



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.

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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 sub-milligram 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 stable 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

Table 2

Pharmacokinetic properties and likely extent of postmortem redistribution for selected drugs of abuse

Drug/drug class	Common dose (mg)	Usual blood levels (mg/l) ^a	Main active metabolite or bio-marker ^b	V _D (l/kg)	T _{1/2} (h)	Extent of redistribution ^c	Selected references
Amphetamine	10–100	0.2	None	3–5	4–30	Low	[107]
Methamphetamine	50–2000	0.2	Amphetamine (~10%)	3–4	10–30	Low	[168,169]
MDMA	50–250	0.3	MDA	Moderate	~8	Moderate	[170,171]
MDA	50–250	0.4	None	Unknown	–	Moderate	[170]
MDEA	50–200	0.5		Unknown	–	Moderate	[110,114]
MBDB	50–200	0.5		Unknown	–	Moderate	[118,170]
PMA	50–100	0.2	None	Unknown		Moderate	[119–121]
Heroin	10–100	–	Morphine, 6-AM	See morphine	<0.1	Low to moderate	[161,172,173]
Morphine	10–100	0.5	None, but bio-conversion from glucuronides	2–4	2–4	Low to moderate	[18,51,99,174]
Methadone	10–120	1.0	EDDP is often measured in urine	3–5	15–72	Moderate	[97,164,175,176]
Codeine	8–60	0.2	Morphine (10%)	4	2–4	Low to moderate	[177]
Buprenorphine	<1–24	0.05	Norbuprenorphine	3–7	2–9	Low to moderate	[178,179]
Meperidine	50–200	1.0					[180]
Oxycodone	5–30	0.2					[181,182]
Tramadol	50–400	1.0	Hydroxy-metabolite (M1)	2–3	5–7	Low to moderate	[183–185]
Alprazolam	0.5–4	0.5	α-Hydroxy-alprazolam	1	6–22	Low	[186]
Diazepam	5–40	1.0	Nordazepam	0.5–2.6	20–50	Low	[187]
Flunitrazepam	1–2	0.05	7-Amino-flunitrazepam	3–6	11–25	Low	[188–190]
Oxazepam	15–60	1.0		0.5–2	4–15	Low	[191,192]
Temazepam	10–20	1.0	Oxazepam	1	5–15	Low	[193]
Zolpidem	10–20	0.5		0.6	2–4	Low	[4,194]
Cocaine	10–100	0.5	Benzoylcegonine, EME*	1–3	0.6	Low	[127,195,196]
THC	5–25	50	11-Carboxy-THC*	9–11	19–96	Low to moderate	[160,197,198]

^a Maximum postmortem blood concentrations following usual doses, although higher concentrations can be achieved in particular situations.

^b Bio-marker of parent drug.

^c Refers to best estimate of author. 6-AM: 6-acetyl morphine, EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, EME: ecgonine methyl ester, MDMA: methylenedioxy-methamphetamine, MDA: methylenedioxy-amphetamine, PMA: *para*-methoxy amphetamine, THC: Δ⁹-tetrahydrocannabinol.

concentration following disruption of cellular membranes. This process is particularly significant for drugs with high lipid solubility or high tissue concentrations relative to blood taken from the heart. Table 2 provides a summary of the volume of distribution and extent of redistribution for selected drugs of abuse.

The drug with the highest lipid solubility and volume of distribution of the substances shown in Table 2, tetrahydrocannabinol (THC) has surprisingly not showed consistent increases in blood concentration after death [92,93]. This has been more recently confirmed [85], despite data that shows reversible uptake into muscle and fat in humans [94]. If this is confirmed with further studies it is likely that redistribution is not simply due to drug gradients between tissues.

The drug with the next highest volume of distribution, methadone, does exhibit moderate increases in blood concentration after death ranging up to four-fold, although there is significant site to site variability [95,96]. Regression

analysis on 31 subjects show a two-fold increase for males and a three-fold increase for females [97].

The more water-soluble morphine shows little change in blood concentration after death in humans [98,99], although increases have been demonstrated in rats [100]. Production of morphine from hydrolysis of glucuronides is likely to be a more significant factor potentially elevating morphine concentrations postmortem (see earlier).

