reports and case series (74 patients studied), with inadequate control groups, multiple confounders, heterogeneous treatments, and definite publication bias. These variables complicate interpretation of the available data and extrapolation into recommendations. Hence, the quality of evidence for all recommendation statements is "very poor" (Table 5) (55). There were 11 deaths;
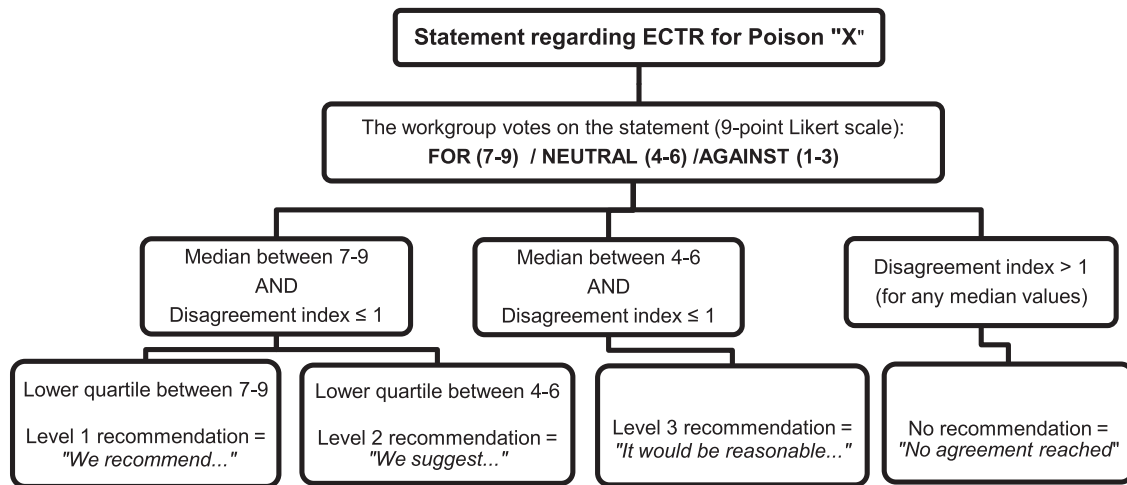
Figure 1. | **Voting process for recommendations**. Each participant assigned a numerical value of 1–9 for each voting statement, with 1 representing strong disagreement and 9 representing strong agreement. This figure illustrates how recommendations were derived from median vote scores. ECTR, extracorporeal treatment.

in all cases, exposure was massive or ECTR was initiated at least 48 hours after exposure (48,56–60). Occasionally, there were anecdotal reports of striking clinical improvement in patients treated within 24 hours of exposure, although the evidence is inconclusive (41,44,45,61–63).

EXTRIP members considered the data suggesting low extracorporeal removal and questionable clinical relevance of the small amount removed. Nevertheless, despite the absence of solid evidence, the workgroup considered the following arguments:

- The risk of permanent sequelae after Tl exposure is substantial.
- Complications associated with ECTR are infrequent and usually mild, as suggested by an internal review.

- There are no life-saving therapeutic alternatives to ECTR for Tl poisoning.
- ECTR significantly enhances Tl removal compared with renal and fecal elimination.
- There is anecdotal evidence of clinical improvement when ECTR is performed early after Tl exposure

For these reasons, the workgroup strongly felt that ECTR is worth the risks, costs, and uncertainty in Tl poisoning. The risk-benefit ratio for HD favors using it when available.

The workgroup readily acknowledged that other interventions capable of enhancing Tl elimination (Prussian blue, multiple dose–activated charcoal) should also be pursued during ECTR. Collectively, these interventions can contribute to removal of a large percentage of the T1 body burden,
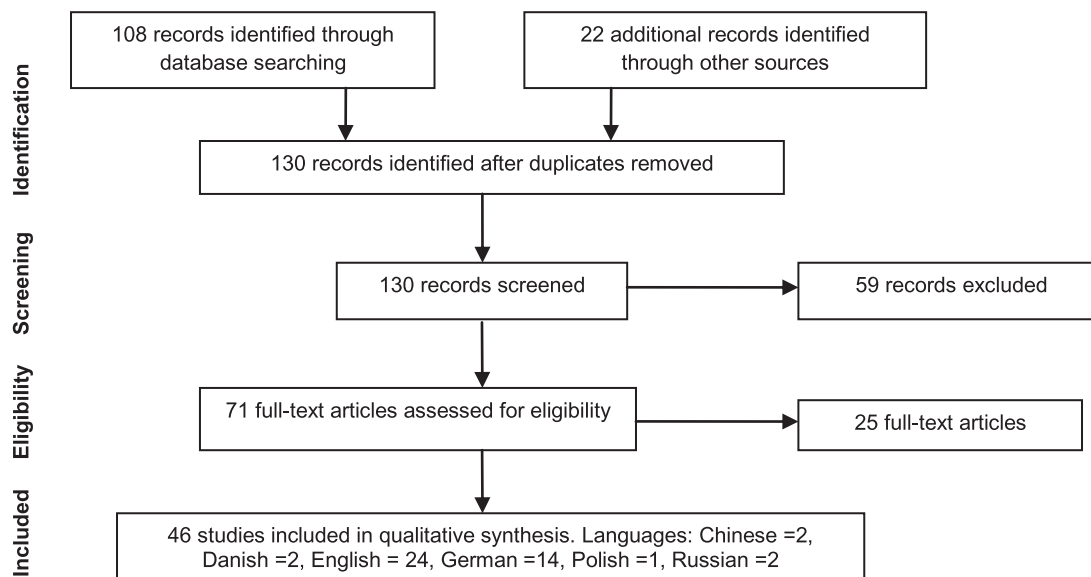

