Amphetamines: An Update on Forensic Issues

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Abstract

Methamphetamine is currently enjoying a resurgence of popularity as a recreational drug. It presents a number of challenges to the forensic toxicologist both analytically and interpretively, and these latter interpretive issues are considered here. This review also discusses the current popular syntheses which account for the widespread domestic synthesis of the drug; the demographics of methamphetamine use in the United States as assessed from the Drug Abuse Warning Network (DAWN) data; developments in research of the neurotransporter pharmacology of the drug and its implications for interpretive forensic toxicology; the psychomotor effects of the drug and its potential for cognitive and functional impairment; interpretive issues related to postmortem blood drug concentrations and how these are impacted by evidence for incomplete distribution and the potential for postmortem redistribution; and, finally, concerns caused by designer methamphetamine analogues. All data indicate that methamphetamine and its analogues will present significant interpretive challenges to forensic toxicologists as the popularity of the drug continues to grow.

Introduction

Amphetamines have undergone cycles of popularity as recreational drugs in the United States and around the world (1)[1]. The current wave of popularity began in the mid 1990s, on the West coast of the United States, and had spread throughout the country by the end of the decade. Some recent data on the incidence of workplace drug test positives by zip code shows that the greatest incidence of amphetamine use is still concentrated in the western United States, but there are elevated incidences of use throughout the Midwest and the South[2]. In many jurisdictions, amphetamine has surpassed cocaine as the stimulant drug of choice among users.

This review considers current trends in the use of methamphetamine; recent advances in our understanding of its pharmacology, especially with respect to changes in brain chemistry; forensic issues, notably cognitive changes and their impact on driving and behavior; and the postmortem forensic toxicology of the drug. Finally, we discuss the increasing reports of intoxication and fatalities involving the methamphetamine analogues paramethoxyamphetamine (PMA) and 3,4-methylenedioxymethamphetamine (MDMA) or ecstasy.

Methamphetamine was first synthesized in Japan in 1919 by Ogata (2), patented in 1920, and later licensed to Burroughs Wellcome, who marketed it as Methedrine®, an anorectic, until it was taken off the market in 1968 because of problems with abuse. It is available in the United States today as Desoxyn®, and amphetamine is available as Adderall®. Both drugs are used for the treatment of attention-deficit disorder (ADD) and attention-deficit hyperactivity disorder (ADHD) in adults and children, narcolepsy, learning disorders associated with fetal alcohol syndrome, and pathological overeating, although there are now several effective, less addictive drugs available for this latter condition (3,4). Most amphetamine and methamphetamine use that comes to the attention of forensic toxicology laboratories, however, is illicit.

A major factor in the renewed popularity of the amphetamines is the ready availability of their manufacturing methods and procedures (syntheses) on the World Wide Web and in Internet discussion groups, coupled with the ready availability of precursors. Two methods of methamphetamine synthesis are currently favored. The first is a reduction of *l*-ephedrine or *d*-pseudoephedrine over red phosphorus with hydroiodic acid. The enantiospecific product with either precursor is *d*-methamphetamine, with yields of 54–82%. The red phosphorus is obtained from matchbook striker plates or road flares, and although the sale of hydroiodic acid is now restricted, it can be synthesized with little difficulty from iodine. Substituting phenylpropanolamine as the precursor results in the synthesis of *d*-amphetamine. This is significant to the toxicologist because the presence of both amphetamine and methamphetamine in a blood or urine sample may result from the ingestion of an illicit batch made using a mixture of starting materials. For this reason it cannot be generally assumed for interpretive purposes that any amphetamine present in a sample resulted from metabolism, and therefore as a basis for estimates of time since last use. The second popular methamphetamine synthesis also results in an enantiospecific product, and involves the reduction of the same *l*-ephedrine, *d*-pseudoephedrine, or phenylpropanolamine precursors, using either sodium or lithium metal in condensed liquid ammonia. The lithium can be obtained from lithium batteries, sodium from electrolytic reduction of molten sodium hydroxide, and liquid

[1] See http://www.nida.nih.gov/Infofax/nationtrends.html.

