Interpretation of Postmortem Toxicology Results: They Do Usually Mean *Something*…

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Why it’s not just about the “numbers”…

- Severe MVA
- Ethanol not detected, but…
- Urine MeOH 530 mg%
- Liver 190, 300 mg%
- Spleen 20, 70 mg%

- Explanation?
The *False* Assumptions

- Postmortem blood drug concentrations reflect those at the moment of death
- Blood drug concentrations are reasonably predictable
- Pharmacokinetics is useful in postmortem cases
- Drug dose can be estimated from postmortem blood concentrations
The Problems...

- Sample Integrity
- Postmortem Neo-formation
- Postmortem Redistribution
- Site-to-site differences
- Postmortem Diffusion
- Trauma Artifacts
- Medical Artifacts
- Delayed Deaths
- Drug Instability
- Drug-drug/alcohol Interactions
- Impaired Metabolism (& PG)
- Impaired Clearance
- Iatrogenic Deaths
- Tolerance / Opiate Deaths
- Improper Use of Literature
- Improper Use of PK
- Unwarranted Confidence
Sample Integrity

- Where is blood from?
  - Is it cardiac blood or “chest” blood?
  - How good is a large volume of femoral blood?
- Is the blood/tissue contaminated?
  - Diffusion from stomach?
  - Ruptured stomach/diaphragm?
  - Aspiration of gastric contents?
- Is the “blood” really “blood”?
  - Or is it pleural fluid, bloody chest fluid?
Non-Homogeneous Blood:

(Don’t get too “hung up” on the source)

- This elderly farmer committed suicide by ingesting strychnine from an old can of gopher (rat) poison.
- Even though postmortem blood was labeled as being from the same site – there was a considerable difference.

<table>
<thead>
<tr>
<th></th>
<th>Ethanol</th>
<th>Strychnine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclavian blood (tube)</td>
<td>240 mg%</td>
<td>8.2 mg/l</td>
</tr>
<tr>
<td>Subclavian blood (bottle)</td>
<td>240 mg%</td>
<td>54 mg/l</td>
</tr>
</tbody>
</table>
Postmortem Fermentation

Blood ON ITS OWN is UNRELIABLE as a specimen for assessing the presence of alcohol at the time of death.

Can get postmortem BAC up to “legal limit” due to fermentation; in RARE circumstances >300 mg%.
Isopropanol Neo-formation

- Isopropanol neo-formation in drowning victims:
  - Small amounts of isopropanol (up to 70 mg/100 ml) are sometimes detected in the absence of measurable levels of acetone
  - Tend to be drowning victims (lakes or rivers)

Footnote: Isopropanol is detected WITH acetone at low concentrations in other cases involving alcoholism, stress, malnutrition and diabetes
Isopropanol Neo-formation - Case

- 10 y.o. boy drowns in storm drain after heavy rain
- Swept through 5 km sewer line and body recovered 5-days later from river
- Blood isopropanol 52 mg%
- Blood acetone less than 5 mg%
- Blood ethanol 70 mg%
- No evidence of “drinking”
Postmortem Redistribution

Main mechanism
- Release and diffusion from major organs
- Time and concentration dependent

- Candidates:
  - High $V_d$ - typically $>5$L/kg
  - ‘Basic’ character

- Increases of 2 – 10 fold or greater
  - Cardiac $>$ subclavian $>$ femoral $>$ antemortem
Example of the Problem of Postmortem Redistribution

- 48 y.o. woman with severe heart disease found dead; also history of depression
- Found unresponsive and taken to hospital (but DOA)
- Blood taken at hospital by local medical examiner
- Blood also taken again at autopsy (12 – 18 h later)
- Cause of death: atherosclerotic C-V disease (MI scars)
- Considerable postmortem redistribution that could lead to mis-interpretation of Toxicology
- Toxicology results…
### Example of the Problem of Postmortem Redistribution - Results

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline</th>
<th>Nortriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antemortem blood (DOA)</td>
<td>0.10</td>
<td>0.34</td>
</tr>
<tr>
<td>Femoral blood (at hospital)</td>
<td>0.20</td>
<td>0.37</td>
</tr>
<tr>
<td>Cardiac blood (at autopsy)</td>
<td>2.20</td>
<td>5.10</td>
</tr>
<tr>
<td>Liver</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>Stomach</td>
<td>trace</td>
<td>trace</td>
</tr>
</tbody>
</table>

Concentrations of amitriptyline and nortriptyline ~10x higher in blood taken at autopsy than blood collected at the hospital.

