Abstract
Post-mortem redistribution and other changes present major obstacles to the interpretation of drug concentrations in the dead. Nevertheless, reasonable assessments can still be made by the pathologist and toxicologist as to the contribution that commonly-abused drugs may have made to the death. The best assessments may be obtained by the implementation of the investigation along the following lines: (1) carefully select, store, preserve and utilize the post-mortem tissue samples intelligently for appropriate toxicological and histological analyses; (2) use as much information concerning the circumstances of the demise as possible to guide the procedures in step 1; (3) factor in prevalence of drug use and estimated fatality risks of such use within the particular group concerned to determine whether or not additional analytical work is required; (4) consider how these drugs behave in the body ante- and post-mortem, with and without disease states, together with any other factors such as tolerance; (5) consider the toxicological results in the context of macroscopic and histological autopsy findings.

Keywords drugs of abuse; fatal; post-mortem; pharmacokinetics; pharmacodynamics; redistribution; site sampling; toxicity; overdose

Introduction
In order to assist the pathologist in his or her assessment of the contribution that drugs of abuse may have made in a death, it is important that the pitfalls of post-mortem toxicology are described for these substances. This review has been compiled to introduce pharmacological data, redistribution, sampling, toxicological and analytical aspects for the common drugs of abuse, together with associated autopsy findings as a guide to interpretation. This is not a comprehensive account of all drugs of abuse. The focus will be on those drugs most frequently implicated in deaths in the UK, as this reflects the authors’ experience. The statistical data presented on the frequency of abuse will be restricted to the UK. It is acknowledged that patterns of drug abuse and toxicity differ in other parts of the world.

Commonly-abused drugs and substances in the UK

<table>
<thead>
<tr>
<th>Alcohol (ethanol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl nitrites</td>
</tr>
<tr>
<td>Amphetamines</td>
</tr>
<tr>
<td>Barbiturates</td>
</tr>
<tr>
<td>Benzodiazepines (typically diazepam and temazepam)</td>
</tr>
<tr>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Cannabis</td>
</tr>
<tr>
<td>Cocaine and ‘crack’-cocaine</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
</tr>
<tr>
<td>GHB and GBL</td>
</tr>
<tr>
<td>Hallucinogens (LSD and ‘magic mushrooms’)</td>
</tr>
<tr>
<td>Heroin and morphine</td>
</tr>
<tr>
<td>Ketamine</td>
</tr>
<tr>
<td>MDMA – ‘ecstasy’, MDA and related phenethylamines MDEA, MBDB</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Volatile substances</td>
</tr>
</tbody>
</table>

Table 1

The current commonly-abused drugs in the UK are listed in Table 1, based on data in the NHS Information Centre Statistics on Drugs Misuse in England, which can be found online in its statistical report for 2007.1 This publication summarizes the types of drugs used and their prevalence of use, as well as trends and patterns in England. The types of drugs used are listed for adults (16–59 years) and children (10–16 years). Cannabis remains the most common drug used by adults, followed by cocaine (all types), MDMA – ‘ecstasy’, amphetamines, alkyl nitrites (incorrectly referred to as amyl nitrates) and hallucinogens (LSD and ‘magic mushrooms’). In 2006 9% of children (11–15 years) in England reported taking drugs in the last month and 17% in the previous year, with cannabis being the most commonly taken drug at 10%. Four per cent of children reported that they had used a Class A drug in 2006.

Although only 0.1% of adults reported using opiates, their toxicity ensures that they are responsible for more deaths than the other drugs of abuse and so figure at or near the top of the tables for drug-related deaths in many countries (e.g. most of the Nordic countries2). Cannabis use, despite being the most widespread of the illicit substances, produces very few deaths due to its low toxicity, although in many cases it may be found in association with other abused substances. However, it should be noted that six deaths potentially caused by acute cardiac problems have been described in Norway.3

Commonly-abused drugs

The range of commonly-abused drugs and substances in the UK is similar to that in many other developed countries and includes the substances listed in Table 1, although there may be regional, temporal and societal differences in the particular favoured drugs and substances.

The abuse of alcohol still causes more deaths than any other substance and, because much literature has been devoted to the subject, it will only be touched upon briefly in this review.
Geographical and temporal variation in the UK

A Scottish Statistical Office report summarizes the drugs of abuse deaths for Scotland in 2007 and for comparison, in earlier years. The corresponding figures for England and Wales for this period are not available at compilation of this review, but there is no reason to doubt that the range of drugs involved in the death statistics is similar to that in Scotland, and to the period 1993–2004 for England and Wales. Anecdotal information indicates that there may be local ‘hot-spots’ for particular types of abuse from time-to-time, although official surveys are not available to confirm these trends.

Of particular note, in the year 2007 Statistical Report by the National Health Service (NHS) surveying drug misuse in England, cocaine usage over the period 1996–2006 has increased 10-fold in England and Wales. This report included self-reporting surveys from adults and could underestimate the respondents’ true usage, particularly for recent drug use and Class A drugs.