Two-fold increases have been demonstrated for MA when femoral and heart blood specimens were compared [101–104]. This appears to be due to diffusion of drug from the pulmonary circulation into the left cardiac chambers [105]. MDMA and PMA have also been shown to undergo increases in blood concentration after death [5,106].

Benzodiazepines show variable changes in the immediate postmortem period, although the reported magnitude of any changes are generally low due to their relatively low volumes of distribution [9,13].

It is worth noting that while femoral blood and perhaps other peripheral bloods show fewer changes than blood taken from the thoracic and abdominal areas, it too will show higher concentrations of drugs following a postmortem period. These processes are not limited to blood. Liver and lung tissue show differences in the concentration of drugs depending on the nature of the drug and whether diffusion of drug has occurred from neighboring tissues or the blood supply. For example, the left lobe of the liver is more likely to exhibit elevated drug concentrations than the right lobe [3].

As with all drugs substantial site to site variability can occur. This is due to not only redistributive processes, but also due to differences in hematocrit, influences of other fluids and other factors affecting the quality of blood even in situations where significant putrefaction has not seemingly occurred [3,9,85,94].

6. Drug monographs

6.1. Amphetamines

This group of strong stimulants are based on the dextroamphetamine nucleus, and include MA, MDMA (ecstasy), methylenedioxy-amphetamine (MDA), methylenedioxy-ethylamphetamine (MDEA), and other designer forms such as PMA, and *N*-methyl-benzodioxazolbutanamine (MBDB) [107]. Their pharmacokinetics and metabolism are diverse as suggested from their chemical names. Their common doses, any active metabolite, half-lives and usual blood concentrations are shown in Table 2.

Oral use of MA typically produces postmortem blood concentrations of up to about 0.2 mg/l. Corresponding blood concentrations of amphetamine is similar or slightly higher than MA.

Neither MA or AM seem to be associated with many deaths. When this does occur it is more likely that the heart has been weakened in some way, e.g. hypertrophy, contraction bands, or a predisposition to arrhythmias with prolonged QT-syndrome [108–110].

MDMA produces peak levels of 0.4 mg/l at 2 h following an approx. 100 mg dose. Under conditions of a single oral dose of MDMA little MDA is detectable in blood [111]. Disproportionate rises in blood concentrations occur with increasing doses of Ecstasy. This may be a cause of toxicity in susceptible persons [112].

Single doses of 75 or 125 mg MDMA significantly increase blood pressure (up to 40 mmHg systolic blood pressure), heart rate (~30 beats/min), and pupillary diameter (mydriasis), but not body temperature. Maximum plasma concentrations of 75 and 125 mg MDMA doses were about 0.13 and 0.24 mg/l at 2.4 and 1.8 h, respectively. The terminal elimination half-lives were about 8 h for both high and low MDMA doses [113].

MDMA and indeed other amphetamines cause significant rises in systolic blood pressure (~40 mmHg) and heart rate

(~30 beats/min). This may be dangerous in persons with compromised cardiovascular function or impaired cerebral blood flows. Significantly, under heat stress MDMA may cause precipitous rises in core body temperature leading to rhabdomyolysis, coagulopathies and kidney failure. Liver damage has also been seen with MDMA [114].

Deaths have been reported with other designer amphetamines including MDEA [110,114–117], MBDB [118]. Deaths reported from PMA seem to outweigh this designer amphetamine's street availability suggesting PMA may be more toxic again on the brain [106,119–126].

6.2. Cocaine

Cocaine shares many of the toxicological features of the amphetamines in that it is a potent stimulant of nerve function. It is an inhibitor of reuptake in dopamine and norepinephrine nerve terminals in the CNS as well as serotonin. Cocaine also acts as a local anesthetic and is still used medically in otolaryngological procedures.

Cocaine as the free base is insufflated ("snorted") or inhaled as a vapor (smoked), or injected intravenously (usually as the hydrochloride salt). In the USA and Europe, cocaine is one of more prevalent illicit drugs.

