Atypical Dialysis Circumstances

Pregnancy - Drug Overdose

Emad Magdy Shawky

Hemodialysis Course, 11th OCT. 2016
10 TIPS To Approach A Pregnant Lady On Hemodialysis
Hormonal changes (Estrogen- progesterone- LH- Prolactine)

- Anovulation (with or without Amenorrhea)
- Endometrial changes
The Miracle Continues Against All Odds
Increasing incidence
- May reach 7% of women on CHD rising from 1% 1980 (Improving Dx service, better anemia control)
- More with residual renal function.
- Less with PD.

Increasing survival rates
- 1st successful 1971
- 30-50% increasing dialysis dose
  - 85% premature
  - 35% LBW (< 2kg)
  - Common complications: Respiratory distress- CP- Congenital anomalies

Kidney Int. 2016 May;89(5)
Medical, Ethical, And Emotional Complexities

The key pre-pregnancy factors predicting outcome include the following:

- Degree of renal impairment rather than the aetiology of renal disease.
- Control of hypertension
- Degree of proteinuria
**CONTRACEPTION**

<table>
<thead>
<tr>
<th>Maternal Renal Outcomes According to Pre-pregnancy Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine &lt;1.5 mg/dl (130 μmol/l)</strong></td>
</tr>
<tr>
<td>- Permanent loss of GFR in &lt;10% of women</td>
</tr>
<tr>
<td>- Greatest risk if GFR &lt;40 ml/min and proteinuria &gt;1 g/day</td>
</tr>
<tr>
<td>- Major determinant of ESRD progression is hypertension</td>
</tr>
<tr>
<td>- 40% risk of preeclampsia if baseline proteinuria &gt;500 mg/day</td>
</tr>
<tr>
<td><strong>Creatinine 1.5-2.5 mg/dl (130-220 μmol/l)</strong></td>
</tr>
<tr>
<td>- Decline or permanent loss of GFR in 30% of women</td>
</tr>
<tr>
<td>- Increased to 50% if uncontrolled hypertension</td>
</tr>
<tr>
<td>- 10% ESRD soon after pregnancy</td>
</tr>
<tr>
<td><strong>Creatinine &gt;2.5 mg/dl (220 μmol/l)</strong></td>
</tr>
<tr>
<td>- Progression to ESRD highly likely during or soon after pregnancy</td>
</tr>
</tbody>
</table>
CONTRACEPTION

<table>
<thead>
<tr>
<th></th>
<th>RFH</th>
<th>NTPR 2001</th>
<th>UKTPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth age</td>
<td>34.9 weeks</td>
<td>36 weeks</td>
<td></td>
</tr>
<tr>
<td>Mean birth weight</td>
<td>2204 g</td>
<td>2493 g</td>
<td></td>
</tr>
<tr>
<td>Low birth weight(&lt;2500g)</td>
<td>50%</td>
<td>45%</td>
<td>54%</td>
</tr>
<tr>
<td>Very low birth weight weight(1500g)</td>
<td>20%</td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>40.7%</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Small for gestation age(&lt;10th percentile)</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Pregnancy across the spectrum of chronic kidney disease

Michelle A. Hladunewich\textsuperscript{1,2}, Nir Melamad\textsuperscript{2} and Kate Bramham\textsuperscript{3}

*Kidney International* (2016) \textsuperscript{2}, \textsuperscript{3}–\textsuperscript{3}; http://dx.doi.org/10.1016/j.kint.2015.12.050
**Medications when planning a pregnancy**
- Initiate prenatal vitamins
- Stop medications not compatible with pregnancy (e.g., statins)

**Contraception when avoiding pregnancy**
- Avoid if possible, estrogen-containing preparations in women with hypertension, vascular disease, or significant proteinuria or who are smokers
- IUDs are not contraindicated in women on immunosuppression

**BP management**
- Intensive hypertension control with pregnancy-safe antihypertensive agents
- Target <140/90 mm Hg

**Proteinuria**
- Suppression of proteinuria with maximal ACEI/ARB until attempting conception or until conception in women with no immunological treatment options

**Immunosuppression**
- Optimization of pre-existing disease (e.g., lupus inactivity for 6 months)
- Ensure disease stability for 3 months on pregnancy-safe immunosuppression
- Switch mycophenolate mofetil to alternative agent (e.g., azathioprine or a calcineurin inhibitor where appropriate)
- Consider repeat kidney biopsy if remission status is unclear

