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Involvement of Amphetamines in Sudden and Unexpected Death

ABSTRACT: In the present study, the effects of amphetamine-class drugs were examined in cases reported to the Victorian coroner from 2001 to 2005 to determine if death can occur from the use of amphetamine-class drugs alone. A total of 169 cases were reviewed where a forensic autopsy detected amphetamine(s) in the blood. Pathology, toxicology, and police reports were analyzed in all cases to ascertain the involvement of amphetamine-class drugs in these deaths. In Victoria, methamphetamine (MA) is the principal abused amphetamine-class followed by methylenedioxymethamphetamine (MDMA). There were six cases in which a cerebral hemorrhage caused death and three cases in which serotonin syndrome was established as being caused by the interaction of MDMA and moclobemide. There were 19 cases in which long-term use of amphetamines was associated with heart disease. There were three cases where amphetamine-class drugs alone were regarded as the cause of death, of which two cases exhibited high levels of MDMA and lesser amounts of MA and/or amphetamine. There were no cases in which significant natural disease was absent and death was regarded as caused by the use of MA. There was no correlation between blood concentration of drug and outcome.

KEYWORDS: forensic science, forensic toxicology, amphetamines, speed, ecstasy, multiple drug use, cardiovascular disease, sudden death, serotonin syndrome, fatal hemorrhage

Amphetamine-class drugs are synthetic amines with sympathomimetic activity in the peripheral and central nervous systems. They include methylenedioxymethamphetamine (MDMA), methamphetamine (MA), methylenedioxyamphetamine (MDA), para-methoxyamphetamine (PMA), and methylenedioxyethylamphetamine (MDEA). Amphetamine-class drugs dramatically increase sympathetic stimulation and circulating levels of neurotransmitters in the periphery, initiating a series of neurochemical changes that can lead to neurotoxicity and sudden death (1).

Desired psychological effects include euphoria, extroversion, and motivation, but these are often accompanied by acute psychotic problems, cardiac, cerebral, and hepatic toxicity (2). The severity of effects is determined by the drug(s) involved, the frequency and environment of use and the presence of tolerance and genetic variability with respect to drug sensitivity and pharmacokinetics (3).

Ecstasy (MDMA) has frequently been reported to cause death, often through the development of malignant hyperthermia or liver damage (4–8). While most cases involve a combination of drugs, deaths from MDMA alone are known (2). Other designer amphetamine-class drugs such as PMA (9–13), MDEA (8,14–17), and 4-methylthioamphetamine (15) have also been reported as causing death. Reports also indicate an increasing number of deaths associated with MA (9,11,18–20).

Prevalence of amphetamine-class drugs in Australia is relatively high. Lifetime admissions of the use of amphetamines and MDMA in persons over 15 years of age are at about 4.0% and 3.4%, respectively (21). Furthermore, ecstasy and designer drug use increased from 1.1% in 1991 to 2.9% in 2001 and amphetamine use increased from 2.6% in 1991 to 3.4% in 2001 (22). Not surprisingly, amphetamine-class drugs are also frequently detected in coroner's cases (up to 7% in drug deaths) (23). However, it remains unclear whether amphetamine-class associated death can occur in the absence of other contributing factors. This study examined 5 years of data (January 2001–December 2005) to determine if people can die from misuse of amphetamine-class drugs alone or whether other factors, such as other drugs or natural disease, are required to cause death.

Methods

Background

The subjects were autopsied at the Victorian Institute of Forensic Medicine (VIFM) during 2001–2005 to obtain information on the manner and cause of their unexpected death. Autopsy included a full macroscopic and microscopic examination of all major organs, and collection of body fluids and tissues for comprehensive toxicological analysis which is designed to indicate the presence of alcohol, drugs of abuse, and a long list of prescription or over-the-counter drugs. This testing included all common amphetamine-class drugs. Femoral blood was taken in most cases (approximately 85% of Group A cases) to reduce artifactual change in blood concentration because of postmortem redistribution (24). Cavity blood samples were analyzed in several cases where a peripheral sample was not available.

Data Collection

Case details including toxicology, pathology and police reports, and coronial findings are available on the VIFM case management system. Coronial cases of deceased males and females of all ages, ethnicities, and locations throughout metropolitan and rural Victoria

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TABLE 1—*Categorization of amphetamine group cases.*

Group	Cause of Death	Drugs Involved
A1	Hemorrhage and presence of amphetamines	Amphetamines and no other significant drug
A2	Amphetamine toxicity and heart disease	Amphetamines and no other significant drug
A3	Amphetamine toxicity leading to serotonin syndrome	Amphetamines and other significant serotonin active drugs
A4	Amphetamine toxicity	Amphetamines only
B	Drug overdose	Death caused predominantly by drugs other than amphetamines
C	Mechanical injury	Amphetamines and other drugs

are included in this database. Comprehensive database searches were conducted to obtain all cases in which amphetamine-class drugs were identified by routine toxicological testing of postmortem samples from January 2001 to December 2005. Only those cases in which amphetamine-class concentrations were quantified (more than 0.05 mg/L) were included as cases of interest. The cases were reviewed for postmortem amphetamine-class drug concentrations, co-associated drugs, pathology findings and circumstances.

