

# Management of toxic ingestions with the use of renal replacement therapy

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Received: 29 June 2010 / Revised: 9 August 2010 / Accepted: 27 August 2010 / Published online: 12 October 2010  
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**Abstract** Although rare, renal replacement therapy (RRT) for the treatment of the metabolic, respiratory and hemodynamic complications of intoxications may be required. Understanding the natural clearance of the medications along with their volume of distribution, protein binding and molecular weight will help in understanding the benefit of commencing RRT. This information will aid in choosing the optimal forms of RRT in an urgent setting. Overdose of common pediatric medications are discussed with suggestions on the type of RRT within this educational review.

**Keywords** Intoxications · Overdose · Dialysis · Pediatrics · Single-pass albumin dialysis (SPAD) · Molecular adsorbents recirculating system (MARS) · Renal replacement therapy

## Introduction

Accidental and intentional intoxications occur in about 7.5 million cases per year, resulting in approximately 10,000 deaths per year in the USA [1]. Data from the Toxic Exposure Surveillance System of the American Association

of Poison Centers identify that 65% of these intoxications occur in people less than 20 years of age, yet this age group only accounts for 11% of the fatalities. While the number of children with toxic ingestions is very small, these patients are ill enough to require therapy in the intensive care unit (ICU) due to respiratory, metabolic or cardiac compromise [2]. Holubek et al. reported a trend in the changes of the etiology of intoxications as well as of therapy between the years 1985 and 2005, noting that more than 19,000 cases of intoxication required extracorporeal therapy as a treatment [3]. They also noted that there was a change in both the etiology (an increase in anti-convulsant overdose) and the therapy [a trend away from charcoal hemoperfusion (CH)] for these intoxications.

The management for toxic ingestions has changed over time. In the early mid 1980s and early 1990s, CH was commonly used as a therapy for intoxications [4]. New forms of renal replacement therapy (RRT), including high-flux hemodialysis (HD) and continuous renal replacement therapy (CRRT) have, for the most part, replaced the use of CH [5]. Additionally, in the last decade, a number of specific rescue therapies have been developed for the treatment of some intoxications, avoiding the need for RRT [6]. Examples of these include naloxone for opiate or narcotic overdose, *n*-acetylcysteine for the treatment of acetaminophen intoxication and fomepizole as the specific treatment for alcohol intoxications [7–10]. Despite these advances in rescue therapy, a significant number of adults and children continue to require RRT as an adjunct to their native renal function for removal of the drug [11].

This review will describe common intoxications in the pediatric age group and their therapeutic intervention with RRT.

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## Toxic ingestions and treatment modalities in pediatric patients

When the pediatric patient presents for the care of a toxic ingestion, it is important to determine the natural elimination process, i.e. whether the toxic substance is hepatically or renally excreted. If a medication is excreted via the renal system in the setting of concomitant kidney injury, the half-life of that medication will be prolonged and, therefore, RRT may be indicated [1, 11].

Currently available data have yet to identify an absolute indication or the best RRT mode to treat intoxications [12]. It is suggested that RRT should be used in the case of worsening metabolic consequences, including metabolic acidosis and lactic acidosis, with or without concomitant hypertension. Further respiratory depression related to a direct central nervous system (CNS) effect of the medication or cardiac dysrhythmias may occur secondary to direct cardiac toxicity. RRT should be considered in the setting of impairment with underlying organ dysfunction and in the face of worsening metabolic and respiratory compromise. In addition, the basic level of medical care needs to be done as indicated (e.g. saline diuresis, enteral charcoal placement or gastric lavage if there is an adequate airway protection) [1, 6].

Extracorporeal therapy modalities to support the elimination of intoxications would include RRT, peritoneal dialysis, CH, HD (both standard as well as high flux) as well as CRRT [5, 11].