**Weight reduction if necessary**
- Nutritional consultation
- Encourage active lifestyle
Medications
- Folic acid 5 mg od
- Low-dose aspirin (75–81 mg) od to be continued or started after conception and continued until 34–36 weeks’ gestation
- Vitamin D and iron replacement as required

BP management
- Intensive hypertension control with pregnancy-safe antihypertensive medications
  - Target <140/90 mm Hg
  - Blood pressure should be monitored and logged using a home devise validated in early pregnancy
  - Otherwise, blood pressure should be documented each visit

Laboratory assessments
- Renal function tests including serum creatinine, urea and creatinine clearance, and proteinuria should be repeated every few weeks based on the severity and rate of progression of kidney disease
- Levels of uric acid, liver enzymes, platelet count, and urine protein should be documented to use as a baseline in the case that superimposed preeclampsia is suspected later in pregnancy

Fetal surveillance
- Biophysical profiles
- Fetal growth assessments
- Placental function studies
  - Monthly (first trimester) then alternate week (second trimester) then weekly (third trimester)
CONTRACEPTION

- IUD
- Bleeding - Infection
- Oral contraceptives
- Hypercoagulability (access)
- Barriers
- Safety

ACKD Journal, Vol 20, No 3 (May), 2013
IUD
Bleeding- Infection
Oral contraceptives
Hypercoagulability (access)
Barriers
Safety
**Challenges In Prescription**

- **Plasma volume** increased by 30% >> hemodilution >> anemia
- **WT gain rate** plasma vol plus fetal and placental develop
- **Polyhydramnios** as high BUN >> fetal osmotic diuresis
- Bone and mineral metabolism placenta converts some 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 >> adjustment of vitamin D, Ca supplement
- **Respiratory alkalosis** hyperventilation (progest mechanical) – hyperemesis >> compensation by M.Acidosis
- **EPO resistance**, cytokine release >> anemia
DOSE AND ADEQUACY

Target BUN < 50 mg/dL or even < 45 mg/dL

Nephrol Dial Transplant (2015) 0: 1–20
DOSE AND ADEQUACY

There was a trend toward better infant survival in women who received dialysis ≥ 20 hours per week and a weak correlation between numbers of hours of dialysis and gestational age (p=0.05). Seventy-nine percent of infants received dialysis ≤ 12 hours a week. The authors concluded that increasing dialysis time may improve outcome, but prematurity remains a major cause of morbidity and likely contributes to a high frequency of long-term medical problems in surviving infants.

Polyhydramnios occurs usually between 19 and 20 weeks of gestation. It is associated with peak frequency of spontaneous second trimester abortion and with the onset of premature contraction and labor, and it is related to changes in fetal epidermal and renal function. It has been hypothesized that fetal skin may act as a diffusing membrane permitting the extension of the fetal extracellular fluid space to the amniotic fluid causing biochemical changes of the amniotic fluid.

**Intensive Hemodialysis Associates with Improved Pregnancy Outcomes: A Canadian and United States Cohort Comparison**

Live birth rate, %

<table>
<thead>
<tr>
<th>Hemodialysis intensity, hours per week</th>
<th>0 - 20</th>
<th>21 - 36</th>
<th>37 - 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>75</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

\[ P = .02 \]

Intensive Hemodialysis Associates with Improved Pregnancy Outcomes: A Canadian and United States Cohort Comparison

Intensive Hemodialysis Associates with Improved Pregnancy Outcomes: A Canadian and United States Cohort Comparison

Dialyzer type, ultrafiltration volume

- **Small surface area dialysers**
  - Reduce UF rate per session
  - Avoid hypotension
  - Avoid abrupt osmolarity changes
Dialyzer type, ultrafiltration volume

**Dry BW assessment**

- Predicted Wt gain: after 3m>> 0.5 Kg/wk
- Clinical: Bp control, (edema not reliable)
- Hematocrit & Albumin levels

Measure Hematocrit & Albumin at the initial first-trimester visit.

A rise in either value strongly suggests intravascular volume contraction, Opposite is not true.
Heparin

- Pregnancy is a hypercoagulability state so theoretically there are increased requirements but it is not a rule.