The drug misuse death statistics for England and Wales over the period 1993–2004 show that heroin and morphine continue to be implicated specifically in more drug-abuse deaths than any of the other listed drugs; e.g. in 2004, out of the total of 1427 deaths attributed to drug misuse, 744 were reported to be due to heroin/morphine. A slight downward trend noted for heroin/morphine deaths of 1% was noted over a period of 5 years from 1999 to 2004. However for cocaine, the figure of 147 deaths in 2004 represents a 68% increase over the 1999 total, reflecting the increased usage reported in the NHS survey.

Despite coming second, after heroin/morphine deaths, methadone deaths show a significant downward trend during the period 1999–2004, the figure for 2004 of 200 deaths involving methadone misuse being 33% less than the figure for 1999. This reflects a move to supervised dispensing, reducing the availability of diverted methadone.

Benzodiazepines continue to be used and abused to alleviate dysphoria and anxiety following abuse of other drugs, but although they rank close to methadone, being credited with involvement in 206 deaths in 2004, their relatively low toxicity indicates incidental involvement in most deaths.7 It has been suggested that impairment of judgement may be a factor with mixed drug use.6 Recent press coverage (September 2008) suggests that diazepam is becoming very popular as the supply of good quality heroin declines.

The involvement of amphetamines and dihydrocodeine in fatalities shows a marked decrease during the period, down by 35% (35) and 33% (81) respectively for 2004. On the other hand, MDMA and codeine show an increase of 85% (48) and 108% (54) respectively over the period 1999–2004.

The national programme on Substance Abuse Deaths (npSAD) publishes online summaries of its 6-monthly surveillance reports for drug misuse deaths for the UK. For example, the 18th report covered the period January to June 2006. As for previous surveys, most of the cases (76%) comprised males, about three-quarters being under 45 (74%). Ninety-six per cent were classified as white. Heroin/morphine alone or in combination with other drugs accounted for the highest proportion (47%) of the fatalities.

Although barbiturates are included in the NHS survey, being classified with benzodiazepines as ‘tranquillizers’, they seldom show up in the drug deaths statistics except in special circumstances such as the suicide of a veterinary surgeon, since they are not readily available on prescription and, furthermore, due to their low frequency of occurrence, some laboratories may no longer routinely screen for their presence.

For other drugs, although no figures are available, various elements of society may favour particular substances, e.g. ketamine seems to be favoured by young men in parts of the West Country seeking the ‘K-hole’ experience. Substances such as alkyl nitrites (poppers) and GHB or GBL may be encountered particularly in individuals associated with the ‘gay scene’.

Alkyl nitrites, cannabis, ketamine, LSD and psilocybin are implicated in very few deaths and therefore pharmacological details of these substances will not be included in the tables.

General points on the interpretation of post-mortem drug levels

The proper interpretation of any drug findings must be carried out with knowledge of the limitations and statistics of the analytical results, the nature of the particular samples used for the analysis (see below), cognisance of post-mortem changes and as much information about the victim and circumstances as possible.10 In particular, tolerance to a drug is a crucial issue when dealing with suspected acute overdose cases and without such information interpretation may necessarily be only tentative.

Analytical results are seldom of use without such information and the evidential value of the findings depends upon the types and numbers of tests and samples used and the prevalence of drug use in that particular population.11–13

Some authors urge extreme caution in the interpretation of any post-mortem drug data.14 However, as long as the toxicologist and pathologist are aware of all the variables that may affect the results, and sufficient information about the victim and circumstances is available, then it is feasible to form a considered opinion that is almost always better than none, and essential for the death certificate. As the understanding of drug redistribution advances, allowances for the types of drugs that have the greatest propensity to redistribute can be factored into the assessment of contribution of that particular drug in the death.15 The factors that predispose redistribution are described in more detail below.

If drugs of abuse are not involved directly in a death by overdose or atypical reactions, then the extent of their involvement may also be required by the Coroner or Procurator Fiscal to attempt to ascertain contribution to death in terms of impairment of behaviour or judgement, as described later.

Pharmacological data are of limited use in interpretation of the analytical data because they apply to live subjects, and post-mortem changes such as autoysis and putrefaction enhance drug redistribution.16 Furthermore, saturation of metabolic pathways for some drugs in overdose may have to be considered. Additional problems of interpretation are generated by the fact that the clinical data usually apply to plasma or serum of quite small populations and seldom to whole blood. For drugs such as MDMA that are not used medicinally, information on expected levels from known dosage is not as extensive as drugs such as morphine, methadone and the benzodiazepines. Pharmacological data on drug metabolites are also extremely limited. In any case, pharmacological data of the parent drug often only apply
to a limited, healthy population and to extrapolate them to a population of drug addicts some of whom will be in poor health, is not to be recommended. Extensive ante-mortem data for ‘normal’ abused drug levels in other body fluids, such as urine and vitreous humour, and tissues are not available.