In addition amphetamine-class positive cases were also searched on the National Coroners Information System (NCIS) database for Victorian cases. The NCIS is a national internet-based data storage and retrieval system for Australian coroners' cases (25). Information concerning every death reported to an Australian coroner since July 2000 (January 2001 for Qld) is stored within the system.

Cases were placed into three categories based on the relative contribution of amphetamine-class drugs to the death compared to the other primary drugs. Concentrations used to assess likely significance were obtained from the following references (23,26). In cases where one or more drugs were present in potentially toxic concentrations, those detected in "therapeutic" concentrations were not regarded as having a significant contribution to death. For example, where 2 mg/L of MA was detected concomitantly with 0.02 mg/L of diazepam, MA was considered to be the main contributor to toxic effects and diazepam was considered to be an incidental finding (23,26). Considering many amphetamine-class drug users often administer a range of prescribed and illicit drugs, the presence of incidental concentrations of a variety of drugs was a common finding in this study.

In Group A cases, amphetamine-class use either was associated with some form of natural disease (sub-categories A1: hemorrhage and A2: heart disease); was associated with a known drug interaction (A3: serotonin syndrome); or was regarded as a direct cause of death (sub-category A4). In Group A cases, drugs other than amphetamine-class drugs were regarded as incidental findings (except for sub-category A3) and were not regarded as a significant drug contributor to death (i.e., presence of low concentrations of other drugs relative to their pharmacological potency). See Table 1 for summary of classifications.

In Group B cases, the "other" drugs were present at toxic levels and were regarded as a substantial drug factor in death (i.e., the use of heroin with death occurring shortly after injection, or a suicidal drug overdose other than an amphetamine). Group C cases were those involving death from other causes but where amphetamine-class drugs were detected, i.e., vehicular deaths, hangings, etc.

An ideal control group was not feasible in this study. Coronial cases present a sub-set of deaths and in no way represent a randomized population that is required for an appropriate comparison. Furthermore, the mechanical injury deaths (category C) involved amphetamine-class users and thus it would be impracticable to predict whether these users may have developed some form of natural disease at a later stage, had they not died due to external causes.

Statistical Analysis

Comparisons among groups were calculated with the Mann–Whitney rank-sum test, and correlations were estimated using the Spearman Rank Order Correlation by the coefficient of determination (r^2). Further analysis was performed using multiple linear regression (MLR) to find a model and association within the variables. All tests were two-tailed, and conducted with the SIGMASTAT package (software release Version 3.0). $p < 0.05$ was considered statistically significant.

Ethical Review

The study was approved by the Department of Justice committee on human experimentation (national). (Ethics approval number EC0632/2006.)

Results and Discussion

The total number of cases identified that had one or more amphetamine-class drugs detected at autopsy was 169. There was a rise in the number of these amphetamine-class positive deaths annually over the 5 years; increasing from 27 cases in 2001 to 46 cases in 2005. With the exception of 40 cases,[1] a full autopsy was conducted with an associated full complement of routine tests including full toxicology.

Thirty-eight patients were women (22.5%). This was consistent with published data on the distribution of gender in Australian amphetamine-class users which indicates higher use in males. The average age of all users (32 years) was slightly higher than the reported mean user age for Australian users of illicit drugs (21) and deaths associated with illicit drugs (11,19,27).

Toxicology Results in Group A Cases

Group A cases was the cohort of most interest to this study. The age, gender, pathology, and toxicology findings, site of blood collection, and known length of use of amphetamine-class drugs of the 31 deceased persons in this category are shown in Table 2.

