Poisoning with illicit substances: toxicology for the anaesthetist

G. T. C. Wong[1] and M. G. Irwin[2,3]

1 Clinical Assistant Professor, 2 Professor & Head, Department of Anaesthesiology, University of Hong Kong, Hong Kong
3 Chief of Service, Department of Anaesthesiology, Queen Mary Hospital, HKU-Shenzhen Hospital, Hong Kong

Summary
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Correspondence to: G. T. C. Wong
Email: gordon@hku.hk

> All substances are poisons. There is none which is not a poison. The right dose differentiates a poison and a remedy (Paracelsus: 1493–1541)

Toxicology is the study of the nature, effects and detection of poisons and the treatment of poisoning. Poisons can be substances that are inherently toxic to tissues, adversely affect physiological function or therapeutic substances taken in excess. Injury can result not only from the direct effects of the poison but indirectly from injuries sustained while the patient is intoxicated or in various phases of withdrawal. This is particularly relevant to those affected by sensorium altering substances such as opioids, cocaine, amphetamines, ketamine or with compounds emerging from clandestine labs purporting to produce 'legal highs' or 'herbal highs'. Anaesthetists use actual (e.g. muscle relaxants) or potential poisons daily but are either capable of managing their effects (e.g. ventilation) or carefully titrate their administration to avoid toxicity and will be already familiar with the pharmacology of many of these substances. The drugs may also interact with those used peri-operatively and therefore it is apposite to understand the toxicology of these substances, when practising in anaesthesia or intensive care. This review will focus on illicit substances. These have been a problem, of course, for many years but the range of drugs is increasing along with accessibility as many of these substances can be manufactured in illegal laboratories and even sold via the internet. We will first place the problems in context, provide some succinct information on some of the compounds, with anaesthetic implications where available, and conclude with recent developments in managing patients following ingestion. Since it has not been possible to study many of these compounds in clinical trials or even in humans as they may have no therapeutic indication, the evidence base for anaesthetic implications is rather thin, based on case reports and/or anecdotal experience. Although numerically important, opioid and benzodiazepine overdose will not be covered here as the pharmacological and toxicological aspects should be sufficiently familiar to most anaesthetists.

Epidemiology of poisoning

Poisoning can affect all age groups. Figures from the Centre for Disease Control and Prevention estimated that in 2009, 41,592 poisoning deaths occurred in the United States, three quarters of which were deemed unintentional. This was second only to motor vehicle accidents as a cause of unintentional injury and death for all ages. It was estimated that in the preceding year over 91 per cent of such deaths were caused by drugs, most commonly analgesics, which includes methadone, hydrocodone and oxycodone, followed by cocaine and heroin [1]. Across England and Wales, figures from the Office for National Statistics showed that of the 2747 drug poisoning deaths in 2010, 1784 were attributable to drug misuse and, again, most commonly associated with heroin and morphine. Opioids still dominate among the substances of abuse to be implicated as a cause of death, but cocaine, amphetamines and the newer psychoactive substances together come close to one tenth of deaths [2].

Those that manage to make it into the statistics may represent the tip of the iceberg. Based on data from the British Crime Survey of 2009/2010, it is estimated that in the 16–59 age group, 6.6% had used cannabis, 2.4% powdered cocaine and 1.6% ecstasy in the year of the survey [3]. Drug intoxicated individuals may be accident prone, from both compromised judgement and motor skills. The latter is supported by data from Norway where

close to three quarters of drivers with blood positive only for amphetamines and methamphetamines were performance-impaired in clinical testing [4].

Historical perspective of substances of abuse

A more detailed review on this interesting area can be found in an editorial by King and Kicman [5] and a brief summary is provided here. Since 2005, the term 'new psychoactive substances' has been adopted by the European Community to describe what was once referred to as 'designer drugs' or 'legal highs'. Traditional drugs of abuse such as opioids, cocaine, amphetamines and cannabinoids had their roots in traditional medicine, where they had and still have therapeutic roles, but their use is tightly regulated. Designer drugs are essentially chemical analogues of some of these controlled substances, 'designed' as it were, to provide a similar experience to the parent compound. Initially fuelled by the demand to replicate the highs produced by opioids, this trend fell out of favour following the discovery of the now well-known neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) produced in the synthesis of MPPP (1-methyl-4-phenyl-4-propionoxypiperidine), a reverse ester of pethidine. This contaminant destroys dopaminergic neurons, thus chemically inducing Parkinson's disease.