Significance of a ‘positive’ result
The predictive value of a positive result depends on the prior probability of that drug occurring as indicated above. For example, for a known intravenous drug user, the number of tests carried out to measure heroin metabolites and morphine need only be minimal to obtain a good qualitative result. On the other hand, a positive result for ketamine in the post-mortem blood sample of an elderly individual who has not been in hospital should be treated with circumspection and further independent tests carried out on separate samples as well as the original one, to confirm or refute its presence – the false-positive situation. Depending on the test used, the false-negative rate may also need to be considered as additional testing may be necessary. This is particularly important with immunoassay-based screening tests, some of which may not cross-react sensitively to particular drugs or metabolites in a class.

Multi-substance usage and interactions
Multi-drug use or drug use concurrently with alcohol is commonly encountered and obviously adds to the interpretative burden for the toxicologist and pathologist. There are various effects taking place and the outcome will depend on the numerous factors that normally apply, not least dosage, state of health, genetic aspects of the individual and mode of use, plus the relative amounts of each substance. The temporal relationship, pharmacological properties, antagonism, enhancement of effects, synergism and metabolism are additional factors that come into play when multiple drug use is involved. Some of the common combinations of substances that are likely to be encountered are briefly described.

A fairly common combination is that of alcohol and cocaine because the former prolongs the stimulant effects of cocaine due to a trans-esterification process in the body producing cocaethylene which has a longer half-life than cocaine itself. Pharmacokinetic effects with higher concentrations of alcohol (> 100 mg% in the blood) may also prolong half-life for cocaine due to liver overload, thereby also contributing to longer-lasting effects.

The use of alcohol with heroin or methadone produces a significant number of fatalities each year. It has been suggested that alcohol enhances the toxicity of heroin indirectly through the association with infrequent use and therefore poorly-developed tolerance.

Prior use of prescribed medicines, such as antidepressants and anxiolytics, most commonly diazepam, may contribute to the overall pharmacological picture of central nervous system (CNS) depression and these too may have been taken in overdose; either due to amnesia or deliberate intent. For opiates and opioids, the use of antinauseant agents such as cyclizine and possible abuse of these should also be considered.

Speed-balling is the term used for the combined use of cocaine and heroin. Users may resort to heroin to come down from the effects of cocaine. Heavy tobacco or caffeine use may contribute additional problems such as hypertension, hyperthermia and tachycardia, causing severe adverse effects with concomitant illicit stimulant use.

It is important to be aware of substances that may be added to illicit drugs to enhance their effects. For example, piperazines may be added to MDMA to provide a synergistic effect, although this may be done during manufacture. These piperazines are also supplied on their own as ‘legal highs’ and their use is increasing rapidly. One of these, 1-(3-chlorophenyl) piperazine, is also found as a metabolite of the antidepressant trazadone, and has been implicated in an acute overdose.

The presence of cutting agents that are drugs themselves, such as diltiazem, lignocaine and phenacetin, may complicate matters further, as described later.

Technical issues
Sampling
A review of guidelines for sample collection post-mortem has been published by Flanagan et al. The authors list the collection, sampling, preservation and transportation requirements for reliable and relevant toxicology analyses post-mortem, to ensure that the maximum amount of useful information may be derived. They make recommendations as to chain of custody procedures and sample integrity to enable the evidence to stand challenge in a court of law, and therefore the procedures are suitable for both coronial and forensic investigations.

The most useful sample, and the most readily available, is generally blood and this must be taken from an isolated peripheral site to minimize the effects of drug redistribution. The more decomposition that has taken place, the less useful the blood analyses become, especially from a quantitative aspect. It is, therefore, important to carry out sampling as soon as is reasonably possible after death. It is usual for the samples to be haemolysed and therefore most post-mortem data apply to whole blood rather than plasma or serum as with clinical data. This should be borne in mind when attempting to relate the post-mortem findings to clinical data.

Esterases in blood in particular may continue to decompose drugs and metabolites during storage so it is important that storage guidelines such as the use of fluoride and chilling are followed to reduce this effect. Urine and vitreous humour are much better in this respect than blood due to the lack of esterases and so are valuable for drugs with ester functionality, such as heroin, its metabolite 6-MAM and cocaine. The proper use of fluoride, anticoagulant and a gas-tight storage vessel is also necessary for good alcohol analyses and is useful for the preservation of many volatile substances. It may also be useful to compare drug levels within peripheral and cardiac blood samples to help assess the degree of redistribution.

Oxidation of drugs or metabolites in stored blood may also occur and low temperatures should help to retard this.

As already indicated, other body fluids, such as vitreous humour, urine and CSF, are also valuable to enable the best possible picture to be built up. Vitreous humour tends to be more resistant than blood with respect to post-mortem changes due to its isolation from the circulation and distance from the body cavity. It is therefore less susceptible to redistribution and putrefactive effects when compared with blood. An issue with vitreous humour and CSF that needs to be remembered when interpreting
analytical findings is the temporal relationship that concentrations of substances in these fluids have with the blood. Changes in levels of substances lag behind those in blood because of the time taken to cross the blood–ocular barrier or the blood–brain barrier in the case of CSF. The equilibrium concentrations in the various fluids during steady-state drug administration obviously depend upon the pharmacological properties of the drugs.