Figure 2. | **Literature search strategy.** Forty-six articles were retained for analysis after identification, screening, and review.

Table 3. Criteria of dialyzability

Dialyzability[a]	Primary Criteria: Tl Removed (%)[b]	Alternative Criteria 1: CL_{EC}/ CL_{TOT} (%)[c]	Alternative Criteria 2: $T_{1/2\ EC}$/ $T_{1/2}$ (%)	Alternative Criteria 3: Re_{EC}/Re_{TOT} (%)[c]
D, Dialyzable	>30	>75	<25	>75
M, Moderately dialyzable	>10–30	≥50–75	≥25–50	≥50–75
S, Slightly dialyzable	≥3–10	≥25–50	≥50–75	≥25–50
N, Not dialyzable	<3	<25	>75	<25

These criteria should be applied only if measured or calculated (not reported) endogenous half-life is > 4 hours (otherwise, extracorporeal treatment is considered not clinically relevant). Furthermore, the primary criteria are preferred for poisons having a large volume of distribution (>5 L/kg). Reproduced with permission from *Clinical Toxicology* (2). $CL_{EC,}$ extracorporeal clearance; $CL_{TOT,}$ total clearance, representing the sum of CL_{EC} and endogenous systemic clearance; $Re_{EC,}$ amount recovered during ECTR; $Re_{TOT,}$ total amount recovered, representing the sum of Re_{EC} and amount recovered via endogenous routes of elimination; $T_{1/2,}$ half-life; $T_{1/2\ EC,}$ half-life during ECTR.
[a]Applicable to all modalities of extracorporeal treatment, including hemodialysis, hemoperfusion, and hemofiltration.
[b]Corresponds to percentage removal of ingested dose or total body burden in a 6-hour extracorporeal treatment period.
[c]Measured during the same period of time.

Table 4. Executive summary of recommendations

General statement
    ECTR is recommended in severe Tl poisoning (1D)
Indications for ECTR
    ECTR is indicated if ANY of the following conditions are present:
        If Tl exposure is highly suspected on the basis of history or clinical features (2D)
        Assuming Tl concentrations are readily available, if Tl concentration is >1.0 mg/L (2D)
        Assuming Tl concentrations are readily available, if Tl concentration is between 0.4 and 1.0 mg/L (3D)
Timing of ECTR
    ECTR should be initiated as soon as possible, ideally within 24–48 hr of Tl exposure (1D)
Cessation of ECTR
    ECTR is suggested until Tl serum concentration is <0.1 mg/L for a minimal duration of 72 hr (2D)
Choice of ECTR
    Intermittent hemodialysis is the preferred initial ECTR, especially after an acute Tl ingestion (1D)
    Intermittent hemoperfusion or continuous renal replacement modalities are valid alternatives if intermittent hemodialysis is not available (1D)

ECTR, extracorporeal treatment; Tl, thallium.

potentially improving clinical outcome. Although it is difficult to predict the benefit of performing ECTR in patients with massive exposures, there is no evidence to conclude that ECTR is futile in this context. It is possible that removal of a relatively small percentage of the total body burden of Tl results in lower concentrations in a toxic compartment (*i.e.*, the CNS), thereby translating into clinical benefit.

  2. Indications for ECTR: ECTR is indicated if ANY of the following conditions are present:

A. If Tl exposure is highly suspected on the basis of history or clinical features (2D).
B. Assuming Tl concentrations are readily available, if Tl concentration is >1.0 mg/L (2D).
C. Assuming Tl concentrations are readily available, if Tl concentration is between 0.4 and 1.0 mg/L (3D).

