Interpretation of laboratory drug analyses for forensic and medicolegal purposes

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Scope

• Understand the need to consider analytical data in the context of all other relevant evidence

• Explain reasons for the differences in drug concentrations observed for samples taken in life and after death

• Explain the value of drug-metabolite ratios in estimating the time since exposure

• List advantages and disadvantages in comparison with blood of other available samples including urine, vitreous humour, bile and homogenised tissue
Interpretation of samples

- Role of drugs / toxins in a death or in the behaviour of a suspect or victim
- Evaluation of criminal poisoning or adulteration
- Drug-facilitated sexual assault
- Non-accidental poisoning in children
- Driving under the influence
- Adherence to drug treatment
- Occupational exposure
General principles

• **Consider** analytical results in the context of all other evidence available, e.g. clinical features of the exposed individual.

• Consider validity of the data
  – **chain of custody**
  – **appropriate sample collection and labelling**
  – **use of an appropriate anticoagulant/preservative**
  – **accuracy and limits of detection of analyses.**

• **Sample type** (e.g. blood, plasma) and timing

• **Reporting units** (free acid base or salt?)
Case 1 – Toxicokinetics (back extrapolation)

- An adult male driver leaves the scene after a collision with a lamp post.
- The Police trace and arrest him 4 h later and a blood sample is taken 5 h after the collision.
- The results give a blood ethanol concentration of 48 mg/dL.
- Would the ethanol concentration at the time of the collision be over the legal limit of 80 mg/dL?
Back extrapolation – zero order substance

17 mg/dL/h
(vs 15 and 20 mg/dL/h)
Case 1 – Considerations

- Legal definition of intoxication based on blood or breath concentrations – no need to have other evidence
- Well defined population kinetics, including variability, with legal precedent
- Blood concentrations could be affected by
  - Incomplete or continuing absorption
  - Drinking between the accident and the arrest (the ‘hip flask’ defence)
Case 2 – back extrapolation

• A 22 year old female intravenous drug user attends the Emergency Department following an alleged methadone overdose.

• No features of methadone toxicity are found and she discharged after 8 h observation.

• Readmitted 21 h later with coma and hypotension and subsequently dies.

• A blood sample from the second admission contains methadone 0.45 mg/L.

• Is it possible that she had methadone toxicity at the time of the earlier discharge?
Back extrapolation – first order, long T1/2

- $T_{1/2} = 13 \text{ h}$
- $T_{1/2} = 20 \text{ h}$
- $T_{1/2} = 30 \text{ h}$

Approximate methadone therapeutic range

Time (24 h clock)

discharge from hospital

Blood sample
Case 2 – back extrapolation

• More difficult to draw reliable conclusions as
  – First order drug
  – Variable elimination
  – Less info on kinetics after overdose
  – Less info on concentration-effect
  – Tolerance
  – Further drug use after discharge
• Consider other evidence that might be available, e.g.
  – Recorded features of poisoning
  – QT interval prolongation
• Worth locating blood samples taken in life where possible
Case 3 – back extrapolation

• A 17 year old male is seen in the ED after a paracetamol (acetaminophen) overdose.

• The doctor misunderstands guidance and does not send a blood sample for paracetamol concentration, instead discharging the patient on the basis of the reported dose ingested.

• The patient develops nausea and vomiting and re-attends the following day.

• Paracetamol concentration then is 12 mg/L. There are liver function abnormalities.

• It is alleged that the paracetamol concentration would have warranted treatment if a sample had been taken on the first attendance.

• Is this correct?
Back extrapolation – first order, short T1/2

- T_1/2 = 4 h
- T_1/2 = 3 h
- T_1/2 = 5 h

[Paracetamol] (mg/L) vs Time (h)

Blood sample

Overdose Initial medical assessment
Case 3 – back extrapolation

Unreliability of estimates as

- First order drug
- Variable elimination
- Short half life
- Measured blood concentration close to limit of detection
- Effect of paracetamol poisoning on estimates of half life
Back extrapolation – first order, long T1/2

T 1/2 = 4 h

[Paracetamol] (mg/L)

0 4 8 12 16 20 24
Time (h)

Overdose Initial medical assessment

Blood sample

100 150 200
Case 4 – ? Fatal poisoning

- 25 year old male psychiatric in-patient (Schizophrenia), weight 81 kg
- Regular high dose olanzapine therapy
- Frequent sedation with lorazepam and haloperidol
- Suffers cardiac arrest following use of sedation
- Post mortem – no specific cause of death identified (possibly suffocated by a pillow)
- Post mortem femoral blood concentrations of administered drugs available
- **Did the drugs cause the death?**
Case 4 – ? Fatal poisoning

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Haloperidol</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h dose</td>
<td>30 mg</td>
<td>10 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>(max licensed dose = 20 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM concentration (femoral)</td>
<td>0.5 mg/L</td>
<td>14 mcg/L</td>
<td>16 mcg/L</td>
</tr>
<tr>
<td>Approximate therapeutic concentrations</td>
<td>0.002-0.48 mg/L</td>
<td>5.6-16.9 mcg/L</td>
<td>50-240 mcg/L</td>
</tr>
<tr>
<td>Concentrations associated with toxicity</td>
<td>&gt; 0.080 mg/L</td>
<td>&gt;50 mcg/L</td>
<td>300-600 mcg/L</td>
</tr>
<tr>
<td>Concentrations associated with fatality</td>
<td>1.24 mg/L (1 case)</td>
<td>1900 mcg/L</td>
<td>60 mcg/L (2 cases)</td>
</tr>
</tbody>
</table>
Case 4 – considerations

