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Postmortem toxicology of drugs of abuse

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Abstract

Conducting toxicology on post-mortem specimens provides a number of very significant challenges to the scientist. The range of additional specimens include tissues such as decomposing blood and other tissues, hair, muscle, fat, lung, and even larvae feeding on the host require special techniques to isolate a foreign substance and allow detection without interference from the matrix. A number of drugs of abuse are unstable in the post-mortem environment that requires careful consideration when trying to interpret their significance. Heroin, morphine glucuronides, cocaine and the benzodiazepines are particularly prone to degradation. Moreover, redistributive process can significantly alter the concentration of drugs, particularly those with a higher tissue concentration than the surrounding blood. The designer amphetamines, methadone and other potent opioids will increase their concentration in blood post-mortem. These processes together with the development of tolerance means that no concentration of a drug of abuse can be interpreted in isolation without a thorough examination of the relevant circumstances and after the conduct of a post-mortem to eliminate or corroborate relevant factors that could impact on the drug concentration and the possible effect of a substance on the body. This article reviews particular toxicological issues associated with the more common drugs of abuse such as the amphetamines, cannabinoids, cocaine, opioids and the benzodiazepines.

Keywords: Postmortem; Toxicology; Drugs of abuse; Specimens; Concentrations

1. Introduction

The detection of drugs of abuse in postmortem cases can provide some special difficulty compared with clinically derived specimens. When determining the concentration of drug in biological matrices it is important to know the stability of the substance in such tissues. This situation is relevant no more so than in forensic toxicology where tissues are likely to be exposed to the elements for prolonged periods. The extent of chemical change in the postmortem interval, or even metabolism postmortem, may affect the interpretation of results. Some drugs are known for their unstable nature [1,2].

One advantage over clinical situations is that many more alternative specimens can be collected in a postmortem setting. These may include hair, muscle, fat, lung, brain, bone, and even larvae of insects feeding on the host.

This work focuses on toxicological issues associated with the analyses of postmortem specimens that are traditionally used and those not so commonly used; details analytical features and artifacts associated with the analysis of post-mortem specimens and finally provides monographs on the five main drug abuse classes. These monographs provide more toxicological details relevant in a postmortem setting.

2. Scope

This paper reviews the current knowledge of the post-mortem toxicology of drugs of abuse and particularly focuses on the relative advantages of specimens that can be collected and the factors that affect drug concentration including artifacts. The review focuses on the current state of knowledge and includes published works referenced in MedLine over the last 10 years.

The drugs of abuse covered in this paper include amphetamines particularly amphetamine, methamphetamine (MA), methylenedioxy-methamphetamine (MDMA, ecstasy), *para*-methoxy amphetamine (PMA), cocaine, cannabinoids,

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opioids particularly morphine, methadone and heroin, benzodiazepines and related drugs such as zolpidem.

3. Types of specimens

The choice of specimen is often dictated by the case being investigated, however the most common specimens used for the analysis of drugs of abuse in postmortem cases are blood, liver and urine. However, specimens such as vitreous humor and hair have important uses in routine cases, whilst brain, muscle, fat, bone and pleural effusions and have more specialist applications.

In cases of extreme putrefaction, muscular tissue, hair and bone can be useful specimens, although the physical state of the body will determine what specimens are available for collection. Body fluids in putrefied bodies is rather liquefied tissues and while useful to screen for the presence of drugs quantitative results are of little use. In some cases analyses of drugs in fly larvae in decomposing cases provides an insight as to the presence of drugs in the corpse.

Liver has been a stock solid tissue for use in postmortem toxicology and often the results in this tissue supplement any blood toxicology data. Since some drug diffusion is possible from the small bowel the use of tissue from deep within the right lobe is preferred [3].