The next era of designer drugs involved the manipulation of amphetamine, producing an array of substances that energise the consumer and elicit feelings of euphoria and empathy. The terms 'empathogens' or 'entactogens' were used to describe these phenethylamine compounds to which ecstasy belongs. Although not a designer drug as such, gamma-hyroxybutyrate was also popular in the club scene but once its status changed to being a schedule drug, it too underwent modification and gamma butyrolactone became prevalent. Tryptamine derivatives were also available in the 1990s alongside the phenethylamines. In the early 2000s, piperazine compounds arrived after being considered unsuitable for therapeutic use by pharmaceutical companies. Further trawling of the lines of failed pharmaceutical products for potential 'legal highs' yielded the cathinone derivatives including mephedrone. As these products were derived from chemicals obtainable from legal sources, their promulgation and distribution became more extensive.

Toxidrome

Most of the newer substances of abuse have actions at multiple receptor types but may differ in their patterns of effects [6]. Drugs that produce a sympathomimetic syndrome do so by inhibiting reuptake of catecholamines, eliciting mainly stimulatory effects in the user and examples of such agents include benzylpiperazine, mephedrone and diphenylprolinol. Other drugs act predominately on the serotonergic system and thus manifest signs of serotonin syndrome in toxicity. Those agents that tend to produce entactogenic feelings (e.g. phenylpiperazines, methylone) do so by causing serotonin release in the CNS whereas those with hallucinogenic properties (e.g. 5-methoxy-N,N-diisopropyltryptamine, 2,5-dimethoxy-4-bromoamfetamine) are serotonin receptor agonists [6].

Cannabinoids

Cannabis is probably one of the most frequently used recreational drugs and is consumed as a mixture of dried shredded flowers and leaves of the hemp plant Cannabis sativa (marijuana), as resinous secretions of the cannabis plant (hashish) or synthetically as a yellow resinous oil (dronabinol). Delta-9-tetrahydrocannabinol (THC) is believed to be the most psychoactive component of cannabinoids contained in cannabis. Although its toxicological effects may be familiar to some, it is worth bearing in mind that advances in cultivation methods have enabled higher THC yield from plants and that hashish oil or resin can contain a very high quantity of THC. This potentially would increase the likelihood of more significant levels in the blood and enhanced intoxication. Although risk perception following cannabis use is less impaired than with alcohol, it is one of the most common drugs detected in drivers involved in motor vehicle accidents [7].

Given the prevalence of its use, it has been suggested that a history of illicit drug and especially cannabis use should be obtained routinely in the pre-anaesthetic assessment, although patients may be reticent to disclose it [8]. It is also difficult to predict the degree of intoxication as this is not linearly related to plasma levels [9]. The nature of the interaction between the sedative effects of cannabis and general anaesthesia may not be easily predictable. There is a lack of data in humans but animal studies indicate that THC may prolong the sedative effect of general anaesthesia [10, 11]. Acute intoxication with agitation can be treated with benzodiazepines or, probably more safely, with alpha-2 agonists [12]. Smoking marijuana leads to a greater respiratory burden of carbon monoxide and tar than smoking a similar quantity of tobacco [13]; it is also claimed that it causes more airway irritation due to the higher temperature at which marijuana leaves burn [14]. Therefore, one should be prepared for dealing with airway complications such as bronchospasm. Recent inhalation of marijuana smoke before anaesthesia has been associated with uvular oedema [15]. Tachycardia is

probably the most common cardiovascular problem but postural hypotension may occur at higher doses. Seizures can also occur.

Cocaine

Cocaine is available as the hydrochloride salt that can be injected or snorted or as free base ('crack') which can be smoked. This drug inhibits reuptake of noradrenaline and dopamine in sympathetic nerve endings and in the brain to produce a feeling of excitement and pleasure. This accumulation of catecholamines at the nerve endings is also responsible for an array of cardiovascular side effects, including tachycardia, hypertension, arrhythmias and myocardial ischaemia. It may even precipitate myocardial infarction in up to 6% of patients presenting with chest pain [16]. At higher doses, it may cause depression of myocardial contractility. Fever may also be present, generated from a combination of altered temperature regulation, vasoconstriction and motor agitation. There is also a reduction in seizure threshold. The human liver combines cocaine and alcohol to produce a third substance, cocaethylene, which intensifies cocaine's euphoric effects and has a significantly longer duration of action compared with the parent compound [9]. Unfortunately, the prevalence of cocaine abuse in the young is astoundingly high, with 90% of female abusers falling within child bearing age [17]; thus, providing anaesthesia for the cocaine affected patient may not be a rare event.