- Concentration (blood) to effect (brain) relationship
- Inter-individual variability
- Tolerance
- Effects of multiple toxins
- Post mortem effects
Post mortem blood

- Central sites
  - Heart
  - SVC
  - (Subclavian)
- Peripheral sites
  - Femoral
  - Iliac
- Other sites
  - Cavity blood
  - Haematoma blood

Dinis-Oliveira et al, Toxicological Mechanisms and Methods 2010; 20: 363-414
Post mortem blood sampling - considerations

- Time between
  - poisoning and death
  - death and sampling (consider storage conditions and position of body)
- Mode of death (e.g. burning, drowning)
- Haemolysis (e.g. iron, chloroquine)
- Redistibution (q.v.)
- Drug stability (e.g. cocaine, LSD) and volatility (e.g. ethanol, CN, toluene)
- Spontaneous production (e.g. ethanol, GHB)
- Contamination (e.g. lidocaine, lithium)
- Decomposition /putrefaction (e.g. alcohols, acetaldehyde, phenethylamine)
- Embalming (e.g. methanol)
Post mortem redistribution

- Tissue to blood redistribution
  - Liver
  - Heart
- Absorption from
  - GI tract
  - Bladder
  - Respiratory tract
- Lipid soluble, large Vd, basic drugs especially

Figure 1 Median blood clozapine and norclozapine concentrations before (♦) and after (○) death in patients dying from causes other than clozapine self-poisoning (*P < 0.0001, Wilcox ranked pairs test).

Flanagan RJ. ADRB 2008; No 250
Other specimens

Urine

• Simple to obtain

• Reflects substances in blood in the hours prior to death

• High concs, useful for screening

• Concentrations less well correlated with clinical effects

Dinis-Oliveira et al, Toxicological Mechanisms and Methods 2010; 20: 363-414
Other specimens

Stomach contents

• Generally qualitative analysis - useful for directing further studies

• Visual examination may reveal tablets

• Stomach contents are not homogeneous

• Post mortem distribution from blood to stomach

Dinis-Oliveira et al, Toxicological Mechanisms and Methods 2010; 20: 363-414
Other specimens

Bile

• Helpful for drugs concentrated in liver and excreted in bile

Dinis-Oliveira et al, Toxicological Mechanisms and Methods 2010; 20: 363-414
Other specimens

Liver

- Concentrates many drugs/metabolites
- Non uniform distribution
- Right peripheral liver least susceptible to redistribution effects
Other specimens

Hair

- Historical record of drug/chemical exposure
- Plenary lecture
Other specimens

Vitreous humour

- Protected from
  - metabolism (e.g. ethanol)
  - Putrefaction
  - Charring
  - Trauma
  - micro-organisms
- Diabetes/insulin related deaths
- Data available for ethanol but limited for others

Dinis-Oliveira et al, Toxicological Mechanisms and Methods 2010; 20: 363-414
Other specimens

Marrow

- When soft tissue has degenerated
- Concentrations correlate with those in blood
- More research needed to evaluate role

Dinis-Oliveira et al, Toxicological Mechanisms and Methods 2010; 20: 363-414
Case 5 – Acute or chronic poisoning?

• A 67 year old Asian female with chronic severe depression has been treated with amitriptyline for more than 2 years

• She is found dead in her own home. There is no suicide note

• PM does not reveal a macroscopic cause of death

• Toxicology results follow

• Did amitriptyline overdose cause the death?
Case 5 – Acute or chronic poisoning?

Koski, 2005
Case 5 – Acute or chronic poisoning?

<table>
<thead>
<tr>
<th>Femoral blood</th>
<th>Amitriptyline</th>
<th>Nortryptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h dose</td>
<td>150 mg</td>
<td>-</td>
</tr>
<tr>
<td>PM concentration (femoral)</td>
<td>3.8 mg/L</td>
<td>0.02 mcg/L</td>
</tr>
<tr>
<td>Approximate therapeutic</td>
<td>0.05-0.1 mg/L</td>
<td>0.05-0.1 mg/L</td>
</tr>
<tr>
<td>concentrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentrations associated with</td>
<td>&gt; 0.3 mg/L</td>
<td>-</td>
</tr>
<tr>
<td>toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentrations associated with</td>
<td>0.55 – 16.1 mg/L</td>
<td>0.29 – 6.5 mg/L</td>
</tr>
<tr>
<td>fatality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case 5 – Acute or chronic poisoning?

• Low concentration of nortriptyline implies acute recent exposure…

• …unless CYP2C19 slow metaboliser
  – 3-5% Caucasians
  – 15-20% Asians
Final thoughts

• Stay independent
• Stick to what you know (don’t be drawn to comment outside your expertise)
• Don’t have words put in your mouth. Beware the ‘just answer yes or no’ question).
• Don’t overstate what can be concluded from the evidence available
• Don’t expect your fee to be paid as quickly as your report was demanded