[2] See http://www.questdiagnostics.com/corporatehealth/news/dti.htm.

ammonia from agricultural sources or specialty gas suppliers. Yields are comparable to the prior method. The ready availability, high purity, and potency of these products account in great part for their renewed popularity. Furthermore, both syntheses result in the enantiomerically pure *d*-isomer, which is several times more centrally potent than the *l*-form, or a racemic mixture, making the synthetic product more potent than in previous eras of popularity. The toxicity of chemicals in the laboratories where the drug is manufactured is generally related to risk of chemical burns from acids, bases, and liquid ammonia, as well as fire and explosion risks from various solvents (5).

Demographics

Prevalence of the use of the drug can be evaluated anecdotally from the experience of forensic toxicologists engaged in workplace drug testing, human performance testing, or coroner and medical examiner toxicology. In spite of limitations in the methods used for data collection, the Drug Abuse Warning Network (DAWN)[3] data sets collected from hospital emergency departments and from coroner and medical examiners offices are instructive. The DAWN Emergency Department data are collected from 21 major cities and a national panel of 500 regional hospitals outside major metropolitan centers. For 1999, this data set indicates than nationwide, methamphetamine/speed was mentioned in 2% of drug-related emergency admissions. This was a decline from 11,500 mentions in 1998 to 10,000 in 1999; however, this change was not statistically significant. Changes in incidence in individual cities were significant, however, showing increases in incidence of 58% and 33%, respectively, in St. Louis and Seattle and decreases of 49%, 46%, 24%, and 19%, respectively, in Atlanta, Dallas, Phoenix, and San Diego. Two thirds of cases collected came from areas outside of major cities, whereas 80% of the cases in the 21 DAWN cities came from five major western cities: Seattle, San Francisco, Los Angeles, San Diego, and Phoenix. This suggests a pattern of spread of the drug eastward across the United States and from the cities into more rural areas.

A preliminary report of the 2000 data from the Community Epidemiology Workgroups (CEWG) notes a rebound in methamphetamine emergency room mentions, particularly on the West coast, and confirms the move of the drug to areas outside of the major cities in areas including Seattle (6).

DAWN recently released the medical examiner data set for 1999, which reflects a similar pattern[3]. These data were collected from 42 major metropolitan areas nationwide and collates reports of drug-caused and drug-related deaths. Nationally, total drug abuse deaths increased 5% between 1997 and 1998 and 15% from 1998 to 1999. Also, while the incidence of mentions of methamphetamine/speed declined 20% between 1997 and 1998, they increased 38% between 1998 and 1999. As a class, amphetamine use still ranked sixth among drugs mentioned in 1999, up from ninth in 1998, and was present in 4.95% of all reported drug-caused or drug-related deaths in 1998 and in 5.92% in 1999. In many individual cities, the rates were much higher than the national average. In 1999, methamphetamine was the second most frequently detected drug in Oklahoma City, identified in 23% of drug-caused or drug-related deaths. Other cities reported rates as follows: San Diego, 25%; Las Vegas, 18%; Salt Lake City, 16%; Phoenix, 17%; San Francisco, 16%; and Seattle, 12%. There were some significant differences in the demographics of the methamphetamine/speed class, being ranked the sixth most frequent drug in white decedents (present in 5.9% of drug-caused and drug-related deaths), fifth among Hispanics, but unranked (< 15th at 1.3%) among blacks.

Taken together, these data sets support the proposition that the major metropolitan areas in the West are probably saturated with methamphetamine and that continued growth in use of the drug will occur in more rural, and from a public health perspective, less-studied areas of the country (7). Consequently, this is an important drug class to consider in any death investigation or emergency treatment analytical scheme, regardless of the jurisdiction in which the case occurs.

Consistent with the DAWN and CEWG data, our own work suggests that methamphetamine is favored predominantly by white males aged 21–37 years of age (8,9). Simon et al. (10) have reported on the demographics of a group of active single-drug methamphetamine users in southern California. Their mean age was 32 (± 8.25), and they were predominantly Caucasian (85%), but divided about equally between men and women. The majority of these users were using the drug daily; 39% were using four or more times daily, using a mean amount of 0.72 g/day (0.03–3.5). The majority used the drug by snorting (72%) or smoking (70%), with 78% reporting that the drug "goes with sex" as a motivation for use.