Autopsy blood results alone could lead to mis-interpretation!!
Just because it’s “femoral”… don’t always rely on a single specimen

- 47 y.o. woman with multiple drug overdose
- Very unusual femoral:cardiac codeine distribution
- BE CAREFUL about relying on ONE specimen – wherever it is from!!!!

<table>
<thead>
<tr>
<th></th>
<th>Codeine</th>
<th>Alprazolam</th>
<th>Phentermine</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral blood</td>
<td>7.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac blood</td>
<td>1.62</td>
<td>0.337</td>
<td>0.99</td>
<td>44</td>
</tr>
<tr>
<td>Liver</td>
<td>6.7</td>
<td></td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>9.2 mg</td>
<td>1.2 mg</td>
<td>7.6 mg</td>
<td>74 mg</td>
</tr>
</tbody>
</table>

Plus 50 mg/100 ml blood ethanol
Site-to-site Differences

Site-to-site differences in blood drug concentration are often seen for drugs that do NOT typically undergo postmortem redistribution

– e.g. benzodiazepines, acetaminophen, barbiturates

– Usually seen after overdose and may be due to:
  • Incomplete distribution
  • Postmortem diffusion or related phenomena
Postmortem Diffusion

- Term usually reserved for diffusion of alcohol from the stomach into nearby organs (esp. liver) and blood vessels
- Can also be due to movement of gastric contents to trachea and lungs and subsequent diffusion into major central blood vessels
Unusual Drug Distribution…

- 38 y.o. woman found dead after ‘fight’ with CL husband
- Empty pill contains nearby; holographic will
- Unusual distribution between blood and liver…

<table>
<thead>
<tr>
<th></th>
<th>Diphenhydramine</th>
<th>Amitriptyline</th>
<th>Nortriptyline</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral blood</td>
<td></td>
<td>0.88</td>
<td>0.27</td>
<td>570 mg/l</td>
</tr>
<tr>
<td>Subclavian blood</td>
<td>0.83</td>
<td></td>
<td></td>
<td>660 mg/l</td>
</tr>
<tr>
<td>Liver</td>
<td>195</td>
<td>532</td>
<td>17</td>
<td>3500 mg / 88 g</td>
</tr>
<tr>
<td>Gastric</td>
<td>32 mg</td>
<td>71 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Severe trauma can cause rupture of the stomach and diaphragm, causing release of alcohol and drugs into the chest cavity.

- Severe risk if blood collected by “blind stick”
- Risk of widespread diffusion of drugs into “central” vessels
High Alcohol in a “Jumper”

A young man drunk a jug of cheap wine, then jumped 120 feet into a parking lot:

<table>
<thead>
<tr>
<th>Initial samples: (PMI 13h.)</th>
<th>EtOH mg%</th>
</tr>
</thead>
<tbody>
<tr>
<td>chest blood</td>
<td>890</td>
</tr>
<tr>
<td>vitreous</td>
<td>70</td>
</tr>
<tr>
<td>urine</td>
<td>310</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Later samples: (PMI 67 h.)</th>
<th>EtOH mg%</th>
</tr>
</thead>
<tbody>
<tr>
<td>l. femoral blood</td>
<td>620</td>
</tr>
<tr>
<td>r. femoral blood</td>
<td>670</td>
</tr>
<tr>
<td>neck blood</td>
<td>980</td>
</tr>
<tr>
<td>upper chest blood</td>
<td>1450</td>
</tr>
</tbody>
</table>
A young man was driving a pickup truck on a two lane highway. He drove head on into a Greyhound bus. The collision and ensuing fire killed three people, including both drivers.

