Issues in Postmortem Xenobiotic Measurements

Barry K Logan PhD, DABFT
Did drug or alcohol use, cause or contribute to, this persons death, or intoxication?

Answers the Question:

Forensic Toxicology
# Postmortem Vs Clinical Toxicology

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>Postmortem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Collection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resampling Possible</td>
<td>No Resampling Possible</td>
<td></td>
</tr>
<tr>
<td>Limited to antecubital</td>
<td>Various samples available</td>
<td></td>
</tr>
<tr>
<td>Homogeneous</td>
<td>Heterogeneous</td>
<td></td>
</tr>
<tr>
<td>Limited Volume</td>
<td>“Unlimited” volume</td>
<td></td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Order form</td>
<td>Chain of custody form</td>
<td></td>
</tr>
<tr>
<td>Unconfirmed analysis</td>
<td>Confirmation required</td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>Heavily Controlled</td>
<td></td>
</tr>
<tr>
<td>Automated</td>
<td>Manual</td>
<td></td>
</tr>
<tr>
<td><strong>Interpretation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Static Sample</td>
<td>Postmortem Redistribution</td>
<td></td>
</tr>
<tr>
<td>Preserved</td>
<td>Stability and Neogenesis</td>
<td></td>
</tr>
</tbody>
</table>
Postmortem Alcohol

Alcohol May Form in Postmortem Specimens

Neogenesis Prior to Collection:
- Trauma
- Body Cavity Fluid Collection
- Wet/Warm environment
- Delay in collection
- Lack of refrigeration

Embalming:

Post Collection Formation:
- Negligible with adequate preservatives
### Postmortem Alcohol

#### Alcohol May Form in Postmortem Specimens

<table>
<thead>
<tr>
<th></th>
<th>Postmortem alcohol production</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mildly decomposing</td>
<td>3%</td>
<td>Zumwalt, 1982</td>
</tr>
<tr>
<td>Mild to moderate decomposition</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Moderately decomposing</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Severe Decomposition</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Total (130 cases)</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Decomposed</td>
<td>19%</td>
<td>Gilliland and Bost, 1993</td>
</tr>
</tbody>
</table>

Reference:
- Zumwalt, 1982
- Gilliland and Bost, 1993
Postmortem Alcohol


- Autopsies 48-92 hours after death
- 23/42 (55%) had alcohol present presumed postmortem artifact.
  - 21 were 0.01 – 0.09g/100mL
  - 2 greater than 0.10
  - 0.11 and 0.19g/100mL
Postmortem Alcohol

Neogenesis Prior to Collection
- Trauma
- Body Cavity Fluid Collection
- Wet/Warm environment
- Delay in collection
- Lack of refrigeration

Embalming

Post collection EtOH formation:
- Negligible with adequate preservatives
Postmortem Alcohol – Best Practices

- Avoid cavity blood.
- Mix whole blood with 2.0mg of potassium oxalate + 10mg of sodium fluoride per mL of blood (1%).
- Perform duplicate analysis by GC.
- Extraneous volatiles peaks by GC can indicate decomposition.
- Analyze more than one specimen in cases of decomposition.
- Look for agreement between matrices, adjusted for water content.
Postmortem Toxicology

Observations:

Postmortem drug concentrations can differ from site to site.

Concentrations can change over time.

Blood is not serum/plasma.
Postmortem Redistribution (PMR)

• The changing of drug concentrations between the time of death and specimen collection, usually due to diffusion from an area of high concentration to one of lower concentration with subsequent movement of fluids within the body.

• Results: The concentration of a drug measured in postmortem blood is often dependent upon the collection site.
Postmortem Redistribution

• Net change is a function of multiple factors:
  • Pharmacokinetic properties of the drug
  • Chemical characteristics of the drug
  • Orientation of the body
  • Putrefaction
  • Drug dosage
  • Interval between drug ingestion and death
Postmortem Redistribution


- ...A site and time dependence was observed for postmortem blood-drug concentrations. The heart blood-drug concentrations were, in general, significantly higher than those of peripheral specimens. As a result of this phenomenon, the analysis of peripheral blood specimens and solid tissues is often necessary before a definitive interpretation of postmortem toxicological analyses is possible.
Mechanisms of PMR

• **Determinative Factors**
  • Drug kinetics and properties
  • Acid/base properties, lipophilicity, protein binding, potential for postmortem metabolism