Pharmacology

Amphetamines act both centrally and peripherally, with both sites being significant from a forensic perspective. Consistently present side effects resulting from peripheral stimulation include increased pulse and blood pressure and pupillary dilation. Centrally, the stimulant effects of the drug are significant, resulting in excitation, increased alertness, anorexia, and locomotor stimulating effects leading to hyperactive reflexes and ataxia.

Stimulants work centrally by increasing the dopamine concentrations in the synaptic cleft. In contrast to cocaine, which does so by blocking the reuptake of dopamine into the presynaptic neuron, the amphetamines stimulate presynaptic production and release of dopamine into the cleft. In rodents and primates, high- dose methamphetamine administration leads to decreases in brain levels of dopamine and serotonin (5-HT) and a reduction in the activity of their respective synthetic enzymes tyrosine dehydroxylase and tryptophan hydroxylase. Recent work has shown that after both acute and chronic administration of methamphetamine in an in vitro system, methamphetamine caused a decrease in striatal uptake of dopamine and 5-HT as soon as 30 min after exposure (11,12). This effect was reversible and persisted less than 24 h. Washing the drug out of the

[3] Available at http://www.samhsa.gov.

synaptosomes failed to extinguish the effect. These findings are most readily explained by a reversible modification to the structure of the dopamine and 5-HT transporters. Methamphetamine promotes the formation of reactive oxygen species to which aminergic transporters are known to be susceptible. Even after chronic administration in their model, the transporter activity returned after 24 h, but declined again after eight days, suggesting a second distinct effect, that of neurotoxicity and associated terminal degeneration. Further studies showed that other transporter systems are also affected (13). Norepinephrine uptake was also shown to be inhibited by methamphetamine administration; however, washing residual methamphetamine out of the cell preparations eliminated this effect. This suggests that the mechanisms affecting norepinephrine are distinct from those affecting dopamine and 5-HT. Gamma-aminobutyric acid (GABA) reuptake was found not to be affected by methamphetamine administration.

Gygi et al. (14) have further explored the molecular basis for development of tolerance to methamphetamine effects. They demonstrated that following a subsequent high-dose methamphetamine challenge, methamphetamine concentrations in the brains of rats receiving a long-term methamphetamine pretreatment were decreased compared to non-exposed animals. In contrast, the plasma methamphetamine concentrations in the exposed animals were higher than in the non-exposed animals following the same challenge. These findings suggest that tolerance is not principally due to enhanced metabolism or increased renal clearance of methamphetamine. Overall, there was a fourfold change in distribution between brain and plasma ratio of methamphetamine suggesting the existence of an active transport mechanism for methamphetamine, which is inhibited by chronic exposure. Interestingly, there was no cross-tolerance between methamphetamine and cocaine, suggesting a specific transporter may be at work. This is confirmed by other workers. Using a rat model, Riviere et al. (15) have shown that methamphetamine effects are not reliably predicted from serum concentrations. In the first hour following intravenous administration, they found that brain methamphetamine concentrations were eightfold higher than in the serum.

These findings are important in forensic toxicology because they raise questions about the strict interpretability of blood or serum methamphetamine concentrations and the possibility of relating these to behavioral effects or in predicting toxicity when neither the dose, duration of administration, nor time since last ingestion are typically known with any accuracy.