### Peritoneal dialysis

Peritoneal dialysis (PD) has been used in the past as a treatment modality for acute intoxications [13]. PD can be performed for acute intoxications as it is used in the settings of acute kidney injury (AKI) or end-stage kidney disease (ESRD). The mechanism of toxic clearance in PD is by diffusion, and the factors that affect clearance include volume and frequency of exchanges of the PD solution and the concentration of the intoxicant present in the serum. The advantages of using PD as a continuous form of RRT are (1) its relative simplicity, (2) availability, (3) avoidance of anticoagulation and (4) lower cost compared to other RRT treatment modalities. The disadvantage (using urea as a marker of clearance) is that compared to HD or CRRT, PD is the least effective model of elimination [14]. Small molecular weight medications (i.e. lithium) can be eliminated by PD, but due to the greater clearance that HD and CRRT offer in general, PD should be used only when other options for RRT are not available or feasible [15].

## Charcoal hemoperfusion

With the diminished availability of CH cartridges as well as a decreasing expertise among health professionals with using these membranes, CH treatment has become less common. CH was commonly used in the past as a way to bind protein-bound intoxicants. The use of CH membranes is associated with hypothermia, hemodynamic compromise, coagulation abnormalities and thrombocytopenia and hypocalcemia [16]. CH was often coupled with HD in line to negate some of the side effects. The difficulty of performing sequential CH with hemodialysis is the large extracorporeal volume that would be necessary to use these in tandem. It would not be unusual that a 400- to 500-mL extracorporeal circuit would be needed to support both systems in sequence. The cost of keeping a “ready to go” CH cartridge available with a relatively short shelf life and a reduction in the manufacturing of these cartridges have resulted in the decreased use of this method [5].

## Hemodialysis

Hemodialysis comes in standard as well as high-efficiency or high-flux modalities, both of which use clearance by diffusion. The major difference is the pore size of the membrane, the type of membrane and the amount of dialysate flow that occurs. Typically, with flux or high-efficiency HD, membranes with a larger pore size (as large as 20 kDa) are available for the clearance of intoxications. With the advent of high-flux or high-efficiency HD membranes, the use of CH has essentially become something of the past [17].

## Continuous renal replacement therapy

The use of CRRT has become commonplace in pediatric ICU settings during the last decade and a half [18]. CRRT either in a convective mode by effecting mass transport of the medication across the membrane or in a diffusive mode is often used in patients with AKI. Studies using sieving coefficients have clearly demonstrated that there is a higher clearance of larger molecular weight molecules and higher protein membrane mediations when convective clearance is used [19]. Therefore, if CRRT is to be used for intoxications, the focus should be predominantly on a convective modality. A large disadvantage of CRRT for intoxications is that it is less efficient and the patient has less mobility as compared to HD [12].

If intoxicants have a large volume of distribution, HD can be used to remove the initial intravascular load of this

intoxicant, followed by CRRT, thereby avoiding the rebound that would occur as HD is discontinued.

Single-pass albumin dialysis/molecular absorbent regenerating system

In the last decade, the use of single-pass albumin dialysis and a molecular absorbent regenerating system has been reported for hepatic dysfunction. These are essentially a CRRT circuit with an additional albumin-based dialysate circuit that allows for protein-bound molecules to transfer from the patient’s blood into the protein of the dialysate [20]. These systems can be used for protein-bound intoxicants, but they are not readily available at most institutions. Single-pass albumin dialysis has the additional cost of the albumin. No comparison data evaluating clearance by these new treatment modalities to high flux HD are available. There are also a number of case reports on the use of these therapies [21–23].

**Extracorporeal membrane oxygenation**

In the case of poor patient hemodynamics and a patient *at extremis*, then extracorporeal support with venous arterial extracorporeal membrane oxygenation (ECMO) may be necessary to support the patient hemodynamically [24]. Once stable, RRT can be added to the ECMO circuit for elimination of the intoxicant

**Treatment of intoxications: decision issues**

Before beginning RRT for a toxic ingestion, the following issues about that intoxication need to be considered:

1. Was it delivered as a short or prolonged release product?

2. What is the volume of distribution?
3. What is the molecular weight?
4. What is its protein binding?

The medication half-life needs to be characterized. If the patient has been overdosed with a sustained release product, there will be an ongoing slow delivery of medications into the plasma space with subsequent complications. This is where the use of gastro-intestinal (GI) elimination in addition to RRT may be necessary.