There were six cases in which a hemorrhage was found in the brain (sub-category A1). These included subdural or subarachnoid, berry aneurysm or ruptured internal carotid artery aneurysm. Two of the cases also had some form of heart disease at death. All of these cases were associated with MA (median 0.4 mg/L, range 0.2–5.6 mg/L) and one primarily with MDMA (0.2 mg/L) and a trace of MA (<0.05 mg/L). In four cases, the history was

[1]These cases did not receive a full autopsy upon successful objection by senior next of kin as provided by Section 29 of the *Coroners Act 1985 (Vic).*

TABLE 2—*Details of the 31 Group A (amphetamine-caused) deaths.*

Case	Year	Sex/Age	Cause of Death/Autopsy Findings	Toxicology*	Duration of Drug Use†	Admin. Route	Specimen Type
A1: Hemorrhage and presence of amphetamines							
1	2003	M/56	**Subarachnoid hemorrhage** **Ruptured internal carotid artery aneurysm** (no autopsy due to objection)	MA 0.2	>5 years	i.v.	Plasma (antemortem hospital sample)
2	2003	M/44	**Methamphetamine toxicity** Coronary artery disease (90% LAD) Partial brain hemorrhage	Amphetamine 0.5 MA 5.6 Ethanol 0.03	>10 years	p.o.	Blood cavity
3	2003	F/30	**Subarachnoid hemorrhage** **Ruptured right middle cerebral artery aneurysm** Heart globular contour Cardiac hypoxic damage Pulmonary edema	MA 0.2	7 years	i.v.	Femoral blood
4	2004	M/46	**Unascertained, but likely to be related to amphetamine use** Epilepsy Diabetes mellitus Hepatitis C Pulmonary edema Enlarged spleen (300 g) Minor acute subarachnoid hemorrhage Thin chronic subdural hematomas Thrombocytopenia	MA 1.6 Amphetamine 0.1	Unknown	Unknown	Femoral blood
5	2005	M/19	**Acute subarachnoid hemorrhage** **Ruptured berry aneurysm** Cardiomegaly (531 g) Heart globular outline Enlarged liver (3217 g) Pulmonary edema	Amphetamine 0.02 MA 0.02 MDMA 0.2 MDA 0.03	Unknown	p.o.	Femoral blood
6	2005	F/16	**Hemorrhage from cerebral arteriovenous malformation** Nephrotic syndrome	MA 1.4	>5 years	p.o.	Blood cavity
A2: Toxicity associated with amphetamines and no other significant drug present plus heart disease							
7	2001	M/37	**Ischemic heart disease** **Left ventricular hypertrophy** Cardiomegaly (545 g) Coronary artery disease (90–95% lumen) Scarring of ventricular myocardium Atheromatous streaks on carotid arteries Hepatitis C	MA 0.8 Amphetamine 0.1 Fluoxetine 0.2	>20 years	i.v.	Femoral blood
8	2001	M/23	**Combined drug toxicity** Coronary artery disease (95% LAD) Acute thrombosis Cardiomegaly (458 g) Congested lungs	MA 0.14 MDMA 0.05	>5 years	p.o.	Femoral blood
9	2001	F/21	**MDMA toxicity** Probable cardiac arrhythmia (reported by pathologist at autopsy) Mild myocardial fibrosis Congested lungs	MDMA 0.5	>5 years	p.o.	Femoral blood
10	2001	M/25	**Combined drug toxicity** Contraction band necrosis Cardiomegaly (390 g) Mild brain edema Liver congestion Pulmonary edema Enlarged spleen (480 g)	MA 0.3 MDMA 1.3 Pseudoephedrine 0.2	>2 years	p.o.	Femoral blood
11	2002	M/44	**Toxicity to amphetamines** Coronary artery disease (80% LAD, 60–70% RCA) Pulmonary edema Hepatitis C	MA 0.5	>5 years	i.v.	Femoral blood
12	2003	M/30	**Combined effects of drugs** Coronary artery disease (80% LAD, 50% RPP, minor LCV) Cardiomegaly (620 g) History of cardiac dysrhythmia	MA 0.1 MDMA 0.1 Ethanol 0.05	>3 years	p.o.	Femoral blood
13	2004	F/47	**Myocardial ischemia and fibrosis** Cardiomegaly (470 g) Contraction band change Pulmonary edema	Amphetamine 0.2 THC 6	>20 years	p.o.	Femoral blood