Essentially, all drugs of abuse are detectable in bile, although buprenorphine, tramadol, other opioids, and benzodiazepines and colchicine appear to be present in higher concentrations than blood [4–13]. The relative concentration to blood increases with rising molecular weight; however liver perfusion and biliary secretion will play a major determinant on the bile concentration. The interpretative value is limited although bile results have been used to differentiate from acute and chronic use of heroin [14]. However, high biliary concentrations of morphine are seen in acute use when high doses are used, i.e. in hot shots.

Muscle [15–21] has been used by toxicologists in special types of analyses. Muscle will often represent the greatest single mass of drug in a body and will therefore represent a greater body burden of drug than any other tissue mass. This applies particularly to drugs of abuse with high volumes of distribution ($V_D > 2$ l/kg). However, muscle is a difficult tissue to work with and care is required to ensure complete drug extraction [16,19]. Variability in the concentration of drugs has been found in muscle tissue [15,16]. Unequal perfusion of tissue and other postmortem artifacts results in 20-fold variations in concentration, hence it is not recommended to use this tissue alone for any quantitative purposes, unless of course there is no alternative. Similar considerations apply to fat [5,19].

Bone [19,22–24] has also been used by toxicologists in special types of analyses. MA, morphine and benzodiazepines have been detected in bone and bone marrow in human remains [19,25–28] and MA in experimental rabbits [29]. This specimen may therefore be useful to determine past exposure, although it is unlikely that bone or bone marrow will be able to provide information on the extent of drug exposure.

Vitreous humor has had wide application in toxicology for many years to determine alcohol (ethanol) particularly when putrefactive formation is suspected. Drugs of abuse have been detected in this fluid [13,30–32]. Vitreous is also used to determine glucose, urea and creatinine and certain other electrolytes [33–39].

Brain has been used for many years by toxicologists as a means to determine the concentration in a tissue where many toxic substances exert their effects. However, given the uneven distribution of drugs in this tissue and importantly the often highly localized sites of action of drugs of abuse in this organ results have also been difficult to interpret with any more certainty than peripheral tissues. Some recent papers examining drugs of abuse in brain are listed [5,9,40–42].

In addition, pleural effusions can also provide evidence of drug exposure when no blood specimen is available [43].

Hair analysis has been used extensively for the analysis of drugs of abuse to provide evidence of longer term exposure (or abstinence) of drugs and can provide important information as to the time course of drug use. Selected articles are only cited [44–50]. Recent studies have used segmental analyses to determine degree of exposure to heroin and assess the risk of heroin use [51]. Segmental analyses have been used extensively to establish a history of drug exposure [52–55]. Drug incorporation into hair is a complex phenomenon and a number of factors affect retention, hence care should be exercised in the interpretation of hair results [56].

Finger and toe nails are another form of the keratin found in hair. Drugs are deposited in nails, albeit at a much slower rate proportional to the growth rate of the nail [57–60]. In common with hair, care needs to be exercised to ensure external contamination is avoided or at least considered in any interpretation of results in these "external" specimens.

Larvae (maggots) found in putrefying bodies can be used to obtain evidence of the presence of drug in the body [30,31,61–70].

Gastric contents are useful to determine a possible time of drug administration and to distinguish oral from other routes of administration. However, the absence of drug does not preclude earlier oral ingestion and small quantities of drug can derive from bile, especially during agonal processes when vomiting of bile can occur. For example, biliary concentrations of morphine are very high leading to submilligram amounts of morphine in gastric contents.

A summary of postmortem specimens used and their relative merits for the analysis of drugs of abuse is shown in Table 1.

4. Postmortem stability

Postmortem changes will occur for all of the drugs of abuse. The extent of these changes varies significantly between drugs. Heroin and cocaine are not only rapidly

Table 1
Relative merits of postmortem specimens for drugs of abuse

Specimen	Particular advantages
Blood/plasma/serum	Preferred specimen for most substances
Bile	Morphine, buprenorphine, tramadol, benzodiazepines, MDMA
Bone	Qualitative analysis of morphine, benzodiazepines, amphetamines
Brain	Centrally acting drugs, e.g. morphine, cocaine, limited literature data
Fat	THC, and other drugs, but little literature to interpret results
Gastric contents	Orally administered drugs/poisons
Hair	All substances, particularly basic substances, and most metals
Muscle	Most drugs, however literature contains little data to interpret concentrations
Pleural effusion	Most drugs, but drugs subject to concentration changes, hence difficult to interpret
Vitreous humour	Ethanol, some biochemistries, e.g. glucose, urea, creatinine

converted into their respective hydrolytic products during life, they undergo rapid bioconversion in situ after death. Moreover, unless special precautions are undertaken, hydrolysis may even occur in the collection vessel.