Forensic Issues

Three significant forensic issues are considered here: intoxication, behavioral effects, and death. Undeniably, amphetamines alter the function of a number of physiological systems and can put sufficient stress on these systems resulting in injury or death. They are also mind-altering drugs, and hence their voluntary ingestion has implications for activities requiring both application of community standards of behavior and situation-appropriate decision-making. Their voluntary use under these situations introduces both criminal and civil liability for the user. Their toxic effects, acting on organ systems including the heart and brain, can result in tissue damage, arrhythmia, tachycardia, and hypertension, any of which can be further exacerbated by pre-existing medical conditions, making even low-dose recreational drug use a life-threatening event. Rhabdomyolysis is also associated with chronic methamphetamine use (16), but importantly cannot be established postmortem because of perimortem tissue changes and degradation. Chronic stimulation results in sleep loss with associated exhaustion and sleepiness, anxiety, irritability, exhaustion, depression, confusion, suspiciousness, paranoia, delusions, hallucinations, irrational behavior, and diminished attention and concentration. Overlaid on this is a change in values, self-perception, and self-image, along with increased willingness to accept risk, poorer psychomotor performance, and conversely, a perception of improved performance (8).

Recreational users are de facto engaging in illegal and felonious activity, in which context the possession and use of weapons is common. When coupled with the paranoia and delusions associated with the drugs, this often results in violence (17,18). Ellinwood describes 13 cases of murder committed by subjects using amphetamines (19). The murders appear related to amphetamine-induced paranoid thinking/delusions, panic, emotional lability, and lowered impulse control, triggered by a specific situation leading to violence. Ellinwood noted that there are many cases of individuals under the influence of the drug in which "murder or mayhem are avoided by the slimmest of margins" (19).

Admissions to emergency rooms also indicate violence as a consistent factor in this group (20–22). Among the same group there is a strong association between high-dose or high-intensity amphetamine use and the development of psychotic states with paranoia, delusions, and pseudohallucinations.

Low-dose therapeutic administration of amphetamines for the conditions listed earlier most likely do not have a profoundly impairing effect on an individual in stable, monitored therapy. Deviations from a prescribed course, however, whether in terms of size or frequency of dose, duration of therapy, or combination with other drugs, may lead to many of the symptoms experienced by recreational users as outlined in the prior section. Based on clinical literature, normal therapeutic use would involve the administration of 20 to 40 mg/day in divided doses, although some treatment protocols have gone up to 60 mg (23), and clinicians may exceed this based on the refactoriness of the patient's condition. Individuals receiving this or higher doses are likely to experience some disorientating excitatory effects that can lead to impairment. Even so, therapeutic use rarely approaches rates of use reported by a group of 65 current users, whose mean daily dose was 720 mg, with one user reporting up to 3.5 g (10).

A recurring issue with amphetamines is their impact on psychomotor performance and cognitive ability, particularly as it relates to driving, and the associated civil and criminal liability. In a timely effort to collect data on this cognitive impairment issue, Simon et al. (10) conducted a series of tests of cognitive performance in a group of 65 active methamphetamine users. These workers have reported a generalized decline in cognitive perfor-

mance across a number of measures as an effect of long-term use. This is in marked contrast to improvements in cognitive performance reported in older literature based on low acute doses of amphetamines (24). These findings, particularly impairment in the ability to focus on the task-at-hand and in the ability to filter and to ignore extraneous information, provide additional mechanisms for driving impairment and over and above fatigue and sleepiness, which have been proposed elsewhere (8).

Amphetamines have directly caused a number of deaths, and contributed to many more, as reflected in the DAWN data discussed earlier. We have reported elsewhere on the cause and manner of death in a series of 146 deaths involving methamphetamine (9). Deaths were attributed to methamphetamine alone with concentrations as low as 0.09 mg/L in the absence of any other risk factors (median 0.96 mg/L, $n = 13$). In these cases, the mechanism is most likely stimulant-induced arrhythmia, although stroke, aortic dissection, and berry aneurysm are also frequently encountered. In addition, 15% of methamphetamine deaths were traffic fatalities, and the significance of this is discussed later. When methamphetamine is used in combination with other drugs, median concentrations in drug caused deaths were lower (0.37 mg/L, $n = 25$), as might be expected. Median concentrations were also lower (0.36 mg/L, $n = 14$) in patients with cardiac risk factors, reflecting the increased risk those individuals assume when ingesting methamphetamine. A report of 15 cases of methamphetamine deaths from Japan reached similar conclusions (25). In both studies, however, there was a considerable range of methamphetamine concentrations in the deaths and significant overlap between those cases where the death was attributed to the drug and cases where the death was clearly due to other causes (falls, trauma, gunshots, etc). Survival after highly elevated methamphetamine concentrations (9.5 mg/L) has also been reported (26).