If RRT is being considered, the molecular weight, protein binding and volume of distribution of the toxin will need to be accounted for. Large molecular weight medications are less well cleared by RRT. Medications that have a high protein binding are also removed less efficiently by RRT. Finally, in medications with a large volume of distribution through multiple compartments of the body, RRT will only clear what is in the plasma space, so the elimination of the intoxicant will be prolonged.

**Management of specific toxic medication ingestions**

Table 1 identifies common medications that are still causes of intoxication in children together with their molecular weight, volume of distribution and protein-bound percentages.

Vancomycin

Vancomycin is a commonly used medication for the treatment of Gram-positive infections. It has a large molecular weight and relatively large volume of distribution, and it is highly protein bound. Vancomycin essentially acts as a double compartment system with an intravascular and extravascular component, respectively. Historically, CH was the treatment for vancomycin intoxication as vancomycin was thought not to be well removed by RRT.

**Table 1** Characteristics of common drugs which may require renal replacement therapy in intoxication

Drug	Molecular weight (Da)	Volume of distribution (L/kg)	% protein bound
Vancomycin	1500	0.2-1.25	75
Gentamicin	477	0.25-0.3	0
Lithium	6.9	0.6-0.9	0
Aspirin	138	0.17	90
Theophylline	180	0.45-0.7	60
Carbamazepine	236	0.8-1.8	78
Valproic acid	144	0.1-0.2	90
Metformin	166	0.5	0
Methotrexate	454	Acute use 0.18 Chronic use 0.4-0.8	50

More recently, the combination of high-flux HD and CRRT has been found to successfully decrease acute vancomycin levels [25, 26]. It is possible to wait for the tissue levels to pass into the vascular space and upon rebound, repeat the HD procedure. Alternatively, sequential therapy of HD followed by convective clearance with high-flow CRRT (as a way to prevent secondary rebound and for elimination) may be used.

#### Aminoglycosides

Aminoglycosides are also commonly used antibiotics for the treatment of Gram-negative infections. In contrast to vancomycin, they have a lower molecular weight and lower volume of distribution and are minimally protein bound. These medications are easily cleared by both standard as well as high-dose HD. If prolonged therapy RRT is necessary, high-volume hemofiltration (preferably in convective mode) for ongoing elimination of this medication may be used [27].

#### Lithium

Lithium is a relatively common medication seen in both accidental and purposeful overdoses. Lithium can occur both as an acute intoxication in patients naïve to this medication or an acute intoxication in a patient on the medication chronically. The latter setting results in higher saturation of the medication, resulting in both the natural decay and RRT clearance taking longer as compared to the patient naïve to the medication. This thought process is important in determining the degree of time needed for elimination. Lithium has a relatively small molecular weight, a medium to large volume of distribution and low protein binding. Many clinical series have shown that lithium is easily removed with standard or high-flux HD. It has been further shown that the volume distribution is a little larger than that of other medications. In the case of an overdose of extended-release lithium, the sequential use of HD followed by hemofiltration will allow for ongoing elimination of lithium, preventing the rebound effect [28–30].

#### Aspirin

Aspirin overdose has continued to be common, primarily in the adolescent suicidal population [31]. It has a relatively small molecular weight and small volume of distribution, but it is highly protein bound. Aspirin has been shown to be eliminated very easily with high-efficiency HD, with the aim of avoiding the metabolic consequences of the CNS as well as the metabolic consequences of aspirin overdose [32].

#### Theophylline

Theophylline is a medication that is being used less and less. Historically, theophylline was only cleared with the use of CH. Because of its relatively small molecular weight, medium to higher level of volume of distribution and mild to high protein binding, CH was preferred with this medication. With the use of high-efficiency HD, theophylline can be easily cleared. A prolonged release of a long-acting form of theophylline may necessitate HD followed by CRRT for ongoing elimination [33].

#### Carbamazepine

Carbamazepine is a common medication used for seizures. Carbamazepine intoxication, like lithium intoxications, can occur in an acute or acute on chronic setting. Relative to other medications, carbamazepine has a relatively large volume of distribution and is highly protein bound, yet the molecular weight is relatively small. Historically, carbamazepine was thought to be cleared only by CH [34]. However, high-flux HD can clear carbamazepine very easily despite the high protein binding and the high volume of distribution [35]. The use of serial HD therapies or sequential HD followed by CRRT may be necessary. Recent work by Askenazi et al. noted that albumin added to the dialysate solution during diffusive CRRT enhanced the clearance of carbamazepine as opposed to albumin-free dialysate [36].

