How do I eliminate toxins in severe poisonings?

Bruno Mégarbane, MD, PhD

Réanimation Médicale et Toxicologique, INSERM U71144 - Université Paris-Diderot
Hôpital Lariboisière, Paris, France
bruno.megarbane@lrb.aphp.fr
The poisoned patient requiring extracorporeal elimination

Only 0.04% of poisonings require renal extracorporeal support. When required, the technique should be available within a short time.

Goldfarb DS. Goldfrank’s Toxicologic Emergencies
What are the evidence to support the benefit to clear toxicants and improve patient’s outcome?

Low evidence data - no randomized prospective study
Which poisonings to treat with extracorporeal elimination?

Decisions have to rely on:
- Knowledge of the technique principles and drug kinetics.
- Reports with removal kinetics (before, during, and after elimination)

**Extracorporeal renal support should be considered**

1. Poisoning with a drug which elimination could be enhanced.

AND

2. Severe features or toxicity

OR

3. Failure to respond to full supportive care
4. Impairment of the normal route of elimination
4. Raised blood concentrations with good PK/PD correlations
When assessing efficacy, the clinical response must be considered in addition to the evidence of enhanced elimination:

- To enhance elimination
- To reduce duration of poisoning
- To reduce severity or mortality
- To correct renal failure
- To correct electrolytic abnormalities

With a better safety and a lower cost than other treatments.
Case report: combination of several elimination methods in a historical poisoning with 100 g meprobamate

Blood concentration: 460 mg/l

- Osmotic diuresis during 26 h 2 g
- Hemodialysis during 11 h 8.5 g
- Hemoperfusion during 8 h 7.5 g
- Liver metabolism 9.2 g

- Two successive gastric lavage at H8 and H26 66 g

Pontal P. Nouv Press Med 1982
Hemodialysis is the extracorporeal method of choice to enhance the elimination of toxicants
Guidelines of good practice of hemodialysis

Reduce circulatory instability:
Vascular reactivity
- \( \text{HCO}_3 \) rather than acetate dialysate
- Reduce dialysate temperature to 35°C
- Control of ultrafiltration rate

Plasma volume
- Sodium > 145 mmol/l in dialysate
- Glucose-containing dialysate
- Avoid rapid fall in urea concentration
- Limit ultrafiltration if shock or in the 1st setting

Cardiac contractility
- Calcium > 1.75 mmol/l in dialysate
- Avoid hypokaliemia (dysrrhythmia)

Increase dialysance:
- Prefer dual lumen catheter
- More permeable high-flux synthetic membranes with larger surfaces
- Higher blood flow > 400 ml/min

Preserve biocompatibility:
- Use non-cuprophan membranes
- Limit bacteria and endotoxin in dialysate

Schortgen F, AJRCCM 2003
Which drugs?

Characteristics for removal by hemodialysis

- MW < 500 D
- Water solubility and low steric hindrance
- Poor binding to plasma proteins: <60%
- Small volume of distribution <1 l/kg
- Low endogenous clearance <4 ml/min
- Single - compartment kinetics

How to anticipate the removal of toxin?

<table>
<thead>
<tr>
<th>% free drug / $V_D$</th>
<th>% drug removed by 6h-hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>20 - 50%</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>&lt; 10%</td>
</tr>
</tbody>
</table>

Goldfarb DS. Goldfrank’s Toxicologic Emergencies

Gwilt PR. Clin Pharmacol Ther 1978
## Distribution volume

<table>
<thead>
<tr>
<th>Clearance by dialysis</th>
<th>Vd</th>
<th>Fraction eliminated in 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mL/min</td>
<td>500 L</td>
<td>1%</td>
</tr>
<tr>
<td>200 mL/min</td>
<td>50 L</td>
<td>17%</td>
</tr>
</tbody>
</table>

Half-life of elimination: $T_{\frac{1}{2}} = 0.693 \frac{Vd}{CL}$
Potential indications of dialysis in clinical toxicology

Which drugs?

1- Salicylate
2- Lithium
3- Toxic alcohols (methanol, ethylene glycol)
4- Metformine

Others: amanita toxin, acetaminophen, aminoglycosides, atenolol, borate, bromide, carbamazepine, disopyramide, glyphosate, meprobamate, metformin, methotrexate, paraquat, phenobarbital, phenytoin, procainamide, sotalol, trichloroethanol, theophylline...

In all these cases, the role of hemodialysis needs further demonstration
Hemodialysis in salicylate poisoning

- The method of choice.
- HPF achieves marginally better clearance but cannot correct the acid-base, electrolyte and fluid balance, common in salicylate poisonings.