The pharmacokinetics of this drug has been studied in humans in controlled settings. The terminal elimination half life of cocaine ranges from about 40 min to 4 h, depending on dose [127]. Cocaine is rapidly metabolized to a range of hydrolytic substances of which BE and EME are most significant. The biologically active ethyl *trans*-esterification analog cocaethylene (CE) is found in significant amounts in tissues of persons co-consuming ethanol. The formation of cocaethylene is route dependent but does not occur post-mortem suggesting the active involvement of enzymes to facilitate bio-transformation [128,129]. Anhydroecgonine methyl ester (methylecgonidine) is only formed during smoking of cocaine as a result of pyrolysis [127,130]. It has a different profile of activity to cocaine acting as a muscarinic agonist to lower blood pressure [131].

BE and EME are commonly used to identify past use of cocaine when the parent drug is no longer present in blood. The predominate species in urine is BE and EME, although about 1–9% is cocaine [132]. Detection times using a 300 ng/ml cut-off is about 1–4 days [133], although this can be about a week in long term users [134]. Oral use leads to greater amounts of EME and CE due to first-pass metabolism. In contrast to urine the predominant species in hair, sweat and oral fluid is the parent drug itself [47,54,135]. Depots of cocaine in tissue can result in detectability in oral fluid well beyond that expected based on its blood pharmacokinetic profile [133]. The pharmacokinetics of cocaine in these alternative specimens requires more evaluation before their use can be optimized.

Cocaine is a potent stimulant with commonly used doses ranging from about 10 to 100 mg. Tolerance can set in quickly leading to a rapid escalation of doses up to over

1 g daily. As with other illicit drugs covered here there is no defined “safe” or “therapeutic” blood concentration. Since postmortem hydrolysis continues to occur after death, measurement of cocaine concentrations is unlikely to yield useful interpretive information [136]. It appears the brain cocaine is more stable to hydrolysis than other tissues [2].

Excessive use of cocaine can lead to a number of life threatening conditions. Ischemic heart disease is typified by contraction bands and sudden arrhythmic death. Pathological core temperatures leading to rhabdomyolysis, intravascular coagulation, renal failure and convulsions can also occur [137–140]. Its use with alcohol and with heroin and other narcotics increases its toxicity significantly.

6.3. Benzodiazepines

The benzodiazepines are a large group of substances typified by diazepam and alprazolam, but with a significant difference in potency and physicochemical properties. Non-benzodiazepines acting on a similar receptor system include zolpidem, zopiclone and zaleplon. These latter drugs are becoming increasingly used due to their lower profile of side-effects. Benzodiazepines and their close relatives bind to the gamma-aminobutyric acid (GABA) receptor affecting chloride movement through ion channels. This results in a reduction in activity in a number of key areas in the CNS involved in arousal and emotions.

While these drugs have a large medical use, their ability to relax, induce sleep and to assist in coping with mood swings between use of harder drugs such as heroin, cocaine and amphetamines means they are widely used (and abused) in the drug seeking community. Their use in drug facilitated assault and their ability to increase crash risk on the road is also noteworthy. Consequently, toxicologists need to be able to detect these drugs in biological specimens and to understand their toxicology.

The pharmacokinetics varies substantially between members from short acting hypnotics oxazepam, zolpidem and midazolam to long acting anti-anxiety agents diazepam, alprazolam and flurazepam. Profiles of selected members are found in Table 2. Some members are metabolized to active substances, e.g. diazepam to nordiazepam, flurazepam to desalkyl-flurazepam, while most are metabolized by hydroxylation and/or glucuronidation.

From a toxicological perspective given their diversity in potency and structure very few laboratories would be able to measure all drugs in this class in one analytical method. Immunoassay screens will often have difficulty with the morphine potent members, e.g. lorazepam and triazolam, and will not detect the non-benzodiazepines such as zopiclone or zolpidem [141]. For this reason, a chromatographic screen is recommended to at least supplement the traditional immunoassay screen. Recently, the development of LC–MS as a routine toxicological tool a number of assays have been developed for the wider group of benzodiazepines [142–145]. This technique has the advantage of also allowing the

simultaneous confirmation and quantification of the drugs in the specimen.

