Investigating drugs of abuse at autopsy

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Abstract

Post-mortem toxicology is an important diagnostic part of the investigative process, not least when drugs of abuse are suspected, some of which require special attention. This review summarises key information regarding current common drugs of abuse, including amphetamines, benzodiazepines, cannabis, cocaine, ketamine, pregabalin as well as new psychoactive substances (NPS). The importance of sufficient and appropriate information (such as case circumstances and drug history) in addition to scene evidence and other considerations (including analytical and sampling factors) are presented that are relevant to the interpretation of results and the pathological process.

Keywords amphetamines; autopsy; benzodiazepines; cannabis; cocaine; ketamine; NPS; opiates; pregabalin; toxicology

Introduction

There are two primary issues relating to the investigation of drugs of abuse at autopsy. Firstly, as with any drug, evidence of drug use may not be immediately apparent aside from any needle marks from intravenous administration or presence of tablets/material in the stomach. Secondly, the nature of drugs of abuse is continually changing and does not necessarily constitute "classical" drugs of abuse such as heroin, cocaine, MDMA and other amphetamines.[1] In the last decade or so, whether it be the increased use of gamma-hydroxybutyrate (GHB) followed by so-called "legal highs", there have been many hundreds of new compounds that have been abused, also notwithstanding increases in the abuse of some prescription drugs (e.g. pregabalin, gabapentin and opioids such as oxycodone and fentanyl). Of particular note are the so-called "legal highs" (as were) which have invariably been synthesised to mimic the effects of controlled drugs but following legislative changes these are either controlled under the Misuse of Drugs Act 1971 or the more controversial Psychoactive Substances Act 2016. As such, in the UK and around the world these compounds are referred to as "novel or new psychoactive substances" (NPS). Having first entered drug markets via accessible websites, "head shops" in the street or some market stalls, access is now more restricted to less accessible websites (e.g. the so-called "dark web") or other purveyors of illicit drugs. This article will describe the necessary considerations for "classical" drugs of abuse as well as more recent NPS and other drug oddities that may be encountered at autopsy.

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Amphetamines

Amphetamine itself and related compounds are part of the phenethylamine class of compounds. This class also includes methamphetamine, MDMA and some "designer drugs" such as PMMA (para-methoxymethylamphetamine) and PMA (para-methoxyamphetamine) amongst many others.

Amphetamine and methamphetamine in particular are potent central nervous system stimulant drugs which are widely abused for their euphoric effects and psychoactive properties.[2] Concentrations of amphetamines in post-mortem blood can be difficult to interpret, particularly due to the overlap (largely through tolerance and differential abuse situations) between those found in non-fatal cases and those found in cases where the drug may be implicated.[3] Death from amphetamine toxicity following an acute excessive dose may not occur immediately but after several hours during which time the individual may experience tachycardia, hypertension, hyperthermia, convulsions, unconsciousness and respiratory and cardiac failure.[3] In this situation, the blood concentration at the time of death may have decreased significantly. Myocardial infarction and cerebral haemorrhage have also occurred in some abusers. Findings at the post-mortem examination may include organ congestion and haemorrhaging.

MDMA (3,4-methylenedioxymethylamphetamine), also known by the street names 'Ecstasy', 'E' and 'XTC') and its metabolite, 3,4-methylenedioxyamphetamine (MDA) are amphetamine-derived compounds. MDA is a metabolite of MDMA, but may also be present in "Ecstasy" tablets itself. Adverse effects from MDMA can include various clinical symptoms such as visual hallucinations, confusion, agitation, sweating, coma and cardiotoxic effects such as tachycardia, hypotension, myocardial infarctions and in some cases arterial spasm.[4] Other common toxic symptoms include hyponatraemia (usually due to excessive water intake) and/or hyperpyrexia; leading to secondary features such as cerebral oedema, seizures, organ damage and ultimately death.

Of some note and consideration for amphetamines, is that methamphetamine is a known metabolite of the anti-parkinson's drug selegiline, therefore the prescription history of the deceased is important. Also some amphetamines (e.g. PMA, PMMA and 4-methylthioamphetamine) have a pronounced delayed effect which can result in unintended excessive ingestion.[3] Finally, it should be noted that phenyl-2-ethylamine is a common putrefactive compound that is also obviously a phenethylamine, which can create potential "false positive" situations with laboratory presumptive immunoassays for amphetamine(s) that may cross-react with its presence, requiring confirmation using more specific techniques.

Cocaine

Cocaine is a drug abused primarily for its central nervous system stimulant effects. These effects include increased energy and alertness, excitement, euphoria, increased confidence and increased talkativeness. In addition, the use of cocaine may be associated with increased risk taking behaviour and aggression. In high doses, the effects of cocaine use may also include paranoia, bizarre and violent behaviour, hyperactivity and restlessness. Once the stimulant effects of cocaine subside, the user may experience "come-down" effects such as low mood, depression,

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anxiety and irritability. A relatively small number of deaths due to acute cocaine toxicity are seen considering its wide use; however cardiotoxicity has been implicated as a major contributory factor in cocaine induced deaths resulting in symptoms including myocardial infarction, ventricular tachycardia and fibrillation, cerebrovascular accident and pulmonary dysfunction.[5] There is also evidence that cocaine use accelerates atherosclerosis and other vascular disease issues.[6] Convulsions have also been reported when the drug is used excessively.