Indications:

- Severe features: acute renal failure (impaired elimination), coma, seizures or non-cardiogenic pulmonary edema
- Metabolic acidosis resistant to correction: pH < 7.2
- Contra-indications of urine alkalization: renal or cardiac insufficiency
- Elevated concentrations > 1.2 g/l or 1 g/l, 6 H post-ingestion
  Lower threshold for children or chronic salicylate poisoning (> 0.6 g/l)

Mokhlesi B, Chest 2003
Lithium poisonings are uncommon but potentially dangerous with severe neurological disorders. Lithium poisonings are associated with a narrow therapeutic index, leading to acute, acute-on-chronic, and chronic poisoning. In previously untreated patients, 6663 cases of lithium poisoning were reported in 2012 in the US. In treated patients who develop progressive lithium accumulation, poisoning can be compounded. Minor to moderate to severe neurotoxicity and delayed toxic effects are associated with lithium poisoning. 

Hemodialysis in lithium poisoning

- Dialysis ability to enhance Li elimination is well-documented.
  - $t_{1/2}$ from 12-27 to 3-6 h
  - clearance from 10-40 to 70-170 ml/min

- **Rebound** occurs following dialysis-induced rapid drop in Li plasma level.
  - Li concentration measurement should be repeated /6-12 h

Fig. 1. Concentration-time profile of plasma lithium concentrations in a patient with an acute lithium intoxication. The dashed curve represents predicted profile without intervention. Solid line represents the Bayesian estimated profile with three episodes of haemodialysis. The horizontal lines represent the therapeutic range of lithium.

*Jaeger A. 1993
Okussa MD. 1994
Scharman EJ. 1997
Kerbush. Pharmacol Toxicol 2002*
Hemodialysis and lithium concentrations

• 1978. Hansen and Amdisen
  - If Li level cannot be less 1 mmol/l in 30h
• 1979. Thomsen and Schou
  - If Li higher 4 mmol/l with cardiovascular signs
• 1988. Amdisen
  - All CNS symptomatic with increasing Li levels
• 1987. Dyson
  - If renal failure with rising or very high Li levels
• 1988. Bismuth
  - Only if renal failure or severe renal disease
• 1985 & 1993. Jaeger
  - Severe intoxication (coma, seizures)
  - Deterioration of status despite treatment
  - Acute on chronic or chronic poisoning
Indications of hemodialysis in lithium poisoning

- **Severe poisoning** (coma, convulsions) + Renal failure

- **Elevated plasma concentration thresholds**
  - 6-8 mmol/l in acute overdose
  - 4 mmol/l in acute/chronic overdose
  - 2.5 mmol/l in chronic accumulation

- **Kinetic criteria**: amounts expected to be removed with 6h-dialysis > amounts spontaneously eliminated by kidneys within 24h

  However, none of these criteria have been validated

- Primary treatment is based on supportive care.
- Serum Li concentration is not sufficient to decide to undertake dialysis. This parameter should be taken with others, including type, severity, impaired renal excretion and spontaneous expected kinetics.
- Clearing plasma from Li is not a guarantee to obtain favorable outcome.
Simple decision tree for dialysis indications

Vodovar D. Clin Tox 2016

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>91 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>87 %</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>57 %</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>98 %</td>
</tr>
</tbody>
</table>
Toxic alcohol poisonings

Offending chemicals in suicide, unintentional and epidemic poisonings

- Ethylene glycol: 4867 exposures/year (mortality: 0.09%)
- Methanol: 2418 exposure/year (mortality: 0.05%)

Toxicity is due to enzymatic degradation by alcohol dehydrogenase

Methanol $\text{CH}_3\text{OH}$

- Ethylene Glycol $\text{CH}_2\text{OH} - \text{CH}_2\text{OH}$
- Glycolate $\text{CH}_2\text{OH} - \text{COO}^-$
- Oxalate $\text{COO}^- - \text{COO}^- + \text{Ca}^{++}$