Individualization

Dialysate constituents

- **K**: 3 meq/l
  - Intensive dialysis with risk of hypokalemia

- **HCO$_3^-$**: <25 meq/l
  - Target serum 18-22 mmol/l

- **Na**: 135 mmol/l

Hemodialysis International 2016; 20:339–348
Minerals and water soluble vitamins

- Give at increased doses, because they can be partially removed by intensive dialysis.
- **Folic acid** at a higher dose of 5 mg daily if on dialysis.

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No supplement</td>
</tr>
<tr>
<td>E</td>
<td>No supplement</td>
</tr>
<tr>
<td>C</td>
<td>≥170 mg/d</td>
</tr>
<tr>
<td>Thiamine</td>
<td>3 mg/d</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>3.4 mg/d</td>
</tr>
<tr>
<td>Niacin</td>
<td>≥20 mg/d</td>
</tr>
<tr>
<td>B₆</td>
<td>&gt;5 mg/d</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1.8 mg/d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minerals</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>2,000 mg/d (from phosphate binders)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1,200 mg/d</td>
</tr>
<tr>
<td>Magnesium</td>
<td>200-300 mg/d</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg/d</td>
</tr>
<tr>
<td>Carnitine</td>
<td>330 mg/d</td>
</tr>
</tbody>
</table>

Hemodialysis International 2016; 20:339–348
BMD

placenta converts some 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3

- **Phosphate**: monitored frequently, may stop phosphate binders or need supplementation (important to fetal skeletal development)

- **Calcium**: increase dialysate calcium to 1.75 mmol/l – oral supplementation (1-2 g/d) - take care of hyper or hypocalcemia
Anemia

- **Target**: 11 g/dl.

- **EPO**: increase dose by 50%.

- **Iron**: monitored monthly (IV supp).

- **CBC weekly**.

- **<8 g/dl>> blood transfusion.**
Hypertension And Superimposed PET

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placental passage</th>
<th>Teratogenicity</th>
<th>Fetal/neonatal effects</th>
<th>Safe in pregnancy</th>
<th>Safe in breast feeding</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylodopa</td>
<td>✔</td>
<td>X</td>
<td>X</td>
<td>Often used first line. Maternal side effects may limit use (e.g., drowsiness)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>✔</td>
<td>X</td>
<td></td>
<td>Fetal growth restriction in some studies. Fetal bradycardia with atenolol in first trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca-channel antagonists (e.g., nifedipine, amlodipine)</td>
<td>✔</td>
<td>X</td>
<td></td>
<td>Labetalol often used first line. Excreted into breast milk, but widely used without reports of neonatal side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>✔</td>
<td>X</td>
<td>Proximal tubular necrosis</td>
<td>Theoretically, may cause intravascular volume contraction and reduce capillary filtration, but can be used with caution for fluid overload or difficult-to-control hypertension. Excreted into breast milk (≤5% therapeutic dose), but widely used without reports of neonatal side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>✔</td>
<td>X</td>
<td></td>
<td>Usually used in combination with methyldopa or labetalol. Excreted into breast milk, but no adverse effects reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>✔</td>
<td>X</td>
<td></td>
<td>Prolonged exposure can result in renal insufficiency and impairment in the urine-concentrating ability. Enalapril, captopril, and quinapril are excreted in small amounts with no adverse effects reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MA Hladunewich et al.: Pregnancy and chronic kidney disease*
When to suspect pre-eclampsia?

Aspirin (75–150 mg/day)

The aim of aspirin is for the prevention of preeclampsia or perinatal death

Advances in Chronic Kidney Disease, Vol 20, No 3 (May), 2013
Fetal Assessment

- **Serial ultrasound examinations** are important for the early detection of fetal growth restriction.
- **Assessment of the fetal heart rate** (particularly during the last portion of a session).