There are a number of emerging indicators that blood drug concentrations should be interpreted with caution, including studies of postmortem distribution and redistribution of methamphetamine. In 1993, Miyazaki et al. (27) reported on the distribution of methamphetamine in blood from various sites in eight individuals. In the subjects they considered, methamphetamine concentrations in blood from the left heart were consistently 1.9–2.6 times higher than in the right heart. In three cases, they also examined pulmonary vein blood and noted these concentrations were higher than in blood from any other site examined. Barnhart et al. (1999) reported that the heart blood (site unspecified) methamphetamine concentrations were consistently higher than the femoral blood concentrations in 20 methamphetamine-related deaths (28). The authors attributed those differences to postmortem redistribution from the myocardium. Moriya and Hashimoto (29), responding to Barnhart et al., argued that redistribution from the myocardium would affect the left and right heart concentrations equally, and they propose redistribution occurs from the pulmonary circulation and support this with some animal and human data. In summary, there is evidence for site-dependent differences in concentrations of methamphetamine, and this factor should be considered in interpreting the results. As recommended elsewhere, peripheral blood should be used whenever possible in postmortem forensic toxicology (30).

When taken together, factors such as the potential for incomplete distribution, redistribution, and changes in distribution and uptake based on tolerance and prior exposure provide additional grounds for exercising caution in the strict interpretation of quantitative blood methamphetamine results.

Amphetamine Analogues

Amphetamine analogues will be one of the emerging challenges both analytically and interpretively for forensic toxicologists. There are hundreds of possible modifications to the basic amphetamine structure which retain or modify the stimulant effects of the parent compound. The diversity of these compounds can result in a failure to identify them or recognize them for what they are. A number of analytical schemes for the identification of amphetamines and their analogues have been published recently (31–34). Currently most popular among these analogues is MDMA (Ecstasy), which emerged as a major recreational drug in Europe some time ago, and is becoming more popular in the United States. Its synthesis is straightforward, starting with saffrole isolated from sassafras root bark. This is converted to isosaffrole with base and then oxidized to methylenedioxy phenyl-2-propanone, which is converted by reductive amination to MDMA.

MDMA has become popular for its so-called entactogenic and empathogenic effects. MDMA in low to moderate doses (50–200 mg) produces mild intoxication, euphoria, an increase in physical and emotional energy, a great sense of pleasure, and increased sociability. Muscular effects are frequent, including jaw clenching and deep tendon reflexes. These effects generally dissipate within 24 h; however, muscle tension in the jaw, fatigue, depression, anxiety, and insomnia tend to persist (35–38). As with methamphetamine, these effects raise the issue of intoxication and its consequences for driving or other psychomotor tasks. There are numerous reports of MDMA use as a factor in motor vehicle crashes, and these have been reviewed elsewhere (39).

MDMA has also been implicated in a number of deaths, where factors such as high ambient temperature, elevated drug concentrations, physical exertion, and dehydration lead to hypertension, arrhythmia, and death. Excessive hyperthermia (> 107°F) is attributed to disruption of central neurotransmitter-mediated thermoregulatory control (36,40,41).

Finally, there have been a series of reports of other substances being sold as MDMA, including most notoriously, PMA. This substance lacks the entactogenic effects of MDMA, leading to hyperdosing in pursuit of the same "high". The drug, however, causes extreme hyperthermia, which when coupled with the often-hot atmosphere of the venue, dehydration, and strenuous physical activity, has led to deaths (42–44). These initial reports documented 16 deaths in Australia associated with this drug, and it has recently been linked to a further series of deaths in Florida, Illinois, and the Midwest, where tablets carrying the 3-diamond "Mitsubishi" logo were sold as MDMA while actually containing PMA.

A single death from another analogue compound, 4-methylthioamphetamine (4-MTA, "Flatliner") was reported last year (45).

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