Urine will require careful interpretation due to the averaging effect of the urine in the bladder on concentrations of substances between voids, and the amount of water present, but is nevertheless a useful fluid, again because of its isolation. Some drugs are eliminated in very low or effectively nil concentrations in urine, e.g. THC and diazepam. Urine is a good fluid for screening purposes and assessment of the range of drugs involved. The analysis of urine for total opiates, for example, may very well help towards determining prior usage and therefore the tolerance status. However, the samples must be stored and preserved correctly to minimize the decomposition of the drugs and metabolites.

If no body fluids are available for analyses, as in mummiﬁed or badly decomposed bodies, then tissues such as muscle or samples of organs including the liver, lungs and brain may be used. However, analysis of tissues is more time-consuming and expensive than body fluids and the relative paucity of data makes interpretation much more problematical. On the other hand, if post-mortem redistribution is suspected, then analysis of a liver sample gives more robust data, as does muscle tissue, notwithstanding the relative lack of data for these tissues.

Hair analysis may be useful to help with the assessment of usage and therefore tolerance in the period up to the death. Segmental analyses in particular may go a considerable way towards determining how extensive opiate usage has been. Heroin is analysed routinely in hair because it is preserved in the protein matrix.

### Post-mortem redistribution and changes

Post-mortem redistribution occurs almost as soon as the agonal process has finished, due to lysing of the cells as the biochemical functions necessary to preserve life decline. Organs where there may be a high drug concentration, such as the stomach, intestines and liver, start to experience declining concentrations of drug down the concentration gradient to the lower concentrations in other tissues and blood. Therefore, samples should be taken as soon as possible to minimize the extent of these changes. Some of the pharmacological factors that affect post-mortem drug levels are summarized in Table 2.

Drugs that have high volumes of distribution (> 3 L/kg) are the most likely to undergo post-mortem redistribution, resulting in a rise in blood levels due to diffusion into blood from surrounding tissues. The volume of distribution is a measure of the extent of concentration of a drug within tissues, outside the bloodstream. A drug which is uniformly dispersed throughout the body will have a volume of distribution of 1 L/kg. Drugs that are chemically basic and are very lipophilic tend to have high volumes of distribution. Lipid solubility of a drug is determined by the octanol:water partition coefficient which measures the extent to which the drug localizes within hydrophobic octanol. The lungs act as a reservoir of drugs, such as methadone, that are basic and lipophilic. Following death, diffusion of the drug into the heart may result in an artefactually high level in post-mortem cardiac blood, although there is a generally weak correlation between the central:peripheral blood ratio and the volume of distribution of a drug.

### Pharmacological parameters of drugs influencing post-mortem redistribution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of distribution (L/kg)</th>
<th>Protein binding plasma</th>
<th>Dissociation constant (pKa) at 20 °C</th>
<th>Partition coefficient (log P octanol/water) neutral pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>0.6</td>
<td>0</td>
<td>15.9</td>
<td>−0.3</td>
</tr>
<tr>
<td>Heroin (diamorphine)</td>
<td>25**</td>
<td>0.20–0.35</td>
<td>7.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.5–5.0</td>
<td>0.20–0.35</td>
<td>8.0, 9.9</td>
<td>−0.1</td>
</tr>
<tr>
<td>Methadone</td>
<td>4.0–5.0</td>
<td>0.87–0.92</td>
<td>8.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.6–2.7</td>
<td>0.92</td>
<td>8.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Codeine</td>
<td>2.5–3.5</td>
<td>0.07–0.25</td>
<td>8.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Approx 1</td>
<td></td>
<td>8.8 (25 °C)</td>
<td>−1.5 (ether/water)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5–2.6</td>
<td>0.96–0.99</td>
<td>3.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Temazepam</td>
<td>0.8–1.0</td>
<td>0.97</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>3.2–5.6</td>
<td>0.16 (0.15–0.40)</td>
<td>9.9</td>
<td>1.8</td>
</tr>
<tr>
<td>MDMA</td>
<td>5–8</td>
<td>ca 0.65</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>GHB</td>
<td>0.5</td>
<td>0</td>
<td>4.7</td>
<td>−1.66</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.4</td>
<td>0.96</td>
<td>8.5, 10</td>
<td>5</td>
</tr>
<tr>
<td>Chloroquine†</td>
<td>116–285 (T½ 25–60 d)</td>
<td>0.5–0.7</td>
<td>8.4, 11</td>
<td>4.6</td>
</tr>
<tr>
<td>Citalopram†</td>
<td>12–16 (T½ 33 h)</td>
<td>0.5</td>
<td>9.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Parameters obtained from the general reference works listed in Further Reading.

† In approximate order of decreasing involvement in deaths statistics in UK.