Formaldehyde $\text{HCH}_2\text{O}$

- Glyoxal $\text{CH}_2\text{OH} - \text{CHO}$

Formate $\text{HCOO}^-$

- Metabolic acidosis
- Blindness

Folate

- $\text{CO}_2 + \text{H}_2\text{O}$

ADH

PCCTESS, USA, 2005
**Diagnosis:**

**Osmolal gap:** $MO - CO$

Measured osmolality using the method of the cryoscopic delta

Calculated osmolality

$$= (1.86 \ Na^+ + \text{urea} + \text{Glucose}) / 0.93 \text{ (mM)}$$

**Anion gap:**

$$= (Na^+ + K^+) - (Cl^- + HCO_3^-) > 16 \text{ mmol/l}$$

Metabolic acidosis with AG and OG = poisoning with toxic alcohol

Measurement of plasma methanol or EG concentration: HPLC or GC

Measurement of plasma glycolate or formate

**Early stage:** $OG$ is the greatest and $AG$ the least

With alcohol metabolism: $OG$ & $AG$ approximate

**Late stage:** $OG$ returns to baseline, $AG$ increases

---

Hovda KE. *Intensive Care Med* 2007
Recommended treatments include:

- **Supportive treatments**: intravenous fluids, anticonvulsive medications
- **Sodium bicarbonate**:
  - to correct metabolic acidosis
  - to increase renal elimination of glycolate and formate
  - to inhibit precipitation of calcium oxalate crystals
- **Folinic acid supplementation**, thiamine and multivitamins (ethanol ingestion)
- **Antidotes** (competitive ADH substrate or inhibitor): fomepizole and ethanol
- **Intermittent dialysis**: routinely used to correct acidosis, to remove toxic metabolites and to shorten the course of hospitalization (methanol).
Advantages of fomepizole over ethanol to treat toxic alcohol poisonings

- Ease of administration
  - Fixed loading dose independent of baseline ethanol concentration
  - Intermittent bolus dosing every 12 hours (every 4 hours during hemodialysis)
  - No need for monitoring serum antidote concentrations or continuous infusion
- Wide therapeutic margin
- Absence of central nervous system depression and inebriation
- Absence of metabolic and biochemical adverse effects
- Reduced intensity of nursing care
- Simplification of interfacility transfer
- Ability to forgo hemodialysis in selected patients
- Safety of patient and of medical personnel

+ Possibility to obviate the need of hemodialysis in selected cases

Hemodialysis in ethylene glycol poisoning

**Indications:**
- Significant metabolic acidosis (pH < 7.25 to 7.30)
- Renal failure or electrolyte imbalances unresponsive to conventional therapy
- Deteriorating vital signs despite intensive supportive care
- Repeated HD if EG redistribution within 12 h after ceases.

Patients treated with fomepizole prior to the onset of significant acidosis do not require dialysis.

An absolute EG concentration above 50 mg/dl should no longer be used as an independent criterion for dialysis in patients treated with fomepizole.

Barceloux DG. *Clin Toxicol* 1999

Borron SW. *Lancet* 1999

Hemodialysis in methanol poisoning

**Indications:**
- pH < 7.25-7.30
- Renal failure
- Visual signs or symptoms
- Deteriorating vital signs despite intensive supportive care
- Significant electrolyte disturbances unresponsive to conventional therapy
- Serum methanol concentration ≥ 50 mg/dl

In poisonings involving high concentrations of methanol, without severe acidosis or visual impairment, patients may be successfully treated with the administration of repeated doses of fomepizole without dialysis.

Barceloux DG. *Clin Tox* 2002

Mégarbane B. *Intensive Care Med* 2001
How to administer fomepizole during dialysis

**Regimen**: 15 mg/kg then 10 mg/kg/12h until alcohol < 0.2 g/l or undetectable

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction coefficient (%)</td>
<td>78</td>
</tr>
<tr>
<td>$C_l_{HD}$ (ml/min)</td>
<td>137</td>
</tr>
<tr>
<td>Fomepizole removal rate (mg/h)</td>
<td>83</td>
</tr>
<tr>
<td>To compensate the loss</td>
<td>$\approx 1$ mg/kg/h</td>
</tr>
</tbody>
</table>

*Fassel H. Eur J Clin Pharmacol 1995*

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_l_{HD}$ (ml/min)</td>
<td>80</td>
</tr>
<tr>
<td>To compensate the loss</td>
<td>$\approx 1 - 1.5$ mg/kg/h</td>
</tr>
</tbody>
</table>

*Jobard E. Clin Toxicol 1996*

**If dialysis**: initial loading dose followed by continuous infusion of 1-1.5 mg/kg/h for the entire duration

**Alternative**: reduce dosing interval to 6h after the first injection and further to 4 h.
Hemodialysis duration in alcohol poisoning

Traditional end-point: <20 mg/dl or undetectable, with disappearance of acid-base imbalance or correction of anion and osmol gap.