  Rationale. The workgroup had proposed that indications for ECTR initiation in any poisoning should be based

on criteria such as exposure (*e.g.,* ingestion, contact, or inhalation), measurement of poison in body fluids, paraclinical test results, and clinical symptoms and signs. There is uncertainty about what amount constitutes a tolerable Tl exposure, other than the negligible dose used in nuclear imaging (<10 μg). Furthermore, there is a lack of an available dose-effect relationship in Tl ingestions; toxic symptoms can be manifested at exposures much lower than what is reported as lethal (41,47,64). The consequences of underestimating a seemingly "safe" Tl exposure, when several interventions can be offered, are significant. Although the workgroup initially proposed a Tl ingestion threshold of 4 (suggestion) and 10 mg/kg (recommendation) to initiate ECTR, the workgroup later decided that the decision should not be solely dependent on Tl exposure history, given the risk of inaccuracy. Considering the high toxicity of Tl, active intervention for any nontherapeutic exposure, including ECTR, should be carefully considered.

Table 5. Strength of recommendation and level of evidence scaling on clinical outcomes

Strength of Recommendation (Consensus-Based)	Level of Evidence (Based on GRADE System)
Level 1 = Strong recommendation (The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.)	Grade A = High level of evidence (The true effect lies close to our estimate of the effect.)
Level 2 = Weak recommendation (The course of action is considered appropriate by the majority of experts but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.)	Grade B = Moderate level of evidence (The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.)
Level 3 = Neutral position (The course of action could be considered appropriate in the right context.)	Grade C = Low level of evidence (The true effect may be substantially different from our estimate of the effect.)
No recommendation (No agreement was reached by the group of experts.)	Grade D = Very low level of evidence (Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect.)

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Because confirmatory blood and tissue sample analysis is not usually available in a time frame to guide clinical decisions, clinicians typically rely on a constellation of symptoms and clinical signs to diagnose Tl poisoning (*i.e.*, gastrointestinal symptoms, tachycardia, ascending painful neuropathy, alopecia). The latter two signs are especially reliable but appear late, after the optimal window for commencing ECTR has passed (see next section). The benefit of ECTR in this context appears marginal, although a majority of members still supported ECTR given the risks of long-term sequelae. Severe signs of poisoning, such as CNS involvement (confusion, coma, seizures) are poor prognostic indicators that should induce a lower threshold for ECTR initiation if Tl exposure is suspected clinically.

Serum Tl concentrations, when available, do not correlate with manifestations of poisoning and are difficult to interpret when time of ingestion is unknown. Nevertheless, a high serum Tl concentration is usually associated with significant toxicity, in addition to indicating a window of opportunity for more efficient removal of Tl by ECTR (38). Therefore, in the rare context that the Tl serum concentration can be obtained within a few hours, the workgroup assumed it prudent to initiate ECTR when the serum concentration is >0.4 mg/L and especially if >1 mg/L. When the serum concentration exceeds this cutoff, prominent symptoms will probably be present if not yet manifest. There was no consensus regarding ECTR when concentrations are <0.4 mg/L. The workgroup repeatedly expressed the importance of not delaying ECTR (and other treatment modalities) while waiting for the serum Tl concentration result. Any strong suspicion of exposure should warrant immediate treatment targeted to limit Tl absorption and to enhance its elimination.

Finally, the workgroup proposed some provision in the context of CKD or poison-induced AKI. ECTR would probably be initiated in any case of severe AKI, regardless of whether there is Tl poisoning. However, because Tl is mostly eliminated by the kidneys, it is also reasonable to commence ECTR in cases of marginal Tl poisoning associated with a milder degree of impaired kidney function.

3. Timing of ECTR: ECTR should be initiated as soon as possible, ideally within 24–48 hours of Tl exposure (1D).

Rationale. ECTR also has the greatest potential benefit if commenced before the development of irreversible injury. Further, ECTR removes Tl from the plasma compartment, so prompt initiation of treatment before distribution of Tl into body tissues will maximize Tl removal by ECTR and its potential to reduce Tl body burden. Distribution into peripheral compartments, including the CNS, appears to occur over 24 hours (6,10,11). Thus, ECTR should be initiated as soon as technically possible, once one of the above indications is fulfilled. Although it is anticipated that ECTR is less useful if commenced more than 48 hours after exposure, many members still supported its use in this context.

4. Cessation of ECTR: ECTR is suggested until Tl serum concentration is <0.1 mg/L for a minimal duration of 72 hours (2D).

Rationale. The workgroup agreed that the marginal benefit of pursuing ECTR at some point becomes overridden by the risks associated with the technique. Furthermore, it is unrealistic to base ECTR cessation on the disappearance of symptoms because some patients will experience permanent clinical sequelae. Therefore, a nonclinical cutoff was suggested.