Pickup truck driver:
- Ethanol: Pleural cavity blood (A) - 200 mg%
  Pleural cavity blood (B) - 300 mg%
  Heat denatured liver - 80 mg%

- Blood (A): grey-top tube with fluoride (fluid blood)
- Blood (B): plastic tub (some clots; some fluid - both same BAC)
- Liver: “moist” but firm
No Autopsy was performed, however, an extended external examination was performed:

- Body was extensively burned and partially cremated
- Heat denatured split in chest wall, exposing the heart
- Heat denatured blood and fluid blood in chest cavity
- Blood in abdominal cavity (not taken)
- Diaphragm was intact
- Unknown if stomach was intact (gastric not taken)

Is it possible to say if the BAC of this man was over 80 mg/100 mL at the time of the accident?
Medical Artifacts

- Intravenous lines / pumps
  - May continue to run after death – local buildup
- Medications injected near death
  - e.g. incomplete distribution of lidocaine
  - “terminal” dosages of narcotics
- Organ harvest drugs
  - e.g. papaverine for saphenous vein
Delayed Deaths

- Depressants (narcotics, sedatives) with or without alcohol can cause hypoxic brain damage
  - Resuscitation and hospitalization for hours or days can lead to low or near absent levels
  - Even without resuscitation, drugs can lead to prolonged coma prior to death, and low drug levels
  - Near-fatal ethanol can clear in <24h

- Delayed deaths also a factor with acetaminophen, ethylene glycol and methanol

- Antemortem specimens important!!
Drug Instability

- Cocaine – to benzoylcegonine, methylecgonine etc
- Heroin – to 6-MAM and morphine
- Clonazepam, nitrazepam - to amino analogues
- Morphine glucuronide to morphine?
- Codeine glucuronide to codeine?
Drug – Drug/Alcohol Interactions

- Enhancement of CNS toxicity
  - Narcotics, sedatives, with or without alcohol
- Impaired metabolism
  - Interference with common enzyme system (e.g. P4502D6)
- Serotonergic crisis (e.g. SSRI and TCA)
- Changes in “free” drug (e.g. warfarin / digoxin)
Fatal Drug Accumulation

- 21 y.o. university student living with parents
- History of manic depression, but well controlled
- Watching TV with father, but feeling unwell and went to bed early; 2 h later complained of nausea
- 4 h later was heard to collapse and taken to hospital; died en route; resuscitation failed
- All medication accounted for (no overdose)
- Prescribed: 900 mg chlorpromazine, 125 mg imipramine, 10 mg amphetamine
- No cause of death at autopsy; toxicology…
Fatal Drug Accumulation – Toxicology Results

<table>
<thead>
<tr>
<th></th>
<th>Chlorpromazine</th>
<th>Imipramine</th>
<th>Desipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral blood</td>
<td>0.92</td>
<td>0.60</td>
<td>3.74</td>
</tr>
<tr>
<td>Liver</td>
<td>111</td>
<td>37</td>
<td>261</td>
</tr>
<tr>
<td>Stomach</td>
<td>trace</td>
<td>trace</td>
<td>trace</td>
</tr>
</tbody>
</table>

Results: mg/l or mg/kg

1. Liver levels VERY high (especially metabolite desipramine)
2. Very high desipramine (metabolite) to imipramine suggests accumulation
3. Likely genetic (P4502D6) and/or drug-drug induced accumulation
4. All medications accounted for (none missing)
Impaired Metabolism

Can be due to:

- Genetic impairment due to enzyme deficiency
  - e.g. Cytochrome P4502D6 in 7-10% Caucasians
- Drug-Drug impairment of enzyme system
  - e.g. impairment by SSRIs of CYP4502D6
  - e.g. impairment by ....
- Impairment due to high single drug concentration
- Impairment due to reduced liver function (age, alcohol)
# Juvenile Imipramine Death

- 7 year old boy with severe attention deficit disorder
- Medications: imipramine (150 mg hs); valproate (250 mg hs).
- Collapsed suddenly at school; resuscitation unsuccessful.
- Autopsy negative; toxicology indicates “imipramine poisoning”.
- Physician faced disciplinary hearing, criminal charges and civil trial.

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Imipramine</th>
<th>Desipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac blood</td>
<td>1.1</td>
<td>13</td>
</tr>
<tr>
<td>Femoral blood</td>
<td>0.47</td>
<td>6</td>
</tr>
<tr>
<td>Liver</td>
<td>35</td>
<td>449</td>
</tr>
<tr>
<td>Antemortem Se (15 min after collapse)</td>
<td>0.069</td>
<td>0.942</td>
</tr>
</tbody>
</table>

(All values in mg/l or mg/kg)
Juvenile Imipramine Death

10- Hydroxyimipramine
2- Hydroxyimipramine

CYP2D6

Imipramine

CYP3A4

Desipramine

CPY2D6

Hydroxydesipramines
(and conjugates)