A simple method to estimate the required dialysis time:
Required dialysis time to reach a 5 mmol/l toxin concentration target:

\[
\text{RDT (h)} = \left(\frac{-V \ln (5 / A)}{0.06 k}\right)
\]

V (l): Watson estimate of total body water
A (mmol/l): initial toxin concentration
k (ml/min): 80% of the manufacturer-specified dialyser urea clearance

No difference between the predicted HD duration (7.6 ± 1.9 h) and the actually provided using hourly concentration sampling (7.4 ± 1.9 h).

Hirsch DJ. *Kidney Int* 2001
Metformin poisoning

Metformin-associated lactic acidosis is rare (0.08 /1000 patients /yr) but severe complication in type-II diabetes.

Metformine inhibits neoglucogenosis and reduces hepatic clearance of lactates in the presence of a trigger increasing lactate production.

Two categories of poisonings:
- Metformin-dependent toxic mechanism: elevated serum metformin concentrations, better prognosis in relation to metformin elimination
- Metformin-independent anoxic mechanism: lower serum metformin concentrations, worse outcome dependent on the underlying cause

Baily, Diabetes Care, 1992
Value of lactate in metformin poisoning

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial lactate ≥15 mmol/L</td>
<td>0.57</td>
<td>0.78</td>
<td>4.88 (1.21–19.65)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>pH = 7.2</td>
<td>0.92</td>
<td>0.32</td>
<td>14.9 (1.72–130.72)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Renal LODS score ≥4 points</td>
<td>0.92</td>
<td>0.73</td>
<td>17.3 (1.98–151.34)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prothrombin activity ≤50%</td>
<td>0.92</td>
<td>0.82</td>
<td>59.8 (6.28–568.59)</td>
<td>&lt;0.0004</td>
</tr>
</tbody>
</table>

(r = 0.746; p = 0.0001)  (r = 0.568; p = 0.0001)

Seidowsky A. CCM 2009
Role of hemodialysis in metformin-associated lactic acidosis

**Indications:**
- Severe lactic acidosis with acute renal failure
- Lactate > 5 mmmol/L with increasing kinetics

**Duration:** 16h

Seidowsky A. CCM 2009
Are there alternative extracorporeal renal support techniques with potential interest in toxicology?
Hemodialysis is the extracorporeal method of choice to enhance the elimination of toxicants

**Lower clearance** of continuous vs. intermittent techniques:

In postdilutional HF, the clearance is equal to the UF flow rate, which is usually no more than 4 L/h (67 ml/min), whereas with HD clearance up to 500 mL/min can be achieved.

However, **potential advantages**:

- ↑ clearance of mid-MW solutes (aminosides, iron-DFO, digoxin-Fab)
- Usefulness to remove solutes with larger Vd or extensive tissue binding
- Tendency to ↓ rebounds

Do not underestimate technical innovations which have led to improvements
Why CRRT could be attractive?

1. CRRT can be done in most ICUs
   - Lack of need of specialized support staff
   - HD available in limited number of hospitals and requires complex machines, equipment and trained staff

2. Suitable in hemodynamically unstable patients
   Avoid hypotension and swings in intravascular volume

3. Easy to regulate fluid volume
   - Volume removal is continuous
   - Adjust fluid removal rate on an hourly basis

However, a major issue with CRRT: anticoagulation

Anticoagulation to prevent filter and extracorporeal circuit from clotting (duration, lower flow, hemoconcentration)
Close monitoring of coagulation tests - Regional citrate anticoagulation
CRRT in lithium poisoning

- Improved tolerance
- Absence of rebound due to better intracellular compartment clearance
  (CRRT couple a longer running time to an acceptable clearance)

HD remains the method of choice in severe Li poisonings. However, CVVHDF may be suitable alternative (if HD not available) or adjunctive (6-12h later, to avoid a second HD session).
CVVHD/HDF in methanol poisoning

- IHD is superior to CVVHD/HDF for more rapid methanol and formate elimination
- ↗ blood and dialysate flow increase elimination.
- If only CVVHD/HDF is available then elimination is greater with greater blood and dialysate flow rates.

Zakharov S. Kidney Int 2013
Metabolic acidosis control and metformin elimination was rapid with no rebound.