If cocaine is taken whilst there is ethanol in the bloodstream, an interaction takes place to form cocaethylene.[7] Therefore, the presence of cocaethylene may be evident in post-mortem blood and/or urine and can demonstrate that the deceased had used cocaine whilst there was ethanol in the blood stream. Cocaethylene can prolong the stimulant effects of cocaine and eases its comedown effects.

Of some note and consideration for cocaine, is that cocaine is quickly metabolised and being unstable also breaks down to form benzoylecgonine (BZE) and ecgonine methylester (EME). Therefore, cocaine concentrations in post-mortem blood may not reflect those at the time of death. An additional consideration for cocaine investigations is that as the illicit drug product is often adulterated with other drugs that may or may not present additional toxicity. Typical adulterants include levamisole, lignocaine, benzocaine and phenacetin.

Opiates/opioids

An opiate can be described as a compound found naturally in the opium poppy (e.g. morphine, noscapine, thebaine, papaverine, codeine) whereas an opioid is a synthetic compound, synthesised to provide opiate-like effects (e.g. heroin, dihydrocodeine, methadone, oxycodone, tramadol, fentanyl). Methadone is an opioid drug which can be used for pain relief in some circumstances but is more commonly used as replacement therapy for heroin addiction/withdrawal. Opiates and other opioids are predominantly prescribed for pain relief (usually moderate to severe), both in the short-term and long-term. The concentrations of opiates and opioids found in blood during therapy are very variable and there is a significant overlap between concentrations found in acute fatal poisonings and concentrations obtained therapeutically. Therefore, the toxicological significance of a measured post-mortem blood concentration will depend upon the degree of tolerance possessed by the deceased.[8] The majority of opioids are also prone to post-mortem redistribution and therefore may be artificially elevated after death depending on the site and manner of blood sampling as well as the length of the post-mortem interval. Fentanyl is highly prone to this and particular attention should be placed on the presence, site and number of any fentanyl patches on a body (especially in comparison to any prescribed dose regimen).[9] It should also be noted that fentanyl release/delivery from transdermal patches can accelerate with heat and patients are warned of this, with some case evidence of this even occurring after a prolonged hot bath.[10]

For heroin (diacetylmorphine), the presence of 6-monoacetylmorphine (6-MAM, a specific diacetylmorphine metabolite) as well as codeine, noscapine and papaverine will provide analytical evidence of heroin use (rather than medical diamorphine), however it is not possible to completely exclude additional morphine use. As codeine is metabolised to morphine, it is also important to monitor the relative concentration of codeine versus morphine. Additional analytical merit can be the relative concentration ratios of morphine and its metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[11] Nevertheless, as in all cases involving opiate/opioid drugs, the toxicological significance of any morphine concentration will depend upon the degree of tolerance possessed by the deceased. Therefore, knowledge of an individual's drug history regarding opiate and opioid drugs is very important. It is important to note that tolerance can be gained within a few days of repeated use, conversely, infrequent use or periods of abstinence can result in loss of tolerance with a naïve user having little to no tolerance.

The major risk to life from opiates and opioids is their depressant effect on the central nervous system (CNS), notably causing respiratory depression. The use of other CNS depressant drugs (e.g. benzodiazepines, barbiturates, etc) or alcohol that may exacerbate the CNS effects will reduce the threshold to which an individual would succumb to fatal toxicity so concomitant drug use should be a consideration in such cases, as well as positional asphyxiation in appropriate circumstances.

Of some note and consideration for opioids, is the recent phenomenon of fentanyl and fentanyl analogue abuse as well as other synthetic opioids (e.g. AH-7921 and U-47700) within the wider "new psychoactive substance" phenomenon. In the last few years in the UK (and particularly Canada and the USA), use of fentanils has increased significantly and pose a particular danger to users due to their high potency, even when compared to morphine and heroin.[12] Although fentanyl and its derivatives/analogues (fentanils) have been controlled in the UK for over 30 years, they emerged on the NPS market over the last 5 years or so, typically available as white or coloured powders. More recently, there have been reports and instances of their presence in illicit heroin in particular as an adulterant or replacement as well as in fake medicines. These modes of use present both intended and unintended user consumption and exposure. Care should be taken if any suspected powders are submitted or found with decedents.

Ketamine

Ketamine is a dissociative anaesthetic drug used in human and veterinary medicine. However, due to the production of hallucinogenic effects, ketamine has also gained popularity as a drug of abuse. The toxicity of ketamine is known to be dose-dependent with deaths resulting from direct acute ketamine ingestion being very rare with a significant overlap between the therapeutic or recreational concentrations and those detected in fatalities.[13] Low doses of ketamine can produce drowsiness and perceptual distortions, whereas higher doses can produce euphoria, hallucinations and feelings of alternate consciousness. Adverse effects of ketamine may include anxiety, tachycardia, cardiac arrhythmia, dizziness, vomiting, seizures, delirium, paranoia and potentially respiratory depression.[13] In recent years, there has been an observation of increased bladder problems with ketamine users, especially chronic high dose users.[14] This can result in reduction in bladder size, development of

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