It is advisable to control the patient's blood pressure before anaesthesia induction to avoid hypertensive responses to intense stimulation such as intubation. Preoperative control of anxiety by using benzodiazepines may help alleviate emotional stress. The choice of vasoactive agents is challenging. Beta-adrenoceptor antagonist use alone may not be effective as it may still leave unopposed alpha-adrenoceptor stimulation. Labetalol appears therefore to be a more logical choice but its use is also controversial as it is a relatively weak alpha-adrenoceptor antagonist. Vasodilators such as hydralazine result in reflex tachycardia, undesirable in the context of cocaine-induced tachycardia. The central sympatholytic and sedative properties of dexmedetomidine may make this drug a reasonable choice in this context. There have been a number of case reports where dexmedetomidine has been successfully used to manage hypertension and central nervous system (CNS) excitability from withdrawal of cocaine and opioids where other more traditional agents have failed [18]. Being a potent sympathomimetic, ketamine can potentiate the cardiovascular toxicity of cocaine. Temperature should be carefully monitored. Animal studies indicate that cocaine can increase the minimal alveolar concentration (MAC) requirement using halothane in rats and isoflurane in sheep [19, 20]. Anaesthesia for non-intoxicated patients with urine positive for cocaine metabolites appears to be safe if the QTc interval is less than 500 ms [21].

Regional anaesthesia may be difficult to perform in the cocaine abusing patient. Combative behaviour and altered sensorium may preclude one from obtaining informed consent or getting cooperation to perform certain blocks or procedures. Cocaine use can induce thrombocytopaenia [22] but a formal platelet count is probably unnecessary for an otherwise healthy cocaine user. Hypertension or hypotension may occur with the latter requiring direct vasopressors such as phenylephrine for control. There may be altered pain perception from changes in opioid receptor density [23].

Amphetamines

The term amphetamine is short for alpha-methylphenethylamine and these are essentially a group of indirectly acting sympathomimetic compounds with powerful CNS stimulating effects. Various compounds of abuse have been synthesised from this molecule with various substitutions. One of the better known drugs in this class is 'Ecstasy', the name of which can be a rather undifferentiated term used to describe several compounds related to MDMA (3,4 –methylenedioxymethamphetamine). Chemically they resemble adrenaline and dopamine which is reflected in their biological effects. Furthermore, the methylenedioxy (-O-CH2-O-) substitution on the aromatic ring confers properties akin to the hallucinogen mescaline [24]. Thus, the popularity of Ecstasy is its ability to elevate the user's energy levels in addition to enhancing mood with feelings of euphoria and empathy.

Methylenedioxymethamphetamine causes an acute increase in serotonin, noradrenaline and dopamine in synaptic junctions from both increased secretion and reduced reuptake. This leads to a depletion of stores that accompany the withdrawal of the drug. As these neurotransmitters are involved with the control of mood, thermoregulation, sleep and appetite, it explains the pleasurable and undesirable effects of Ecstasy. Typically it has an onset of an hour after oral ingestion with effects lasting 4–6 h, and a plasma half-life of around 7 h. Blood levels often do not correlate well with the severity of systemic effects. After withdrawal from Ecstasy, users may feel very tired and low and need a long period of sleep to recover. Major side effects include hyperpyrexia from over exertion or from central activation of heat generation and conservation mechanisms with consequent rhadomyolysis. There is some anecdotal evidence for the

use of Dantrolene to assist cooling [25]. Serotonin syndrome, hyponatraemia, isolated liver failure, cerebrovascular accident or sudden death may also be seen. Hyponatraemia results from excessive drinking of hypotonic fluids by users to prevent hyperthermia as well as increased antidiuretic hormone secretion [26]. Liver failure can occur as part of the multi-organ failure accompanying rhabdomyolysis or may be the result of an idiosyncratic immune-mediated reaction [27]. Serotonin syndrome may even cause hyperthermia in those who are not engaged in vigorous activity.

Toxic reactions should be managed with general supportive measures and careful monitoring of vital signs depending on stage of presentation. Life threatening and major cardiovascular metabolic disturbances should be attended to first, where possible, before administering general anaesthesia. The use of labetalol may be preferable over beta-adrenoceptor antagonists alone as the use of the latter results in unopposed alpha-1 adrenoceptor agonism. Judicious use of intravenous fluids is required as the hydration status of the patient may undergo rapid flux dependent upon pre-admission water consumption or activity and on-going body temperature elevation. Along the same lines, serum sodium should be closely monitored. A hyperadrenergic state accompanying acute amphetamine intoxication may increase MAC but chronic use may decrease it [28]. The patient's temperature must be carefully monitored. Hypotension may require direct acting catecholamines, like phenylephrine, but response may be unpredictable.