Specimens are rarely ideal in postmortem cases and without specialist knowledge any results should be considered with caution when attempting to interpret their significance. Key factors include the state and quality of the specimen, stability of drug in the case generally and in the specimen particularly, and the effects of any drug diffusion away from or to other tissues.

Decomposition and eventual liquefaction of tissues occurs during postmortem periods that is very much dependent on the time to discovery of the body, the ambient temperature and other environmental factors. One day in a tropical or very hot environment can show significant putrefaction while weeks at freezing temperatures often show little observable changes.

The nitrobenzodiazepines (nitrazepam, nimetazepam, flunitrazepam and clonazepam) are converted to their respective 7-amino-metabolites as a result of anaerobic bacterial action [1,9]. Depending on the condition of the blood and the benzodiazepine little if any parent drug is present after death, even after overdoses. The actions of anaerobic bacteria on other drugs have not been studied in depth, although other drugs may be affected [71]. Data also suggests that many other benzodiazepines such as diazepam and temazepam are labile and are degraded under putrefying conditions [72,73]. This means that these drugs may not be detected at all in decomposed cases. When extensive putrefaction has occurred and exposure to benzodiazepines may have occurred it is recommended to use other tissues where retention is more likely, such as hair.

Other benzodiazepines are also subject to postmortem change however these changes can be minimized if specimens are stored at −20 °C or lower and specimens analyzed promptly [74]. Curiously, the 7-amino-benzodiazepines are less table than the parent drugs at −20 °C and require −60 °C for reasonable stability [75].

The stability of other drugs of abuse have been investigated [42,76–83]. Blood specimens containing cocaine and benzoylecgonine (BE) degrade over time when stored at ambient temperature and even when stored in fluoride/oxalate tubes [81]. Cocaine in urine stored at −20 °C can change by as much as −37% over a 12-month time period, although other drugs of abuse are reasonably stable [84]. Moderate losses for BE and 11-nor-9-carboxy Δ^9-tetrahydrocannabinol (THC) have also been reported in urine stored frozen [79]. While some loss of cocaine occurs in frozen specimens this is not associated with formation of ecgonine methyl ester (EME) [77].

The acid metabolite of THC, 11-nor-9-carboxy Δ^9-tetrahydrocannabinol (cTHC) shows significant losses in concentration not only when urine is stored at room temperature for several days but also after long-term frozen storage [82,83]. THC concentrations in blood has also been shown to decrease with time, particularly when stored at −20 °C [85].

6-Acetyl morphine (6-AM) undergoes deacetylation to morphine at room temperature and according to the pH of the specimen [86]. However, 6-AM is stable in frozen urine (−20 °C) for at least 12 months [87].

Of particular interest is the instability of morphine glucuronide conjugates. De-conjugation of morphine metabolites to morphine has been observed in liver [88]. Morphine is relatively stable in specimens when stored frozen, but shows significant losses when stored at 4 °C or higher for more than a few days, or in postmortem specimens [89,90]. This issue has been more recently discussed in the Shipman murders [18]. Of further interest is the variability in morphine and morphine glucuronide ratios from different blood collection sites [91]. These data suggests that morphine and glucuronide concentrations from cases in the early stages of putrefaction or when prolonged storage has occurred may have substantially changed from the time of death.

5. Postmortem redistribution

Redistributive processes potentially affect the concentration of all drugs of abuse in postmortem cases as a result of diffusion of drug from higher concentration to a lower