**Volume of distribution for heroin is high since it is lipophilic, however since it is rapidly decomposed it is difficult to obtain a good estimate.

†Selected examples of drugs with high volume of distribution that show a great propensity for redistribution.
Many metabolites of drugs of abuse, because they are more water soluble than the parent substances, suffer less from redistribution but there may be further chemical and microbiological degradation as putrefaction gathers speed. Indeed, fermentation and degradation make for particular difficulties with alcohol. The alcohol metabolite ethyl glucuronide, sometimes said to be more stable than ethanol in post-mortem samples, may also experience decomposition.\textsuperscript{26} GHB may also be produced post-mortem, especially if the samples are not preserved and not chilled adequately.\textsuperscript{2,\textsuperscript{23}} High ambient temperatures and a considerable degree of trauma usually expedite the changes within the cadaver by allowing greater access to microorganisms.

Flanagan and Connally review the collection and preservation of post-mortem samples in order to minimize the effects of redistribution.\textsuperscript{28} They also describe the difficulties in interpreting the analytical results and offer suggestions to enable the toxicologist to get the most reliable toxicology results. For example, the measurement of alcohol in isolated fluids, such as vitreous humour and urine, mitigates some of the effects of post-mortem changes as indicated above.

Decomposed bodies are unsurprisingly associated with major toxicological interpretative issues contributing to the difficulties for the pathologist. The use of remote solid tissues such as muscle should be considered in such cases to help minimize the effects of redistribution.

Particular problems may occur with bodies that have been repatriated from abroad and have been embalmed. Blood is usually entirely coagulated in a well-embalmed body and even when it can be obtained, the constituents of embalming fluid may confound toxicological interpretation. Typically the fluid contains ethanol, methanol and formaldehyde. The latter may react with some drugs, such as those containing a primary amine moiety, to give adducts, complicating the identification of drugs. In contrast, analysis of any remaining urine and vitreous humour in such cases may provide useful data.

### Commonly asked questions

#### When was the drug taken?

The route of administration, tolerance, interactions with other substances, polymorphism of liver enzymes, health and diet are amongst the more important factors that play a part in determining how a drug behaves in the body. Therefore, determining when a drug was taken is an inexact science even in live subjects. Redistribution and sample deterioration further complicate the picture for post-mortem interpretation. However, analyses of several different samples for the parent drug and its metabolite(s) may go some way towards distinguishing acute from chronic use and so may assist the pathologist in his/her deliberations. The half-lives and routes of excretion for commonly-abused drugs are summarized in Table 3.

Heroin is metabolized rapidly to 6-monoacetylmorphine (6-MAM) which has a half-life in blood of 5–25 min. Following an acute intravenous heroin death in a naïve user, depending on how well the blood sample was preserved (see above), significant concentrations of 6-MAM would be expected to be detected with a relatively low concentration in the urine. High levels would also be expected in the vitreous humour because its lack of esterases allows the 6-MAM to last much longer than in blood. 6-MAM is rapidly metabolized to morphine which has a

### Drug half-life, route of excretion, metabolic products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life in blood/plasma</th>
<th>Excretion route</th>
<th>Main metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>Sat kinetics</td>
<td>Urine, lungs</td>
<td>Acetaldehyde, acetic acid, (Et-gluc)</td>
</tr>
<tr>
<td>Heroin (diamorphine)</td>
<td>Av 19 mg%/h (9–29, greater for alcoholics)</td>
<td>Urine, bile</td>
<td>6-MAM, morphine</td>
</tr>
<tr>
<td>Morphine</td>
<td>3 min (1.7–5.3)</td>
<td>Urine, bile</td>
<td>M3 G, M6G**</td>
</tr>
<tr>
<td>Methadone</td>
<td>3 h (1.3–6.7) (1.8 h 6 2.9 h 6)</td>
<td>Urine</td>
<td>EDDP, EDMP</td>
</tr>
<tr>
<td>Methadone</td>
<td>10–97 h</td>
<td>Urine, bile</td>
<td>M3 G, M6G**</td>
</tr>
<tr>
<td>cocaine</td>
<td>0.9 h (0.7–1.5)</td>
<td>Urine, bile</td>
<td>Benzoylglucinone, methylecgonine</td>
</tr>
<tr>
<td>Codeine</td>
<td>2–4 h</td>
<td>Urine, bile</td>
<td>Cod gluc, norcodeine, morphine</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Approx 4 h</td>
<td>Urine, bile</td>
<td>DHC gluc, dihydronorcodeine, dihydromorphine</td>
</tr>
<tr>
<td>Diazepam</td>
<td>21–37 h</td>
<td>Urine, faeces</td>
<td>DMD, temazepam</td>
</tr>
<tr>
<td>Temazepam</td>
<td>3–15 h</td>
<td>Urine, faeces</td>
<td>Tem-glucuronide, oxazepam</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>7–34 h (urine pH dependent)</td>
<td>Urine</td>
<td>Phenylacetone</td>
</tr>
<tr>
<td>MDMA</td>
<td>6–9 h (urine pH dependent)</td>
<td>Urine</td>
<td>MDA</td>
</tr>
<tr>
<td>GHB</td>
<td>0.3–1.0 h (terminal)</td>
<td>Urine (GBL)</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.2–7.2 h (up to 44 h terminal)</td>
<td>Faeces, urine</td>
<td>Norbuprenorphine</td>
</tr>
</tbody>
</table>