A diagnostic challenge occurs when hyperadrenegic states induced by acute amphetamine or cocaine intoxication presents in the late term parturient, the symptoms of which are difficult to distinguish from pre-eclampsia or eclampsia [29]. Liver and renal function tests and, where available, rapid urine screen for cocaine metabolites may aid in the differential diagnosis.

New psychoactive substances

Legal highs refer to substances with psychoactive properties which are not yet scheduled as controlled substances and therefore can be sold freely, either on the internet or by 'head shops'. They are new only in the sense that their potential abuse is newly discovered as some compounds have been in existence for many years. They can be marketed as bath salts or plant food and are usually marked 'not for human consumption' to avoid regulatory countermeasures. Although originating from a rather diverse background, as a group the members bear some chemical similarities to endogenous neurotransmitters such as dopamine or serotonin, or to existing drugs of abuse such as amphetamines [30]. They can be synthesised with relative ease from compounds, the majority of which can be obtained legally in reasonable quantities from commercial suppliers. As quality control is not a priority of recreational drug laboratories, toxic levels of these substances may be reached accidentally in consumers.

Cathinone compounds

One class of compounds to emerge among the designer drug scene early this millennium is the cathinone derivatives. Cathinone is a psychostimulant derived from fresh leaves of the khat shrub, a plant that is naturally found in Africa and the Arabian peninsula, where the practice of chewing these leaves to obtain a high has been around for many centuries. Just before the isolation of the active ingredient from the plant in 1930, two related synthetic compounds, ephedrone (methcathinone) and mephedrone (4 methylmethcathinone) were produced, the former being marketed as an antidepressant in the USSR [31]. Cathinone was only later isolated from khat in 1975, and the abuse potential of cathinone-derived products was soon recognised, leading to a number (but not all of) its related compounds being restricted.

Mephedrone had been popular among abusers and it is snorted or, more commonly, swallowed either neat or dissolved in a beverage to avoid nose burns. The duration of effect is 2–4 h after oral ingestion. From in vitro synaptosomal studies, cathinone-related compounds appear to augment the release of dopamine and noradrenaline [32]. They appear to have a more potent inhibitory effect on monoamine oxidase when compared with amphetamines but a less pronounced effect on serotonin release and reuptake.

Upon consumption, they produce psychostimulatory as well as hallucinogenic effects, with an accompanying peripheral cardiovascular effect attributable to sympathetic activation. In this way, their effects are somewhat similar to those seen with amphetamine use. The toxic consequences are therefore extensions of these pharmacodynamic properties and deaths have been attributable to their use.

Piperazine compounds

Similar to other 'designer' drugs, piperazine compounds began life as failed therapeutics. Originally developed as an antihelminth, it was later investigated as an antidepressant when its potential abuse was recognised because it has similar effects to amphetamines. Benzylpiperazine has a predominately dopaminergic effect causing the release of this neurotransmitter as well as serotonin from

neurons [33]. In vitro studies also suggest that it causes noradrenaline release from peripheral sympathetic nerve fibres. The other popular piperazine compound trifluoromethylphenylpiperazine acts more on the serotoninergic system by binding its receptors and inhibiting its reuptake. When taken together, it emulates the effect of Ecstasy. Like other designer drugs, the relationship between toxicity and dose is not always predictable [33].

Tryptamines

Understandably there are many gaps in the pharmacological and toxicological profiles of these compounds in humans, as the identity, purity, doses and time of ingestion by affected patients are not known. Therefore, the interaction these may have with anaesthesia is even more of an unknown quantity. However, a number of these agents mimic the actions of endogenous neurotransmitters as well as inhibiting their reuptake. It stands to reason that precautions similar to those exercised for patients on monoamine oxidase inhibitors, selective serotonin reuptake inhibitors or selective noradrenaline reuptake inhibitors, should be taken for patients suspected to have consumed these drugs. Their sympathomimetic effects render gauging depth of anaesthesia by purely haemodynamic means a difficult undertaking. Although depth of anaesthesia monitoring may theoretically mitigate some of this difficulty, the intrinsic effect of these stimulants on the processed EEG is not known. Having reuptake inhibitor ability, it is not known whether these agents accentuate endogenous catecholamine responses.

