Can Post-Mortem THC levels be Used to Estimate Ante-Mortem Impairment?

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Marijuana and Impairment

- Cannabis is the most abused drug, after alcohol
- Cannabis use causes impairment of tasks necessary for safe driving
- At least 5% of total driver fatalities now due to THC alone
- Even higher percentage in under 40 yo drivers
- Especially when combined with alcohol
Marijuana and Impairment

- Psychomotor tests are surrogate measures of:
  - Attentiveness
  - Vigilance
  - Perception of time and speed
  - Use of acquired knowledge

- Adverse effects seen with acute THC intoxication:
  - Complex tasks requiring divided attention
  - Tracking
  - Motor coordination
  - Reaction time
  - Visual functions

- Numerous studies document multiplicative effects when combined with alcohol
Marijuana and Impairment

- Driver simulators & on road tests more accurately simulate real driving abilities
- More complex, real-life than psychomotor testing
- Deficits caused by low levels of THC may not be readily apparent in driving tests - test subjects drive slower than normal
- Deficits most pronounced in situations needing urgent evasive action
Metabolism

THC → 11-OH-THC → THC-COOH → Glucuronide
Marijuana and Impairment

- Psycho-active component is $\Delta-9$-THC
  - Active metabolite 11-hydroxy-$\Delta-9$-THC (THC-OH)
  - Inactive metabolite 11-nor- $\Delta-9$-THC-COOH (THC-COOH)

- Levels of THC-COOH only indicate use
  - No impairment from THCCOOH
  - Past studies of total cannabinoids uninterpretable
Marijuana and Impairment

- Measuring THC must be done carefully
- Older studies of culpable drivers had storage issues; often only THC-COOH found
- Blood storage issues
  - Loss of 50% at 8 wks storage if not deep freeze at -60°C
  - THC binds to plastic vials - must be stored in glass tubes
Cannabis Use, THC Plasma Levels, and Impairment

- Plasma levels rise rapidly after smoking
  - Peak in 5-8 min after smoking
  - Can be >100ng/mL at peak
  - Fall to <20ng/mL at 1 hour
  - Fall to <10ng/mL at 4 hours
Cannabis Use, THC Plasma Levels, and Impairment

- Clinical effects begin within minutes of peak blood levels
- Impairment may not be evident until 20 min. after peak
- Therefore, declining THC blood levels are associated with increasing drug effect
  - CNS levels increasing
- Impairment lasts at least 3-5 hrs
- But perceived “high” by users is substantially shorter
- Some evidence of “hangover effect” for 24hrs in impairment of necessary driving skills\(^1,2,3\)
- Residual neuropsychologic effects seen for 12-24 hrs\(^4\)

1. Leirer VO, Aviat. Space Environ 1991
3. Couper F, Drugs and human performance fact sheets 2004:1-100 NHTSA
4. Pope HG et al. /Drug and Alcohol Dependence 1995
Figure 1. Time course of active THC (9-delta-tetrahydrocannabinol) and THC acid (THC-COOH) concentrations in plasma after smoking marijuana with 15 mg in a 70 kg person. A, absorption; D, distribution; E, elimination; □, maximum; ♦, minimum; △, average; --×--, THC-COOH. (Reprinted with permission, Ward and Dye).
THC blood levels, impairment and time after smoking Cannabis

30’, ± impair.

Fig. 1. The level of THC in blood and performance on the SFSTs and the driving task.

Papafotiou K; FSI 2005
Heustis, et al 1992: equations for estimating time since last Cannabis use

Model I: \( \log t = -0.698 \log [\text{THC}] + 0.687 \)

\[
CI = \log t \pm \left( 0.030 \left( 1.006 + \frac{(\log[\text{THC}] - 0.996)^2}{89.937} \right) \right)^{0.5}
\]

Model II: \( \log t = (0.576 \log \frac{[\text{THCCOOH}]}{[\text{THC}]) - 0.176} \)

\( \log CI_2 = \log t \pm 1.975 \times \)

\[
\sqrt{0.045 \left( 1.006 + \frac{(\log[\text{THCCOOH}]/[\text{THC}] - 0.283)^2}{123.420} \right)}
\]
Experimental Tests and Plasma THC levels

- Visual tracking is impaired when THC > 6 ng/mL
- Attention impaired > 9 ng/mL,
- Visual functioning impaired > 12 ng/mL.

Experimental Tests and Plasma THC levels

- Impaired critical tracking task when THC > 2 ng/mL (staying in the lane of traffic)
- Stop signal task impaired > 5 ng/mL (measure of inhibitory control)
- Tower of London task impaired > 5 ng/mL (measure of problem solving ability)
- All subjects impaired in all tasks > 30 ng/mL