Half-lives may vary with tolerance and dose.
Half-lives of many basic drugs, particularly amphetamines, decrease with decreasing pH of urine.
Route of excretion: proportion excreted via each route depends on mode of administration.
*Plasma half-life for surgical patients.
**M6 G is approximately 50 times more potent than morphine in terms of analgesia, since unlike M3 G it can cross the blood–brain barrier. M6 G may be produced in enhanced amounts in heroin abusers.\textsuperscript{48}

Table 3
Liver disease seems to have little effect on the metabolism of hydrochloride. Bingeing on crack-cocaine may produce severe help to distinguish between smoking crack and snorting cocaine that the samples are adequately cooled and preserved to retard ing of crack is said to produce methylecgonidine and, provided cocaine, a free-base form of cocaine, produces even more rapid avoids first-pass metabolism and ensures fairly rapid onset of delivery of therapeutic concentrations since oral absorption is inefficient and this route obviates the need to smoke. Buprenorphine is formulated for sublingual use because of extensive first-pass metabolism. This route is also favoured for therapeutic administration of cannabinoids to achieve reliable delivery of therapeutic concentrations since oral absorption is inefficient and this route obviates the need to smoke. Nasal insufflation (snorting) of cocaine hydrochloride powder avoids first-pass metabolism and ensures fairly rapid onset of action, the drug quickly reaching the brain. The smoking of crack-cocaine, a free-base form of cocaine, produces even more rapid effects than cocaine powder. The intense euphoria experienced following crack use is consequently very addictive. The smoking of crack is said to produce methylecgonidine and, provided that the samples are adequately cooled and preserved to retard decomposition, then the presence of methylecgonidine should help to distinguish between smoking crack and snorting cocaine hydrochloride. Bingeing on crack-cocaine may produce severe toxicological and behavioural problems and it may be possible to distinguish such use by the exceptionally high levels of cocaine itself in the body fluids. The half-life of cocaine is reported to increase with chronic use due to deposition of cocaine into the body tissues, probably adipose tissue. Liver disease seems to have little effect on the metabolism of some of the common drugs of abuse, but exact effects depend longer half-life of 2–3 h. Morphine is metabolized to morphine-3-glucuronide which is excreted in the urine. In general, a high free:total (free + conjugated) morphine ratio indicates that death occurred quickly after heroin/morphine administration. A high total but low free morphine suggests that death was delayed and possibly not due to morphine toxicity. Cocaine is metabolized rapidly in life to benzoylcgonine and has a half-life of less than 1 h. Blood levels continue to fall after death as a result of continued esterase activity. This should be taken into account when interpreting post-mortem levels. Vitreous humour, protected from enzymes in blood, may give a more accurate measure of cocaine levels at the time of death. In general, care should be taken not to attempt to assess the amount of drug involved except in general terms, such as large overdose, broadly therapeutic use and so on.

**Does the route of entry affect drug action?**

The route of entry is important for interpretative purposes and as full an account as possible of the circumstances of the death should assist the investigators. For example, intravenous heroin produces rapid effects, euphoria and coma or death with overdose, sometimes within a few minutes. Clearly, there are no first-pass meta-bolic effects to ameliorate these effects and the syringe may remain in the hand due to a swift demise. Oral morphine and methadone on the other hand are absorbed much more slowly from the gut, and in the case of morphine not always very reliably with entero-hepatic recirculation adding to the problems. Therefore, there is a risk of overdose with these due to accumulation following exces-sive use if there are delayed therapeutic or desired benefits. The circumstances may not be as clear-cut and helpful to the toxicolo-gist and pathologist as the ‘death on the needle cases’ as the vic-tim may continue to function and remove himself/herself from the drug source. 'Chasing the dragon' – smoking heroin powder from foil, is the method of choice for those not keen on needles.