#### Valproic acid

Valproic acid is also another highly protein-bound anticonvulsant [37]. Both the volume of distribution and the molecular weight are smaller than carbamazepine [38]. Valproic acid can be eliminated with the use of high-flux HD followed, if necessary, by CRRT [39–41]. Similar to Askenazi et al. [36], Churchwell et al. regarded albumin-treated dialysate as a way to absorb the valproic acid onto the protein for enhanced elimination. This approach enables CRRT to be used in the case of a hemodynamically compromised patient, but it does add to the overall cost of care [42].

#### Metformin

Metformin use is becoming more common as the obesity rate in the USA goes up. Metformin intoxication in some patients can cause an acute lactic acidosis [43]. Metformin is eliminated naturally through the GI tract, is poorly protein bound and has a mild volume of distribution. Metformin overdose can be treated easily with standard or

high-flux HD as a way to correct the lactic acidosis as well as to remove the medication [44].

### Methotrexate

Methotrexate has been associated with AKI in approximately 1.8% of patients treated in osteosarcoma trials [45]. The clinical symptoms include gastrointestinal distress, hepatic insufficiency, AKI and bone marrow suppression. Like many of the other medications described herein, the natural clearance will be diminished in the face of hepatic or renal impairment. The volume of distribution is affected by whether or not methotrexate is being given as a initial or chronic therapy. In the setting of a chronic therapy the volume of distribution is larger, making the elimination of the medication longer to occur. If RRT is needed, high-flux HD remains the optimal form of clearance compared to other forms of RRT [46]. In the setting of chronic treatment and AKI, clearance may occur over weeks [47].

### Important teaching points

As opposed to the setting of AKI, if dialysis is needed to treat an acute intoxication, the dialysate or replacement bath needs to have the therapeutic levels of phosphorous and potassium in order to avoid electrolyte disturbances [48].

### Summary

Renal replacement therapy is not commonly utilized for treating intoxications in children, and CH, once a common procedure, has essentially been relegated to the past. Despite the perception of poor clearance, many medications that are highly protein bound can be removed through the use of high-flux or high-efficiency HD membranes. Many medication intoxications have a volume of distribution such that a rebound may occur once RRT is removed. If this is the case, serial HD treatments or the use of sequential HD followed by CRRT may be performed until the medication is naturally eliminated. Peritoneal dialysis has a role in RRT and can be considered if other options are not available.

High-flux or high-efficiency HD should always be considered the first line of treatment if the patient tolerates this therapy. High-flux or high-efficiency HD followed by convective mode of CRRT should be considered in the setting of a large-volume of distribution intoxicant. Convective mode CRRT can be considered in a patient that cannot tolerate HD as initial treatment.

### Questions

(Answers appear following the reference list)

- Factor(s) that affect the benefit of RRT for the treatment of drug overdose would include
  - the volume of distribution
  - the molecular weight
  - its protein binding
  - all of the above
- If an intoxicant is highly protein bound, which of the following forms of RRT would be best to use for drug removal
  - standard HD
  - high-efficiency HD
  - peritoneal dialysis
  - diffusive form of CRRT
- If an intoxicant has low protein binding, a small molecular weight and a low volume of distribution, which of the following forms of RRT could be used for drug removal
  - standard HD
  - high-efficiency HD
  - CRRT
  - any of the above
- Comparing the “dialysis bath” in RRT for AKI versus RRT for intoxication in a child without AKI, the bath is
  - identical
  - should have physiologic levels of potassium and phosphorous
- Vancomycin removal is best achieved with either intermittent high-efficiency HD or high-efficiency HD followed by convective CRRT because vancomycin
  - is highly protein bound
  - has a large volume of distribution
  - has a large molecular weight
  - all of the above

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### Answers

1. d
2. b
3. d
4. b
5. d