Kidney Int. 2016 May;89(5)
## Immune-suppressing Drugs

<table>
<thead>
<tr>
<th>Immunosuppression Medications</th>
<th>Possible Increase in Oral Cleft Palate</th>
<th>Rare—Except at Large Doses (Cataracts, Infection and Adrenal Insufficiency)</th>
<th>Maternal Side Effects Include Bone Loss and Possible Osteonecrosis, Gestational Diabetes, Hypertension, Cataracts, Adrenal Insufficiency</th>
<th>(Breast-Feeding Is Not Encouraged If Dose &gt; 60 mg Daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prednisone</strong></td>
<td>Limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>✓</td>
<td>Possible Sporadic Congenital Abnormalities</td>
<td>Transient Immune Alterations in Neonates Hyperkalemia and Renal Impairment</td>
<td></td>
</tr>
<tr>
<td><strong>Tacrolimus and Cyclosporine</strong></td>
<td>✓</td>
<td></td>
<td>✓ Usually Increased Doses Required to Achieve Prepregnancy Target Levels Hyperkalemia, Worsening Hypertension, and</td>
<td>Excreted Into Breast Milk, But 0.23%–0.5% of Maternal Weight-Adjusted Dose</td>
</tr>
<tr>
<td>Drug</td>
<td>Cleft lip and palate, absent auditory canal, hypertelorism, microtia, brachydactyly of the fifth finger, limb abnormalities, and hypoplastic toenails</td>
<td>Chromosomal abnormalities and cytopenia (Only after the first trimester in life-threatening maternal disease)</td>
<td>Toxicity in animal studies, but not teratogenicity</td>
<td>Toxicity in animal studies, but not teratogenicity</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>✔</td>
<td>x</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>–animal data</td>
<td>✔</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Unknown</td>
<td>Unknown</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Unknown</td>
<td>Unknown</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Unknown, but probable</td>
<td>Unknown</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Unknown, but probable</td>
<td>Unknown</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
<td>Unknown, but probable</td>
<td>Unknown</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>Unknown</td>
<td>Unknown</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
<td>x (Only after the first trimester in life-threatening maternal disease)</td>
</tr>
</tbody>
</table>
When to Terminate Pregnancy?

<table>
<thead>
<tr>
<th>Indications for Delivery in Women with Preeclampsia or CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to control blood pressure</td>
</tr>
<tr>
<td>Deteriorating glomerular filtration rate</td>
</tr>
<tr>
<td>Neurologic abnormalities, such as eclampsia, headaches with accompanying clonus and hyperreflexia, or repeated visual scotomata</td>
</tr>
<tr>
<td>Worsening thrombocytopenia</td>
</tr>
<tr>
<td>Increasing liver transaminase levels</td>
</tr>
<tr>
<td>Failure of fetal growth</td>
</tr>
<tr>
<td>Reversed or absent end-diastolic flow on cardiotocography</td>
</tr>
</tbody>
</table>
Significant variations in breast milk composition between pre- and post-HD samples suggest that breastfeeding might be preferably performed after dialysis treatment.

In summary, our findings indicate that breastfeeding can be considered a viable option for newborns of mothers on dialysis.
Enhanced Drug Elimination
Case 1

- A 32 year old woman ingested 20 lithium carbonate 300 mg tablets in a suicide attempt
- She is drowsy and her speech is slurred
- Her serum Li = 6 mEq/L
- Hemodialysis needed?
- Na = 140
- K = 4.0
- Cl = 110
- HCO3 = 26
- BUN = 8  Cr = 1.0
- Glucose = 98
- EtOH = 0.16 gm%  U Tox (+) benzo’s
Case 2

- A 42 year old man brought from a board and care with mumbling, tremor, has a seizure in the ED
- Chronic Li use, no other meds
- BUN = 44  Cr = 2.6  Na = 148
- Li = 3.8 mEq/L
- Repeat Li 4 hours later = 3.6 mEq/L
- Hemodialysis needed?
Enhanced Drug Elimination

- Who needs it?
- Will it work?
- What’s the best technique?
Who needs it?

- Critically ill despite supportive care
  - eg, intractable shock
- Known lethal dose or blood level
  - eg, salicylate; methanol / ethylene glycol
- Usual route of elimination impaired and total body elimination can be increased by 30% or more
- Risk of prolonged coma
- Ingestion of a toxin with serious delayed effects
Will it work?

- **Volume of distribution:**
  - Is the drug **accessible**?
  - How big a volume to clear?

- **Clearance (CL):**
  - Does the method efficiently cleanse the blood?
Volume of distribution (Vd)

- Volume of distribution (Vd) is the theoretical dispersion of the substance in the body.
  - Amount of drug in the body / concentration of the drug in plasma.
  - Affected by obesity, ECF volume
  - Low Vd is < 1 L/kg
Clearance

- Clearance is the theoretical **volume of blood from which the substance is removed per unit time.**
- Depends on the ability of a molecule to pass across the GBM into the urine, a function of **molecular size, charge, urine flow rate** (ml/min). Solute removal is via **convection (filtration)** & modified by tubules.
Two drugs with the same CL

<table>
<thead>
<tr>
<th>Dialysis CL</th>
<th>Vd</th>
<th>Fraction eliminated in 60 min of dialysis</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>

\[ T\frac{1}{2} = \frac{0.693 \text{ Vd}}{\text{CL}} \]
Which method?