Buprenorphine is formulated for sublingual use because of extensive first-pass metabolism. This route is also favoured for therapeutic administration of cannabinoids to achieve reliable delivery of therapeutic concentrations since oral absorption is inefficient and this route obviates the need to smoke. Nasal insufflation (snorting) of cocaine hydrochloride powder avoids first-pass metabolism and ensures fairly rapid onset of action, the drug quickly reaching the brain. The smoking of crack-cocaine, a free-base form of cocaine, produces even more rapid effects than cocaine powder. The intense euphoria experienced following crack use is consequently very addictive. The smoking of crack is said to produce methylecgonidine and, provided that the samples are adequately cooled and preserved to retard decomposition, then the presence of methylecgonidine should help to distinguish between smoking crack and snorting cocaine hydrochloride. Bingeing on crack-cocaine may produce severe toxicological and behavioural problems and it may be possible to distinguish such use by the exceptionally high levels of cocaine itself in the body fluids. The half-life of cocaine is reported to increase with chronic use due to deposition of cocaine into the body tissues, probably adipose tissue. Liver disease seems to have little effect on the metabolism of some of the common drugs of abuse, but exact effects depend on the mechanism of metabolism. For example, chronic liver disease increases the bioavailability of oral morphine but barely affects the intravenous clearance rate. The elimination half-life and volume of distribution remain in the normal range. The pharmacokinetics of heroin seem to be little affected by hepatic impairment. Renal insufficiency appears to be much more important, especially with the accumulation of the active morphine metabolite morphine-6-glucuronide (M6 G) during chronic morphine (or heroin) use, potentially causing severe CNS depression due to its much higher potency than morphine. This applies particularly to the elderly.

Clearly other factors, such as age, genetic factors or even gender, may have a significant bearing on clearance rates and susceptibility to adverse effects. The use of monoamine oxidase inhibitors may precipitate serotonin syndrome with concurrent and subsequent abuse, and use of the stimulant drugs such as MDMA and related drugs of abuse such as the hallucinogens.
tolerance if the user is not aware of the greater potency of a hit.\textsuperscript{5} However, a recent Austrian study of heroin emergencies, including deaths, and purity of the drug did not find that this was substantiated, although it did not rule out an association.\textsuperscript{41}

An example of a cutting agent/adulterant encountered in forensic drug seizures in the UK in the last few years that does have pharmacological activity is the calcium-channel blocker diltiazem, which could have been added to reduce cardiac risks associated with excessive use of MDMA or cocaine. Levamisole, lignocaine, phentacetin, paracetamol and caffeine, amongst a wide range of others, have been found in illicit drugs and in cocaine seizures particularly. Alprazolam has been found in heroin and it may have been added to help reduce anxiety as the effects of the abused drug wear off. Depending on the analyses carried out, some or all of these adulterants will be easily detectable; however, if there is not a comprehensive analysis some may be missed.

In general, the toxicity of adulterants is low in comparison to the active component, unless large quantities are involved when the toxicity of the adulterant itself probably presents the higher risk. Nevertheless, there may be pharmacokinetic interactions causing prolongation of adverse effects of all the components. Lignocaine may have a synergistic effect with cocaine, causing increased seizure activity.\textsuperscript{42} In terms of acute outcomes due to toxic adulterants, there is a report of a series of hospital admissions in 1995 due to heroin cut with scopolamine causing severe anticholinergic toxicity in a great number of users in New York City and other Eastern Seaboard cities in the US.\textsuperscript{43} An earlier incident comprising five cases had been reported in Spain.\textsuperscript{44}

### Pathological findings associated with drug abuse

Drug-related pathology seen at autopsy may be subclassified according to the pathogenesis:

1. Chronic tissue damage (neoplasia, cardiovascular disease, liver, kidney, brain injury);
2. Acute toxicity;
3. Infective complications of drug-taking behaviour;
4. Trauma due to intoxication.

A comprehensive account of drug-associated pathology is beyond the scope of this review, but the common findings in alcohol, opiate and stimulant deaths will be summarized.

### Alcohol

Alcohol-related diseases are a common cause of death in the UK but will not be considered here. Alcohol intoxication is a significant factor in many deaths due to trauma, such as road traffic incidents and falls, drowning, burns and carbon monoxide poisoning. Blood alcohol levels should always be measured in such deaths. The measurement of alcohol levels in urine and vitreous humour often helps to determine whether or not use has been acute or chronic.

Alcohol toxicity alone may result in death due to coma and respiratory depression with blood levels in excess of 300 mg/100 mL, although the lethal concentration of alcohol can vary more than three-fold, according to individual tolerance. This mode of death is more frequent following ingestion of alcohol in combination with other sedative agents. Alcohol intoxication may contribute to deaths due to positional asphyxia or sleep apnoea.\textsuperscript{45} Hypoxia is a powerful stimulant to waking, this reflex being suppressed by alcohol and other sedatives. The diagnosis will depend on details of the circumstances of the death and position of the body. In addition to documented intoxication, suggestive features in the history include previous episodes of sleep apnoea, heavy snoring and death in a supine position. At-risk individuals are typically obese, middle-aged men, with a high prevalence of coronary artery disease. Pathologists are inclined to attribute death to the coronary disease, despite a suggestive history, and it is likely that deaths due to alcohol-related sleep apnoea are under-reported.

Acute alcohol intoxication more commonly results in death due to vomiting with aspiration and respiratory failure. At autopsy, vomitus may be grossly visible within trachea and bronchi, but this should be interpreted with caution, particularly if there has been attempted cardiopulmonary resuscitation; the latter frequently results in post-mortem aspiration of gastric contents. Histology may confirm the presence of food material, oral squames and bacteria in bronchioles and alveolar spaces. If death has been rapid, there is little tissue response, but if delayed there may be oedema and a protein-rich intra-alveolar exudate secondary to acid- or bile-induced alveolar wall damage. Later still there may be an established aspiration pneumonia, at which stage alcohol may have dropped to a low level in the blood; the diagnosis may then depend on witness accounts of intoxication and vomiting. Urine analysis may also help in these instances.