• **Diffusion of Drug from a Reservoir**
  • Gastrointestinal tract, liver, lung, myocardium, fat
  • Diffusion through blood vessels or across tissue

• **Cell and Tissue Changes**
  • Cell death, blood movement, blood stasis and lysis, putrefactive processes
Postmortem Redistribution


• …The underlying mechanisms are complex and of different types. Passive drug release from drug reservoirs such as the gastrointestinal tract, liver, lungs, and myocardium may occur immediately after death and, later on, cell autolysis and the putrefactive process participate in redistribution. There is evidence that basic lipophilic drugs with a large distribution volume are particularly susceptible to PMR.
Postmortem Redistribution

• Redistribution from drug reservoirs

From the stomach and GI Tract to the Liver, Lungs and Heart.

Pellisier-Alicot et al.
Postmortem Redistribution

• From the Liver to the Lungs and Heart:
  • Via hepatic veins to IVC, then heart
  • Less intense/later than other processes
  • Documented for Fluoxetine and Norfluoxetine
  • Intrahepatic differences documented
  • Higher concentrations in the left lobe for solvents and zopiclone.
Postmortem Redistribution

- Redistribution from drug reservoirs

From the Lungs to the Heart and Aorta

Pellisier-Alicot et al.
Postmortem Redistribution

• From the Lungs to the Heart, and Aorta:
  • Receive entire blood flux from right ventricle
  • Lungs accumulate drugs with high PKa and Vd (TCA’s, methadone, chlorpromazine).
  • More intense than redistribution from GI tract
  • Role of pericardial fluid
• From the Lungs to the Liver
  • Across the diaphragm
  • (Amitriptyline and solvents)
## Postmortem Forensic Toxicology

### Subclavian vs. Femoral: TCA’s

<table>
<thead>
<tr>
<th></th>
<th>Case 1 (mg/L)</th>
<th>Case 2 (mg/L)</th>
<th>Case 3 (mg/L)</th>
<th>Case 4 (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>3.4</td>
<td>4.1</td>
<td>2.8</td>
<td>3.0/4.2</td>
</tr>
<tr>
<td>Doxepin</td>
<td>6.7/7.3</td>
<td>6.0/7.2</td>
<td>6.4/4.9</td>
<td>1.7/3.0</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>6.6</td>
<td>5.2</td>
<td>5.9</td>
<td>4.6</td>
</tr>
<tr>
<td>L. Heart</td>
<td>4.6</td>
<td>-</td>
<td>5.0</td>
<td>3.9</td>
</tr>
<tr>
<td>R. Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anderson and Prouty, J For Sci 1990;35(2):243-70
Postmortem Redistribution

- Redistribution from drug reservoirs

From the Myocardium into the chambers of the Heart

Pellisier-Alicot et al.
Postmortem Redistribution

• Postmortem Changes in Fentanyl (Rabbit)

**FIGURE 2.** Plasma concentration–time profiles after patch removal and leaving the animals alive (Grp A), patch removal and killing of the animals (Grp B), and leaving patches on the animals after they were killed (Grp C). Data are expressed as the mean (SD).
Perimortem Changes

Effects of Death and Decomposition on Concentrations of Cocaine and its Metabolites in Juvenile Swine.
Logan, Blaho, Mandrell, Berryman, Goff, Goldberger, Schwilke, Ropero-Miller, AAFS, San Francisco, Jan 1998

• Acute changes in cocaine concentrations occurred perimortem over a period of three hours.
• During decomposition cocaine and metabolite concentrations were stable over a period of up to three weeks in cool weather.
Acute/Perimortem Changes (Central)
Decompositional Changes (Central)
Other PM Artifacts

- Differential distribution at the time of death
- Loss of drug through chemical or enzymatic processes
  - Cocaine, olanzapine, alcohol, some bath salts
- Increase in drug concentration
  - Alcohol, potassium, succinylmonocholine
- Trauma Artifacts
  - Rupture of stomach and diaphragm
Postmortem Change

• Summary
  • Antemortem inhomogeneity
  • Diffusion from Stomach, Liver, Lungs
    • Overdoses
    • Other routes of administration, aspiration
  • Release from tissue for high Vd drugs
  • Acute vs Long Term Change
  • Degradation and Contamination
  • Exercise Care in Interpretation
Questions and Discussion
“I’m not sure what’s wrong with you, we’ll have to wait for the autopsy results.”