- Hemodialysis
- Continuous hemofiltration
- Hemoperfusion
- MARS
Hemodialysis (HD)

- Toxic substance must be \textit{water soluble}, have low MW, low protein binding, and low volume of distribution.

- Clearance of the toxin depends on membrane surface area (\& type), blood and dialysate flow rates.

- \textbf{High-flux membranes} can also remove higher MW toxins.

- Risk for post-HD "rebound" due to redistribution of toxin.
Continuous techniques
Continuous hemofiltration (CVVH, CVVHD)

- Blood passes through large hollow pore fibers, allowing **convective removal** of molecules up to 40kDa.
- Useful in **unstable patients**
- Prolonged duration of therapy, **minimizes rebound effects**
- CL lower than HD or HP, **but it can be performed 24 hrs/day**
Hemoperfusion
Blood passes through a **cartridge with sorbent material able to absorb the toxin**

- Charcoal based, synthetic resins, anion exchange
- Toxic substance must have binding affinity to the sorbent & have a low volume of distribution

- Charcoal efficiently removes molecules in 1000-1500 kDa range, but doesn’t remove protein-bound molecules
- Resins more effective with protein/lipid-bound toxins

- Generally **declining modality** due to limited use, poor life of cartridges (change q2-3hrs), more technically difficult to perform, unable to correct acid-base, fluid, electrolytes

- Could combine with HD however (in series)
MARS
Blood purification system aimed at removing albumin-bound toxins
## Extracorporeal Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Hemo-dialysis</th>
<th>Hemo-filtration</th>
<th>Hemo-perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Water</td>
<td>Water</td>
<td>Water or lipid</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt; 500 Da</td>
<td>&lt; 40 kDa</td>
<td>&lt; 40 kDa</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Low (&lt; 80%)</td>
<td>Low</td>
<td>Low or high</td>
</tr>
<tr>
<td>Volume of distribution (Vd)</td>
<td>&lt; 1 L/kg</td>
<td>&lt; 1 L/kg</td>
<td>&lt; 1 L/kg</td>
</tr>
<tr>
<td>Endogenous clearance</td>
<td>&lt; 4 ml/min/kg</td>
<td>&lt; 4 ml/min/kg</td>
<td>&lt; 4 ml/min/kg</td>
</tr>
<tr>
<td>Distribution time</td>
<td>Short</td>
<td>Longer</td>
<td>Short</td>
</tr>
</tbody>
</table>
### Some Poisonings for Which Extracorporeal Removal May Be Indicated

<table>
<thead>
<tr>
<th>Hemodialysis</th>
<th>Hemofiltration</th>
<th>Hemoperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Aminoglycosides</td>
<td><em>Amanita</em> mushroom</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Desferrioxamine</td>
<td>Barbiturate</td>
</tr>
<tr>
<td>Methanol</td>
<td>Sodium edetate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Theophylline</td>
<td>Meprobamate</td>
</tr>
<tr>
<td>Isopropanol</td>
<td></td>
<td>Theophylline</td>
</tr>
<tr>
<td>β-Blockers</td>
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<td>Atenolol</td>
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</tr>
<tr>
<td>Sotalol</td>
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</tr>
<tr>
<td>Lithium</td>
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</tr>
<tr>
<td>Meprobamate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
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<tr>
<td>Salicylates</td>
<td></td>
<td></td>
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<tr>
<td>Theophylline</td>
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</tbody>
</table>
Lithium

- Alkali metal. Widely used for bipolar disorder.
- Therapeutic range **0.6-1.2 mEq/L**
- **Toxicity = mainly CNS**
  - Tremor, slurred speech, muscle twitching
  - Confusion, delirium, seizures, coma
  - Recovery may take weeks
- Toxicity may occur as a result of **acute overdose or chronic use**
Pharmacokinetics

- **Completely absorbed orally**
  - Volume of distribution approx 0.8 L/kg
  - Slow entry into CNS
  - Initial serum levels do NOT reflect brain levels