- Mean effluent flow rate: 34±6 ml/kg/h
- Mean rate of metformin elimination during the first 24 hours 2.4 ± 0.9 %/h

“Standard use of CRRT efficiently treated MALA in association with symptomatic organ supportive therapies”

Keller G. Plos One 2011
Elimination in acute arsenic poisoning

Ingestion of 10 g of arsenic trioxide ($\text{As}_2\text{O}_3$)

Hepatitis, pancreatitis, neurological disorders, respiratory distress, acute renal failure, and cardiovascular disturbances

IV BAL + DMSA

Elimination over 11-day period: urine (14.5 mg), HD (26.7 mg), PD (17.8 mg), CVVHF (7.8 mg), all amounts negligible with regard to the ingested dose

Arsenic cumulative excretion over 11 days from the time on diagnosis (day 4).

Hantson P. Clin Tox 2002
Charcoal hemoperfusion

Limited indications to exceptional cases of severe poisonings, when repeated-dose activate charcoal decontamination is unavailable or unfeasible:

- Carbamazepine
- Phenobarbital
- Phenytoin
- Theophylline
- Paraquat

Advantages:
- Uses same vascular access and dialysis pumps
- Can be used in series with dialysis
- Not dependent on drug size, water solubility or protein binding - as long as drug binds to charcoal

Inconveniences:
- Greater anticoagulation required
- Saturation of charcoal limits cartridge duration
- Worse tolerance

The ability of hemoperfusion to improve outcome has never been proven.
Plasmapheresis and Exchange blood transfusions

Plasmapheresis:
- Most useful for highly protein bound agents.
- Reports with chemotherapy, antiinfectives, vasodilators, antiepileptics, cardiovascular agents, and immunosuppressants.
- No role in enhancing toxicant elimination.

Exchange Blood Transfusions
- Pediatric experience > adult.
- Overall very limited role in poisoning.
- Appropriate in patients with intravascular hemolysis or severe methemoglobinemia unresponsive to symptomatic treatments or methylene blue.

Ibrahim RB. Pharmacotherapy 2007
Molecular adsorbent regenerating system (MARS) dialysis

- No clearly assessed role in enhancing the elimination of toxicants
- Potential interest to improve liver function in poisoned patients waiting for liver transplantation.

I am interested to investigate its usefulness in some well-defined poisonings

Schmidt LE. Liver Transpl 2003
Wu BF. Hepatobiliary Pancreat Dis Int 2004
Pugliese F. Transplant Proc 2007
MARS usefulness in diltiazem and verapamil poisonings with refractory vasoplegic shock

Time-course of PD parameters

Time-course of PK

Patients with both collapse and cardiac arrest may benefit from IV 20% lipid emulsion in addition to standard ACLS:
IV bolus of 20% LE 1.5 ml/kg over 1 min ➔ infusion at 0.25 ml/kg/min until stable or up to a maximum of 12 ml/kg.

**Mechanisms of action**
- **Fat sink (PK):** likely most plausible.
- **Bioenergetics:** provides energy to the failing myocardium.
- **Positive inotropic properties by** activating voltage-gated calcium channel.

European Resuscitation Council. Resuscitation 2010
Partition constant and volume of distribution as predictors of ILE efficacy for toxicological emergencies

Serum drug concentration decrease plotted against the partition constant and the volume of distribution of eleven drugs with 2% Intralipid® added to the sample
Agents with positive bench evidence for class effect and reported clinical use associated with a positive outcome

<table>
<thead>
<tr>
<th><strong>Na⁺-channel antagonists</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Local anesthetics</td>
<td></td>
</tr>
<tr>
<td>- Tricyclic antidepressants:</td>
<td>Doxepin</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
</tr>
<tr>
<td></td>
<td>Amitryptilline</td>
</tr>
<tr>
<td></td>
<td>Dothiepin</td>
</tr>
<tr>
<td>- Flecainide</td>
<td>[bench model evidence equivocal]</td>
</tr>
<tr>
<td>- Propafenone</td>
<td></td>
</tr>
<tr>
<td>- Cocaine</td>
<td></td>
</tr>
</tbody>
</table>

**Ca²⁺-channel blockers**

- Verapamil
- Diltiazem

**Beta-blockers**

- Propranolol
- Carvedilol
- Nebivolol

**Miscellaneous**

- Haloperidol
What is the exact place of elimination techniques in the management of poisonings?

EXTRIP recommendations
CONCLUSIONS

• For most severely poisoned patients, supportive care and antidotes are all that is necessary; extracorporeal renal support is indicated in limited cases.

• In practice, hemodialysis should be considered in severe poisonings with: salicylates, lithium, methanol, ethylene glycol, and metformin.

Further randomized studies are needed to evaluate hemodialysis benefit.

Further experience is needed to evaluate continuous techniques.