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>THC impairment level</th>
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<tr>
<td>Bramness 2010</td>
<td>DUID drivers</td>
<td>&gt;1.6ng/mL: incr. risk of being judged impaired-CTI</td>
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<tr>
<td>Jones 2007</td>
<td>DUID drivers</td>
<td>1.0ng/mL - Median THC level</td>
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<tr>
<td>Grotenhermen 2007</td>
<td>Meta-analysis</td>
<td>7-10ng/mL equivalent to BAC of 0.05g%</td>
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<td>Khiabani 2006</td>
<td>DUID Drivers</td>
<td>&gt;3ng/mL : drivers more likely impaired</td>
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<tr>
<td>Ramaekers 2006</td>
<td>Lab skills testing after smoking</td>
<td>2-5ng/mL upper and lower limits of impairment</td>
</tr>
<tr>
<td>Menetrey 2005</td>
<td>Oral dronabinol lab study</td>
<td>THC lower levels than smoking</td>
</tr>
<tr>
<td>Papafotiou K 2005</td>
<td>Lab skills study p smoking</td>
<td>&gt;3.18ng/mL (whole blood)</td>
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<tr>
<td>Laumon BMJ 2005</td>
<td>Culpable drivers</td>
<td>&gt;1ng/mL: OR 2.87, with D-R; &gt;5ng/mL= OR 4.87</td>
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<tr>
<td>Drummer 2004</td>
<td>DUID Drivers</td>
<td>&gt;5ng/mL: 6.6X the risk, equivalent to BAC &gt;0.10g%</td>
</tr>
<tr>
<td>Mura 2003</td>
<td>Injured drivers</td>
<td>&gt;1ng/mL: OR 2.5, no D-R; OR 4.6 with EtOH</td>
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<tr>
<td>Swan 2000</td>
<td>15th Drug &amp; Traffic Safety Conf</td>
<td>+THC 6.4 times more likely fatal crash risk</td>
</tr>
<tr>
<td>Crouch 1993</td>
<td>Truck driver fatalities</td>
<td>&gt;1ng/mL</td>
</tr>
<tr>
<td>Terhune 1992</td>
<td>Driver fatalities</td>
<td>11-fold risk if any THC plus alcohol</td>
</tr>
<tr>
<td>Reeve 1983</td>
<td>Test subjects &amp; RST</td>
<td>&gt;3ng/mL-80% impaired, only 38% felt impaired</td>
</tr>
</tbody>
</table>
Countries with per se Limits on DUID and THC in blood/serum

- **Sweden**: 0.3 ng/ml level (serum) for prosecution- “zero tolerance” (LOQ)
- **France, Finland and Poland**: lab LOQ
- **Germany**: 1.0 ng/ml serum, 0.5 ng/ml WB
- **Belgium**: 2.0 ng/ml in plasma (1.0 ng/ml in whole blood)
- **Switzerland**: 1.5 ng/ml in blood
States in the USA with per se Limits on DUID and Marijuana

- Arizona, Delaware, Georgia, Indiana, Illinois, Iowa, Michigan, Minnesota, Nevada, North Carolina, Ohio, Pennsylvania, Rhode Island, South Dakota, Utah, Virginia, and Wisconsin

- Any amount of prohibited drug found in the blood or urine of drivers while operating a motor vehicle is a per se violation of those states’ DUI statutes
Postmortem redistribution of $\Delta^9$-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH)

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- Prior to our 2011 publication, no data was available regarding PMR for THC
- Reasons are multi-factorial
  - ME’s offices have limited funds
  - Drugs studied and quantified when they may be a cause of death or overdose that contributes to death
  - THC not studied due to it is not a cause of death
  - Increasingly noted to be a significant cause of DUID
  - Impaired driving now being increasingly studied
- No prior information whether PM THC levels can be used for assigning impairment
Methods

- 19 consecutive adult autopsy cases from the OCMEO (Syracuse, NY) with + urine THCCOOH
- Matched heart and femoral postmortem bloods
- Free THC, THC-OH and THCA were analyzed by 2D GCMS
- 10 matched heart and femoral postmortem whole blood specimens from non-THCCOOH cases served as controls and to calibrate equipment
- In addition, antemortem specimens were available for testing in three cases.
Results

- THCCOOH was present in all 19 cases.
- 10 cases had quantifiable THC and 11-OH-THC.
- Mean ± SD heart : femoral blood ratios were:
  - 1.54 for THC (range: 0.3-3.1);
  - 1.63 for 11-OH-THC (range: 0.3-2.7);
  - 1.78 for THCCOOH (range: 0.5-3.0).
Results

- Median heart: femoral blood ratios
  - 1.52 for THC
  - 1.73 for 11-OH-THC
  - 1.79 for THCCOOH

- In three cases with antemortem blood also available, PM levels were lower than AM levels in all cases.
Conclusion: THC Exhibits Modest PMR

- First human study to demonstrate THC exhibits modest degree of PMR
- Much less PMR detected than that expected by Vd, lipid solubility, etc; consistent with degree of protein binding
- The antemortem data, if reproducible, indicate that postmortem blood might underestimate antemortem levels
Post-mortem blood tests for impairment

- Used routinely (with proper collection considerations) with many drugs:
  - Alcohol
  - Opioids
  - Cocaine
  - Amphetamines
  - Many others

- Must consider: site of sample, matrix, time, method; storage, tube type; method of death; state of decomposition; Drug characteristics (Vd, pKa, lipid solubility, protein binding, etc)

Conclusions

- Heustis model using THC and THC/THCCOOH ratios not validated for use with post-mortem specimens
- Antemortem serum levels >2-5ng/mL seem to establish impairment
- THC behaves much like other drugs in terms of PMR
- PM WB heart blood specimens average only 1.5X femoral levels
- WB: Plasma ratio is 0.5
- Therefore “built in safety factor” even if using postmortem blood