Blood concentrations of benzodiazepines provide some indication of the usage of the drugs in the recent past, providing the stability of the drug is taken into account (see earlier), particularly in decomposed tissue for all benzodiazepines and the nitrobenzodiazepines in all cases. With some exceptions, parent benzodiazepines are the usual target in blood, hair and solid tissues, although metabolites are targeted in urine. The 7-amino-metabolites of the nitrobenzodiazepines are formed postmortem and need to be targeted with the parent in all postmortem cases. Urinary concentrations do require prior hydrolysis to liberate the glucuronide metabolites of the diazepam family (temazepam, oxazepam) [141].

Poisonings associated with this class of drug are among the most common [107]. Numerous fatalities have been reported with benzodiazepines, particularly in persons with compromised cardio-respiratory function (i.e. elderly persons). They are also very often associated with opioid cases, such as heroin and methadone deaths, where they may play a significant role [146].

6.4. Cannabis

This perennial plant includes various sub-species of *Cannabis sativa* and is the most used illicit drug in many jurisdictions. The main active cannabinoid is Δ^9 -tetrahydrocannabinol. Modern cultivars and strains including “skunk weed” have a THC dried weight content of over 20%, although, most forms of cannabis have THC yields of 2–8%. Sinsemilla cannabis with the flowering heads has a typical THC content of 7–14%. The only other cannabinoids that show significant activity are Δ^8 -tetrahydrocannabinol, Δ^9 -tetrahydrocannabivaryl and cannabivaryl.

Peak THC plasma concentrations in blood rapidly exceed 50 ng/ml within 15 min of smoking and can reach 200 ng/ml with higher THC-content cigarettes [147,148]. THC is rapidly distributed to fat and muscle due its low water solubility resulting in a rapid decline in blood plasma THC concentrations. The half-life of this distribution phase is less than 1 h and plasma THC concentrations greater than 10 ng/ml are uncommon after 1 h even after moderate to high doses of cannabis [149]. Since the blood to plasma distribution is about 0.5, this represents about 5 ng/ml in blood. However, data obtained postmortem suggests that the distribution of cannabinoids between whole blood and serum is variable [150].

While the terminal elimination half-life of THC is 3–13 days blood concentrations are usually below 2 ng/ml after a few hours of last use and only highly sensitive analytical methods are able to detect the terminal stages of drug elimination [151].

In traffic cases blood THC provides a better measure of recent cannabis use, than the urinary metabolite. Recent data suggest that drivers with a measurable THC concentrations (>1 ng/ml) have an elevated crash risk [152–154].

Concentrations at about 5 ng/ml or higher have crash risks comparable to alcohol at 0.15% [152].

In situations where past cannabis exposure can lead to sanctions (workplace, pre-employment testing and prisons), the major urinary metabolite 11-nor- Δ^9 -tetrahydrocannabinol (cTHC) is measured following hydrolysis of the glucuronide. In most cases a cut-off of 15 ng/ml is applied, although cut-offs of 50 or even 100 ng/ml are occasionally employed.

The mean urinary excretion half-life of cTHC was about 1.4 days in both infrequent and frequent users [155]. However, frequent users have apparent terminal urinary excretion half-lives of up to 10 days. The last positive specimens were found after 4 and 17 days for cTHC with a cutoff 15 ng/ml in infrequent and frequent users, respectively [155]. Slightly longer detection times of up to 12 and 25 days have been observed in low and regular use, respectively [156–159].

Concerns have been raised over the possible contribution to death from use of cannabis in persons with compromised cardiac function (e.g. coronary artery disease). Sharp rises in blood pressures and heart rate could give rise to myocardial infarctions in susceptible persons [160]. An increased incidence of stroke should also be considered.

6.5. Heroin and other opioids

Heroin is converted within minutes to morphine through the intermediate 6-AM. All species are active pharmacologically, although both heroin and 6-AM are only present in blood and tissues for a relatively short period. Morphine is often the dominant active species in cases and is removed from the body by metabolism to 3- and 6-glucuronides and excretion in urine and bile. Morphine is rapidly excreted in urine as glucuronides, with up to 85% of the dose recovered in urine within 24 h. Only small amounts of morphine are excreted unchanged (2–10%). The presence of 6-AM in urine distinguishes heroin use from morphine. Small amounts of codeine are also present in the urine of heroin users because of the presence of acetylcodeine in the heroin.