The workgroup considered it reasonable to pursue ECTR until the Tl concentration was <0.1 mg/L. The efficacy of ECTR at removing Tl decreases at lower serum Tl concentrations because ECTR removal depends on its presence in serum (38). The 0.1-mg/L cutoff does not correlate to a "safe" concentration but rather suggests a threshold under which ECTR efficacy becomes limited. Considering the large volume of distribution of Tl, that same concentration should be sustained for a sufficient period to remove Tl that redistributes from extravascular compartments. An empirical cutoff of 72 hours was proposed, although some members proposed that ECTR be extended until clinical improvement is observed.

Ultimately, the decision for pursuing ECTR should be individualized on the basis of history, signs, Tl concentration (if available), and complications of ECTR. Because of the limited availability of laboratories that quantify Tl in serum, this statement implies that some patients will be dialyzed

for at least several days after reaching criteria of ECTR cessation. This would provide for added reassurance and reconcile the views of proponents of longer ECTR duration.

5. Choice of ECTR: Intermittent HD is the preferred initial ECTR, especially after an acute Tl ingestion (1D). Intermittent hemoperfusion or continuous renal replacement modalities are valid alternatives if intermittent HD is not available (1D)

Rationale. The workgroup felt that HD is the preferred initial modality of ECTR in Tl poisoning, on the basis of several arguments:

- Earlier reports suggest better Tl clearance and removal rates with hemoperfusion compared with HD, although it is unclear if this would remain true today. Small- and middle-molecule clearances, for example, have increased dramatically with the use of synthetic membranes instead of less efficient cuprophane filters.
- Intermittent HD is the favored treatment for maintenance dialysis in patients with ESRD and AKI worldwide, so this modality is the most widely available. Therefore, the travel distance to an HD center for a poisoned patient would likely be minimized.
- More physicians and nurses are experienced with HD, with lesser risks of delay and uncertainty.
- Hemoperfusion cartridges are of limited availability in many parts of the world, as is the accessibility of online hemofiltration.
- The complication rate with HD appears favorable compared with that of hemoperfusion (65).

The cost of HD is almost universally favorable compared with that of hemoperfusion. This is largely explained by the cost of monitoring and treating complications, as well as the lower cost of dialysis filters versus charcoal cartridges, which need to be replaced after a few hours because of saturation.

Although intermittent HD appeared to be the favored ECTR among members, alternative ECTR was not discarded. Charcoal adsorbs Tl, so hemoperfusion alone or in series with HD can be recommended if charcoal cartridges are available and if physicians and nursing personnel are comfortable using this technique. Similarly, it is anticipated that Tl would be removed by convection-based (hemofiltration) intermittent techniques. However, peritoneal dialysis, exchange transfusion, and plasmapheresis would not offer results comparable to HD or hemoperfusion and should therefore not be offered unless they are the only option.

The workgroup also preferred the use of intermittent over continuous techniques, at least initially, and especially if commenced shortly after a massive ingestion. The arguments supporting this were as follows:

- Intermittent techniques allow better poison clearance than do continuous procedures. The amount of solute removed by intermittent HD per hour is 2–4 times that by continuous renal replacement therapies. Because the objective is rapid removal of Tl before tissue distribution and the development of toxicity, intermittent HD is therefore preferable.
- Continuous techniques are usually better tolerated hemodynamically, although this is true only when there is concomitant fluid removal, which is unnecessary in Tl poisoning (unless oliguric AKI is present).
- Continuous techniques are often provided only in the intensive care unit, while repeated intermittent HD can also be performed in the renal unit and other wards.

The workgroup proposed that after an initial HD session, daily HD or continuous renal replacement therapies as possible options. There is some rationale to suggest continuous techniques for poisons with a large volume of distribution and a slow intercompartmental transfer rate. Alternatively, more efficient daily intermittent HD followed by pauses in therapy would lead to a rebound in serum Tl concentration, which will increase the amount removed the following day.

Whatever the technique used, operating ECTR characteristics should be optimized to maximize removal (*i.e.*, high blood and dialysate flow, large-surface-area filters, and longer time on ECTR).

Conclusion

The EXTRIP workgroup presents here its first poison review: thallium. Although the substance's dialyzability is low, data suggest that hourly removal with extracorporeal treatments is superior to current alternatives in enhancing Tl elimination. Despite the absence of robust studies, the workgroup strongly recommended extracorporeal removal in cases of severe Tl poisoning and provided specific indications of its application.

Disclosures

No expert members of EXTRIP receive honorarium or are employed by industry. There was no industry input into scientific content, development, or publication of the recommendations. Furthermore, industry presence at meetings is not allowed, nor is

industry awareness or comment on the recommendations accepted. EXTRIP members do not have direct financial relationship with the sponsors.

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