### Opiates

Intravenous heroin abuse is associated with many infectious complications associated with the use of contaminated needles, including hepatitis B and C virus infection, human immunodeficiency virus (HIV) infection with associated immunodeficiency, infective endocarditis and soft tissue sepsis at the site of injection. Heroin may also be smoked or snorted, without the infectious risks associated with intravenous injection.

The mode of death in acute opiate toxicity is respiratory depression and arrest. There may be no specific macroscopic features at autopsy, the most frequent finding being intense pulmonary congestion (‘haemorrhagic oedema’). This reflects progressive hypoxia associated with reduced ventilation. In delayed deaths there may be brain swelling as a result of cerebral hypoxia. Fresh puncture wounds may be apparent in deaths following intravenous injection. Common sites used for injection include veins in the antecubital fossae, wrists and hands, groins and back of the feet. Scars at the sites of previous injection may be apparent and provide evidence of intravenous drug abuse.

Histological changes are also frequently non-specific. Perivascular foreign body granulomas in the lungs are a common finding in long-standing intravenous drug abusers. The most common acute pulmonary change is congestion with intra-alveolar haemorrhage. Aspiration pneumonia may also be evident. Rhabdomyolysis is associated with heroin abuse; this may be secondary to pressure necrosis following prolonged intoxication, venous thrombosis or intramuscular abscesses. Myoglobinuric acute renal failure may result from the muscle breakdown; post-mortem histology of the kidneys will demonstrate myoglobin tubular casts.

### Stimulants

It is the cardiovascular effects of cocaine and other stimulants that are responsible for most deaths associated with their use.
Cocaine may precipitate severe hypertension and result in death due to subarachnoid haemorrhage, intracerebral haemorrhage, infarction or aortic dissection. Cocaine and amphetamines show both acute and chronic cardiac toxicity.\textsuperscript{46,47} Myocardial arrhythmias may occur in the absence of detectable pathology, but frequently there is evidence of myocardial ischaemia associated with accelerated coronary atherosclerosis or coronary artery spasm. An erroneous ‘natural’ cause of death may be provided, if the possibility of stimulant abuse is not considered. It is essential to obtain a full drug history, particularly in individuals with premature coronary artery disease, cardiomyopathy or otherwise unexplained intracranial haemorrhage. It is the authors’ experience that toxicological studies frequently provide evidence of recent stimulant use in such cases, indicating that death results from a combination of acute and chronic cardiovascular injury.

\textbf{Cause of death}

When interpreting post-mortem drug levels, the circumstances and timing of death must be taken into account, in addition to the autopsy findings. This is illustrated by three common scenarios from the authors’ practice in which the cause of death was drug toxicity:

1. \textit{Rapid death within minutes following intravenous heroin injection}. The needle and syringe are next to the body. Urine drug screen is negative but free morphine is at a high level in the blood. Pathological changes are minor. The likely mode of death is rapid respiratory arrest.

2. \textit{Delayed death following intravenous heroin injection}. The deceased is found lying supine on a bed with no drug paraphernalia at the scene. Morphine is at a border-line toxic level in the blood but at a high level in the urine. There is intense pulmonary congestion and oedema and marked brain swelling. These findings suggest a delayed death with a prolonged period of respiratory depression and hypoxic brain injury. Positional asphyxia, with airway obstruction by the tongue, may also play a role.

3. \textit{Delayed death following methadone ingestion}. The deceased is taken to the emergency department after taking a friend’s methadone, severely intoxicated and comatose. He regains consciousness after being given naloxone and takes his own discharge. He is found dead at home the following day. At post-mortem examination there is pulmonary congestion and brain swelling. Methadone is present at a high level in the blood. Police investigations suggest that he did not take any more methadone after leaving hospital. It is likely that he returned to coma with respiratory depression once the naloxone was metabolized, as a consequence of the long half-life of methadone and short half-life of naloxone.

For the reasons explained in this review, post-mortem toxicology is a far from perfect science and toxicological results must always be interpreted with caution. Because of the difficulties and potential errors in the interpretation of post-mortem drug levels, they should not be taken in isolation when formulating the cause of death. In order accurately to define the role of drug abuse in the death, it is essential that as much information about the circumstances of the death is obtained as possible. The stated cause of death must make sense in the context of the apparent mode of death and the autopsy findings. With this careful approach, a reliable cause of death is achievable in the majority of cases. However, errors may result if details of the death are not communicated to the pathologist at the time of the autopsy. Toxicological screening can never be comprehensive and is inevitably guided by information provided by police officers attending the scene of death. Formulation of the correct cause of death requires a team approach between the pathologist, toxicologist, police and Coroner’s office.

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**FURTHER READING**