Morphine (free) concentrations in blood in deaths attributed to heroin can typically vary from less than 0.1 to over 1 mg/l, although the median concentration in Victorian deaths is about 0.2–0.3 mg/l [161]. Total morphine concentrations range to over 2 mg/l, although the median is about 0.3–0.6 mg/l. When morphine is absent in urine or has concentrations less than 1 mg/l this suggests a death shortly after injection and importantly suggests the deceased may not have been a regular user and hence had little tolerance to the drug.

The ability of laboratories to measure the two glucuronide conjugates of morphine independently rather than collectively as total morphine using LC–MS techniques may lead to an improvement in the interpretation of heroin/morphine toxicity [162,163]. However, given the variability in response to morphine and the possibility of substantial tolerance developing it is unlikely that any morphine or metabolite concentration will ever be predictive of toxicity without a complete understanding of the pathology and the

circumstances of the case. This is exacerbated by polydrug use typically seen in heroin users which will increase the inherent toxicity of the drugs used [161].

Morphine and its analogs such as diacetylmorphine (heroin), codeine, oxycodone, hydromorphone, etc. are some of the many dozen opioids that form an important class of analgesics. While there are many important and legitimate medical uses, their abuse is widespread and leads to great harm in the community.

Synthetic derivatives such as methadone, buprenorphine, meperidine (pethidine), propoxyphene and fentanyl show many significantly different physiochemical and pharmacokinetics features to the morphine analogs, although they act in a very similar way to morphine. A summary of these features are shown in Table 2 for selected opioids.

In postmortem context, the morphine analogs are water soluble and show relatively low volumes of distribution. Hence, their ability to become re-distributed after death is relatively small. There is no evidence in humans that morphine concentrations in blood change much after death in the immediate postmortem period. Hydrolysis of morphine glucuronides back to morphine in decomposing specimens or bodies is a particularly important process event and can easily lead to erroneous conclusions (see earlier).

The more lipid soluble synthetic opioids such as methadone, fentanyl and meperidine will show increases in concentration after death (see Section 6). Furthermore, with long half-life drugs such as methadone significant risks are associated with drug accumulation from one dose to the next. This has led to a substantial increase in mortality both on the street and in methadone maintenance programs [164–167].

The development of tolerance to opioids is particularly important in that it seriously limits the ability to interpret the significance of blood concentrations. For example, morphine concentrations in deaths attributed to the use of heroin or morphine can vary from trivially low concentrations to many milligrams per liter. For this reason alone, without a thorough assessment of the circumstances toxicology results provide little guidance. The ratio of morphine and morphine glucuronides can sometimes assist. Acute use can be reasonably assumed when urinary concentrations of morphine are low or even absent and morphine is present in blood.

7. Concluding comments

The analysis of postmortem specimens can provide special challenges for forensic toxicologists. The selection of specimens is large, although not all specimens are suited to the analysis of all drugs. Hence, it is necessary to identify the types of substances expected and tailor the collection of specimens accordingly. The collection of several specimens to guard against the possibility of poor specimen collection is warranted. Invariably, the use of peripheral blood, particularly femoral, is warranted to reduce the number of artifacts.

Many drugs show instability and many drugs show concentration changes even when the postmortem interval is relatively short. Cocaine and heroin are rapidly hydrolyzed to their respective metabolites. Morphine glucuronide conjugates show instability in postmortem specimens producing morphine and substantially affecting the proportion of morphine to total morphine.

Postmortem forensic toxicology provides a challenge to the scientist not only in terms of analysis but also in terms of the proper interpretation of the drug detections. Artifacts caused by poor sampling, poor condition of the body and redistribution severely limit the interpretation of any analytical results. Given the variable responses seen with the drugs of abuse and the often rapid development tolerance, toxicological results must not be interpreted without a full picture of the circumstances of the case and elimination of relevant considerations from a postmortem examination.

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