Recent developments in the general management of poisoning

Much of the acute management of poisoning occurs in the emergency department or intensive care unit and has been extensively covered in toxicology texts. In general, a high index of suspicion should be exercised, as history from the affected individual is not always available. Poisoning should be considered in any patient with inexplicable cardiac, respiratory or metabolic disturbance, especially when accompanied by unusual behaviour or altered sensorium. Irrespective of the substances ingested, the general steps of resuscitation, substance identification, reducing absorption, increasing elimination, specific treatment including antidote administration and supportive measures with a plan for on-going monitoring should be instituted.

Despite the best of general supportive measures, toxic levels of substances may be reached in some cases, potentially necessitating more invasive techniques for elimination. Substances amenable to removal by dialysis are generally those which are water soluble and small. However, most psychoactive substances are, by nature, lipid soluble to facilitate passage across the blood brain barrier. Since the introduction of intravenous lipid emulsion (ILE) as a rescue therapy for local anaesthetic overdose, there have been a number of reports of ILE improving level of consciousness after overdoses of psychotropic drugs thus averting the need for intubation and ventilation [34–36]. Of particular interest is a report of improvement in cardiovascular stability following ILE administration in a patient with cocaine overdose [37]. One of the proposed mechanisms of efficacy involves an expanded plasma lipid phase in reducing free drug levels. In vitro modelling studies predict that the more lipid soluble and the larger a drugs volume of distribution, the greater will be the decrease in serum concentration after lipid administration [38]. However, under certain animal experimental conditions, ILE can actually deepen the depth of thiopental-induced anaesthesia, thus challenging this simplistic view of ILE acting merely as a lipid sink [39]. A systematic review of the literature up to June 2009 drew similar conclusions of possibly some benefits of ILE in lipophilic drug overdoses based on mainly case reports and animal studies [40, 41]. There have not been reports of major adverse reactions among those studies reviewed. However, many undesirable effects of ILE are known when it is used as part of total parental nutrition but it is not likely that hypersensitivity would present following acute administration of ILE [42].

Another important aspect of managing psychostimulant toxicity is the symptomatic control of cardiovascular and CNS overstimulation. The use of the alpha 2 adrenoceptor agonist dexmedetomidine for alleviating withdrawal symptoms from sedative use has been widely reported. Its inhibitory effects on central sympathetic outflow have recently been exploited as a means of attenuating the acute sympathomimetic effects of cocaine use. Dexmedetomidine at 0.1 and 0.3 $\mu g.kg^{-1}$ was able to attenuate the increase in sympathetic nerve activation and skin vascular resistance in human volunteers receiving 2 $mg.kg^{-1}$ of intranasal cocaine [43]. Clinically, it has been reported to be used successfully in alleviating cocaine-induced hypertensive crisis in a patient with aortic dissection [44]. From the CNS point of view, dexmedetomidine has been shown experimentally to counter the decrease in seizure threshold from cocaine toxicity [45]. There is another report of dexmedetomidine use in the treatment of agitation accompanying overdoses of dextromethorphan and MDMA [46]. Thus, this drug has important advantages in the management of several aspects of stimulant overdose and acute withdrawal syndromes.

Conclusions

The true extent of poisoning with psychoactive substances remains undefined but is likely to be underestimated. A lack of quality control and changes in production techniques can yield illicit drugs with a high concentration of the active substance that, in turn, increases the potential for eliciting a greater severity of toxicity. This problem is widespread in society and indications are that new designer drugs are becoming increasingly available [6]. It is almost inevitable that many anaesthetists will be engaged in the care of those poisoned by these substances. The acute cardiac and cerebral toxicity associated with cocaine, amphetamines and cathinone derivatives are mainly attributable to elevated concentrations of catecholamines in nerve endings subsequent to enhanced release and reduced reuptake to various degrees. Haemodynamic instability and changes in anaesthetic and analgesia requirements are probably in those requiring surgery. While the toxicological profile of individual classes of poisons may appear discrete, it is also very important to be cognizant of the likelihood of co-ingestion of different substances, with the clinical picture being overwhelmed with one major substance, quite often alcohol. The use of intravenous lipid emulsion is showing promise in the treatment of drug overdoses. Dexmedetomidine has a promising role as it dampens sympathetic hyperactivity, is analgesic, produces sedation and relieves agitation without respiratory depression. However, further clinical experience with these agents is required to more clearly delineate indications for their use.

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