Hydroxydesipramines
(and conjugates)
Impaired Renal Clearance (Hx)

- 37 year old man found dead at home after missed dialysis appointment
- History of chronic renal failure, hypertension, CAD, peptic ulcer disease and bowel surgery requiring multiple resection; i/v drug use
- Autopsy not performed - diagnosis made on basis of long medical history; toxicology requested because of age and drug history
Impaired Renal Clearance (Tox)

<table>
<thead>
<tr>
<th></th>
<th>Cocaine</th>
<th>BE</th>
<th>EME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclavian blood</td>
<td>trace</td>
<td>51.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Cardiac blood</td>
<td>trace</td>
<td>49.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Vitreous</td>
<td>trace</td>
<td>38.2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

No ethanol detected

BE = benzoylecgonine; EME – Ecgonine methyl ester (mg/L)
Iatrogenic Deaths

- Usually defined as unintended deaths due to adverse effects of medically prescribed drugs
  - Adverse reactions such as anaphylaxis
  - Hematological, hepatic or renal adverse effects
  - Serotonin syndrome and Neuromuscular Malignant Syndrome (NMS)
  - Inadvertent overdose (narcotics)?
    - First three *may* not be dose-related
Tolerance / Opiate Deaths

- Interpretation of postmortem narcotic blood levels very very tricky!
  - Need to have some idea of degree of tolerance
    - If naïve user, interpretation easier
    - If prescribed, need medical record and/or pharmacy record
    - Need to know dose and duration of dosage
    - Preferably need “medication count”
Methadone – Two Cases

Case 1:
- 26 y.o. with dubious history of opiate addiction; new in methadone program
- Dies over w/end after taking 4 x 40 mg methadone in ~48h
- PM Blood methadone 0.34 mg/l (liver 4.6 mg/kg)
- Witness evidence of sedation, loud snoring etc.
- Found dead; no COD

Case 2:
- Young male; well established in methadone program
- Daily dose 130 mg
- Routine blood methadone 0.83 mg/l
- Little or no sedation
- Alive!!
Morphine Specific Issues

– Preferable to have blood levels of unconjugated AND total drug
– If morphine AND codeine is detected, need to assess amount of morphine that came from the codeine
– Elderly can accumulate morphine glucuronide
– May need to assess potential for postmortem hydrolysis of morphine-glucuronide
– Distinguish morphine-3- and -6-glucuronide?
– Oral vs. parenteral? Epidural, intrathecal dosing…
Morphine Death?

- 30 y.o. hospitalized patient with severe hypoxic brain damage due to undiagnosed Addison’s disease
- Medical support withheld with consent of NOK
- Prescribed 10 mg/h i/v morphine; dies 1.5h later

<table>
<thead>
<tr>
<th></th>
<th>Morphine (unconj.)</th>
<th>Morphine (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmortem blood</td>
<td>0.49</td>
<td>0.51</td>
</tr>
<tr>
<td>Antemortem plasma</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

(mg/L)
Morphine Death??

- 78 y.o hospice patient in apparent increasing distress
- Hospitalized for previous 2 – 3 months; NO narcotics
- 40 Hours before death started on oral morphine
- Received TOTAL 90 - 100 mg before death (in 40 hours)
- NO anatomic COD at autopsy…

<table>
<thead>
<tr>
<th>Postmortem blood</th>
<th>Morphine (unconj.)</th>
<th>Morphine (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>(mg/L)</td>
<td></td>
</tr>
</tbody>
</table>
Euthanasia Case

- Mother dying of metastatic breast cancer
- Was prescribed morphine 120 mg tid, plus lorazepam
- Son - physician accused of administering a drug overdose (40 – 50 lorazepam; ?morphine)
- Family member complains; paramedics called.
- Mother resuscitated; taken to hospital, but has hypoxic brain damage; eventually dies; son charged.
Hospital physician gave increasing morphine to relieve “discomfort” while patient was on ventilator 8 – 30 mg/h plus “stat” doses, plus diazepam and “stat” fentanyl (total duration 22 days)
Euthanasia Case

Son charged with
- Manslaughter
- Administering a noxious substance

Plea bargained “guilty” to the latter charge.