- **Eliminated entirely by the kidneys**
  - Half-life 14-20 hours
  - Prolonged in patients with renal insufficiency
  - Promoting saline excretion hastens Li removal
Case 1

- A 32 year old woman ingested 20 lithium carbonate 300 mg tablets in a suicide attempt.
- She is drowsy and her speech is slurred.
- Her serum Li = 6 mEq/L.
- Hemodialysis needed?
- Na = 140
- K = 4.0
- Cl = 110
- HCO3 = 26
- BUN = 8  Cr = 1.0
- Glucose = 98
- EtOH = 0.16 gm%  U Tox (+) benzo’s
Osmolar Gap

- Calculated Osm - Measured Osm = Osmolar gap
- Calculated Osm = 2 (Na) + Glu / 18 + BUN / 2.8
- Significant OG if > 15 mOsm/L

<table>
<thead>
<tr>
<th>Drug (MW)</th>
<th>Toxic level</th>
<th>Corr. Factor</th>
<th>Toxic ΔOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol (32)</td>
<td>&gt;50</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Ethanol (44)</td>
<td>&gt;400</td>
<td>4.5</td>
<td>88</td>
</tr>
<tr>
<td>Ethylene glycol (62)</td>
<td>&gt;25</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Isopropanol (100)</td>
<td>&gt;350</td>
<td>5</td>
<td>75</td>
</tr>
</tbody>
</table>
Case 2

- A 42 year old man brought from a board and care with mumbling, tremor, has a seizure in the ED
- Chronic Li use, no other meds
- BUN = 44   Cr = 2.6   Na = 148
- Li = 3.8 mEq/L
- Repeat Li 4 hours later = 3.6 mEq/L
- Hemodialysis needed?
case 1 . . .

- The Poison Control Center was consulted about hemodialysis
- The toxicologist advised:
  - **IV saline at a rate of 150 cc/hr**
  - **Recheck serum Li in 4 hours**
    - After 4 hrs, the Li was 2.2 mEq/L
    - A 3rd level 4 hrs later was 1.1
    - The patient gradually recovered from her alcohol and benzodiazepine intoxication
Acute vs Chronic Li

- **Acute:**
  - High level, drops rapidly
  - Absent symptoms

- **Chronic:**
  - Often associated w/ renal insufficiency, DI
  - Occurs gradually
  - Symptoms more severe, even with lower levels (eg, 2 - 2.5 and above)
Lithium and dialysis

- Serum level > 6? 8? 10? (acute)
- Level > 4? (chronic)
- Level 2.5-4 with severe Sx?
Solute is often distributed across at least one remote body compartment that is not directly accessible during HD.

If there is any resistance to solute movement between the accessible and the remote compartments, disequilibrium will develop over the dialysis session, reducing the efficiency of toxin removal (e.g., lithium) and will manifest as a large postdialysis rebound.
Extending the HD session beyond 4 hours can to some extent ameliorate rebound, but intermittent HD is an inefficient process that depends on the solute concentration presented to the dialyzer so increasing dialysis session frequency can help.
Lithium: summary

- 2-compartment model
  - Early levels misleadingly high
- Acute vs chronic intoxication
- Dialysis is not rapidly effective
  - Li is slow to leave intracellular compartment
- IV fluids often the best bet
Alcohols

- The ingestion of as little as 1 g/kg of either methanol or ethylene glycol is potentially lethal.
- Poisoning should be suspected in any patient presenting with nausea, vomiting, abdominal pain, impaired consciousness, convulsions, severe metabolic acidosis, AKI and complicated by optic nerve damage if not treated.
- The urine should be examined for the presence of needle shaped crystals of calcium oxalate monohydrate which are pathognomonic for ethylene glycol toxicity.
- Ethylene glycol is metabolized to glycolic acid and oxalate, resulting in renal tubular injury and obstruction.
Methanol, Ethylene Glycol

- **Indications for dialysis:**
  - Elevated level > 50 mg/dL
  - Severe acidosis
  - Increased osmolal gap > 10-15 mmol/L

- **Notes:**
  - HD only - not adsorbed to AC: Continuous extracorporeal treatment is less effective in removing ethylene glycol and methanol but may be used if intermittent HD is not available.
  - Give blocking drug (EtOH, 4-MP) - Note: need to increase dosing during dialysis
Thank you!