Drug Metabolites and Hair Testing

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Urine Drug/Drug Metabolite Testing

- Current urine drug testing under the DHHS Mandatory Guidelines allows testing for Cannabinoids, Cocaine Metabolite, Amphetamines, Opiates, and PCP and Specimen Validity Testing or SVT.
- Numerous other drugs and drug metabolites.
- Whether a parent drug and/or a metabolite is present, a urine positive shows use.
Urine Specimen - Filtered Blood

By Madhero88 - Own work[References here], CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=9665603

Excretion = Filtration – Reabsorption + Secretion
Hair Drug Testing

• Hair, as harvested for testing, was removed from completely outside the body.

• Currently, most testing for drugs of abuse in hair is performed by targeting parent drugs except for the major metabolite of $\Delta^9$-tetrahydrocannabinol ("THC"), 11-nor-$\Delta^9$-tetrahydrocannabinol-9-carboxylic acid or THCA (Carboxy-THC, THCCOOH).

• Major Issue: External contamination by drugs.
Hair Drug Testing (continued)

• Potential remedy to show actual use as opposed to simple exposure:
  – A common metabolite that is **NOT** 1) a separately marketed drug or 2) a manufacturing impurity or 3) a chemical decomposition product or 4) the product of an *in vitro* chemical reaction on the hair.

• Unacceptable candidate marker to show cocaine use:
  – Benzoylecgonine.

• Potentially good candidate marker for codeine:
  – Norcodeine to indicate the use of codeine.
Metabolites in Hair

• By incorporation of the formed metabolite into hair.
  – Lipophilicity or lipid solubility (melanin affinity).
  – Basicity.

• By parent drug metabolism in the hair.
  – Convert the parent drug to the desired metabolite by enzymes in the papilla or hair shaft.
• Commonly, THCA in hair is tested to show use of parent THC.
• Glucuronide: Pichini et al., FSI, 2015.
Cocaine

- Numerous impurities in illicit and pharmaceutical cocaine.
- Multiple metabolites of cocaine have been identified.
- Possible metabolite set to demonstrate use of parent cocaine:

\[
\text{ortho, meta \& para-Hydroxycocaines}
\]
Amphetamines

• Possible metabolite set to demonstrate use of methamphetamine/amphetamine would be the hydroxyamphetamines.

\[
\text{Methamphetamine} \xrightarrow{\text{CYP2D6}} \text{4-Hydroxy- or para-Hydroxymethamphetamine}
\]
Amphetamines (continued)

- *ortho-, meta- and para-* (or 2-, 3-, and 4-)
  Hydroxymethamphetamine themselves may be produced by the action of oxidizing agents on methamphetamine deposited on hair.

- Glucuronide or sulfate conjugates of the hydroxy amphetamines to show use of the parent drugs.
Amphetamines (continued)

- Possible metabolite set to demonstrate use of MDMA/MDA:

\[
\begin{align*}
\text{MDMA} & \xrightarrow{\text{CYP2D6}} \text{3,4-Dihydroxymethamphetamine} \\
\text{MDA} & \xrightarrow{\text{COMT}} \text{4-Hydroxy-3-methoxymethamphetamine}
\end{align*}
\]
Phencyclidine (PCP)

- Possible metabolite to demonstrate use of parent drug:
  - *trans*-PCPdiol (Nakahara *et al.*, JAT, 1997).

- Hydroxyphencyclidines may be produced by the action of oxidizing agents on PCP deposited on hair.
Codeine & Morphine

• Possible metabolites to demonstrate use of either parent drug:
  – Norcodeine (Codeine; CYP3A4).
  – Normorphine (Morphine; CYP3A4).
  – Glucuronide conjugates of either drug (UGT).
Hydrocodone & Hydromorphone

• Possible metabolites to demonstrate use of either parent drug:
  – Glucuronide conjugates (UGT).
  – nor Metabolites (CYP3A4).
Oxycodone & Oxymorphine

• Possible metabolites to demonstrate use of either parent drug:
  – nor Metabolites (CYP3A4).
  – Glucuronide conjugates (UGT).
Metabolites in Hair to Show Use of a Parent Drug

• Choices for metabolites to demonstrate that a drug or drug class was used by a donor currently exist.
• Drug metabolites exist in hair as the result of complex processes that probably include a combination of incorporation and metabolism in hair/hair bulb.
• Drug metabolism may be limited in a small number of cases due to polymorphism and other enzyme inactivation.
Potential Studies

• Incidence of enzymatic oxidation failures.
  – *e.g.* Demethylation of opioids or hydroxylation of amphetamines.

• Incidence of demethylenation (MDMA & MDA).

• Oxidation of surface drug contamination using a broader range of potential hair products.

• White, FSR, 2017.
A **lot** remains to be accomplished.