Cause of death recorded as:
- “Metastatic carcinoma of breast” (part 1)
- with (part 2) “Morphine and Lorazepam Toxicity” and
- “Aspiration Pneumonia” as contributing factors.

- Manner of death “Natural”.
Suicidal Fire Death?

51 y.o. woman found dead in bedroom following a house fire

- Carboxyhemoglobin 84%; cyanide 1.335 mg/L
- Blood meprobamate 96 mg/l
  - “therapeutic” up to 25 mg/l; little or no PMR
- Did she “overdose” and set fire deliberately?
Nope!

- Same woman arrested for impaired driving several months before death (low speed crash into post-office wall)
- Blood meprobamate 98 mg/l after accident
- Long history of meprobamate and other drug abuse
- “Normal” (but intoxicating) meprobamate level
- Fire death: she fell asleep in bed with a lighted cigarette
Tables of “therapeutic” ranges… DON’T USE THEM!!

- Temptation to interpret from tables of so-called “normal” concentrations
  - Nice neat “ranges”
  - Often based on clinical studies or single cases
  - Ranges often do not allow for postmortem change
  - Ranges do not state whether death was delayed
  - Ranges do not state whether other drugs or alcohol present
  - Ranges do allow for individual circumstances
  - Example: fentanyl 1 – 2 ug/l or 50 – 100 ug/l
Improper Use of Pharmacokinetics

- Amount (dose) = $C \times Wt \times V_d$
  - $C$ = plasma concentration of drug
  - $Wt$ = body weight
  - $V_d$ = volume of distribution

- Do not know:
  - Volume of distribution for that person
  - Blood drug concentration at time of death
  - Whether drug concentration was at “steady state”
Improper Use of Pharmacokinetics: Example

- 35 y.o. man died after admission to hospital for severe back pain.
- He was over-medicated with morphine (oral 90 mg p.o. and i/v 15 mg prn) and was also taking prescribed trimipramine (200 mg hs) and clonazepam (2 mg hs).
- Heard snoring loudly at about 6 am of fourth day and found dead about one hour later.

- At a civil trial, main issue was medical opinion regarding morphine dose and monitoring.
- However one non-forensic medical “expert” did some calculations...
## Toxicology Results

<table>
<thead>
<tr>
<th></th>
<th>Antemortem Blood</th>
<th>Postmortem Blood</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimipramine</td>
<td>140</td>
<td>960</td>
<td>5000</td>
</tr>
<tr>
<td>Desmethyltrimramine</td>
<td>70</td>
<td>180</td>
<td>3000</td>
</tr>
<tr>
<td>Clonazepam</td>
<td></td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>80</td>
<td>690</td>
<td>4000</td>
</tr>
<tr>
<td>Morphine (unconj.)</td>
<td></td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Morphine (total)</td>
<td></td>
<td>480</td>
<td></td>
</tr>
</tbody>
</table>

All concentrations ug/L or ug/Kg
Opinion of “Expert”:

- That the person suicidally overdosed on:
  trimipramine (129 x 50 mg) and
  clonazepam (20 x 0.5 mg)

Basis for opinion:
  - pharmacokinetic calculations of total body burden of
    trimipramine and clonazepam (with several flawed
    assumptions including use of hemocrit)
Unwarranted Confidence?

- ME/coroner (and civil) cases are decided on the preponderence of the evidence – i.e. 51%

- Problem: what happens when that opinion is later used in a criminal trial and there is tremendous pressure for a medical / toxicology opinion “to a reasonable medical (or scientific) certainty”? 
What should you do?

- Interpret with FULL consideration of:
  - Circumstances of death
  - Post-death investigation including:
    - Medical history
    - Medication history
    - Autopsy findings
    - Toxicology on alternate specimens!!

- If you don’t have enough information, DON’T offer an interpretation or give clear caveats!
“Medication Counts”

“Rationalize” for each important medication
- Number prescribed
- Date dispensed
- Dosage (e.g. tablets per day)
- Number remaining at death
- Calculate meds “unaccounted for”

Why? Suicide vs. “Build-up”…
Does it all mean *something*?

- Yes, but only as a piece of the puzzle
- The more “pieces” you have, the more accurate your view of the whole picture
- Sometimes you have to look for pieces you don’t have…
  - Circumstances, scene, witness accounts
  - Past medical (including medication) history
  - Autopsy findings
- Recognize that sometimes you *just don’t have enough pieces*…