TABLE 2—*Continued.*

Case	Year	Sex/Age	Cause of Death/Autopsy Findings	Toxicology*	Duration of Drug Use†	Admin. Route	Specimen Type
14	2004	M/42	**Coronary artery disease (90% LAD)** Cardiomegaly (630 g)	MA 0.09 Amphetamine 0.04	Unknown	Unknown	Femoral blood
15	2004	M/40	**Coronary artery disease (50–95% LAD, 20% RCA and LCV)** Cardiomegaly (575 g)	MA 0.4	>3 years	p.o.	Femoral blood
16	2004	M/24	**Toxicity to amphetamines** Cardiomegaly (440 g) Meningeal congestion and edema Pulmonary edema	MA 0.1 MDMA 2.6 MDA 0.1 Moclobemide 0.7	>5 years	p.o.	Femoral blood
17	2004	F/40	**Toxicity to amphetamines** Pneumonia Enlarged spleen (470 g) Pulmonary edema	Amphetamine 0.06 MA 0.6	>5 years	i.v.	Femoral blood
18	2004	M/21	**MA Toxicity** Brain edema (1540 g) Vascular congestion Inflammatory infiltrates within myocardium Pulmonary edema	MA 6.8 Amphetamine 0.6	>2 years	p.o.	Femoral blood
19	2005	M/49	**MA toxicity** Ischemic heart disease Coronary artery disease (75% LAD, 75% RCA, 50% LCV) Cardiomegaly (530 g) Pulmonary edema Hepatitis C	MA 60 Amphetamine 0.02	>13 years	i.v.	Femoral blood
20	2005	M/33	**Toxicity to amphetamines** Cardiomegaly (490 g) Fatty liver, enlarged (3670 g)	MA 0.2 Amphetamine 0.06	Unknown	Unknown	Femoral blood
21	2005	M/50	**Toxicity to MA** Coronary artery disease (75% LAD) Emphysema	MA 0.02 THC 14	Unknown	Unknown	Femoral blood
22	2005	F/42	**Cardiomyopathy** Pulmonary edema Hepatitis C	MA 0.04 Diazepam 0.4 THC 4	>5 years	i.v.	Femoral blood
23	2005	M/28	**Toxicity to amphetamines** Epilepsy Arteriovenous malformation adjacent to corpus callosum Cardiomegaly (495 g)	MA 0.7 Amphetamine 0.2	Unknown	Unknown	Femoral blood
24	2005	M/40	**Coronary artery disease (90% LAD)** Pulmonary edema	MA 0.16 MDMA 0.16 MDA 0.02	Unknown	Unknown	Femoral blood
25	2005	F/34	**MA toxicity** Cardiomegaly (400 g) Pulmonary edema Wolf-Parkinson-White Syndrome Cerebral edema Hepatitis C	Amphetamine 0.04 MA 0.44 THC 6	Unknown	i.v.	Blood cavity
A3: Amphetamines plus serotonin syndrome							
26	2002	M/31	**Mixed drug toxicity** Focal contraction band necrosis Brain edema Cardiomegaly (315 g) Serotonin syndrome Edematous, hemorrhagic lungs Hepatitis C	Amphetamine 0.06 MDMA 1.7 MDA 0.1 Moclobemide 0.3 THC 6	>15 years	p.o.	Femoral blood
27	2004	M/24	**Mixed drug toxicity** Coronary artery disease (95% LAD) Mild cardiomegaly (338 g) Serotonin syndrome Liver congestion	Amphetamine 0.02 MA 0.2 MDMA 1 MDA 0.04 Moclobemide 15	>3 years	p.o.	Femoral blood
28	2005	M/45	**Mixed drug toxicity** Cardiomegaly (460 g) Coronary artery disease (75% LAD) Serotonin syndrome Pulmonary edema	MA 0.12 MDMA 2.0 MDA 0.07 Moclobemide 8.7	>5 years	p.o.	Femoral blood
A4: Amphetamine toxicity alone							
29	2001	F/36	**Amphetamine toxicity**‡ Brain edema (1255 g) Pulmonary edema	Amphetamine 0.1 MA 5.3	<5 years	p.o.	Femoral blood

TABLE 2—*Continued.*

Case	Year	Sex/Age	Cause of Death/Autopsy Findings	Toxicology*	Duration of Drug Use†	Admin. Route	Specimen Type
30	2002	M/30	**Toxicity to amphetamines** Hepatitis C	Amphetamine 0.2 MA 0.2	>5 years	i.v.	Femoral blood
31	2003	M/32	**Toxicity to amphetamines** (Decomposition)	MDMA 93 MDA 1 MA 0.4 Amphetamine 0.1	>14 years	p.o., i.v.	Blood cavity

Causes of death are highlighted in bold.

Cardiomegaly determined by comparison with average human heart weight for age and size (controls) (34).

M, male; F, female; MA, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine; THC, tetrahydrocannabinol; THC-COOH, tetrahydrocannabinol carboxylic-acid; i.v., intravenous administration; p.o., oral/nasal administration; LAD, left anterior descending; RCA, right coronary artery; RPP, right proximal portion; LCV, left circumflex vessel.

*Concentrations in mg/L, except ethanol g/100 mL & THC ng/mL.

†Duration of drug use and administration route determined by information gathered from police and medical reports and witness statements.

‡"Amphetamine" toxicity refers to amphetamines collectively as a class of drugs, rather than amphetamine the drug, as being responsible for the cause of death (reported by the pathologist).

sufficiently detailed to establish that amphetamine use had occurred for at least 5 years. The age range was 16–56, median 37 years.

There were 19 cases identified in the setting of amphetamine-class abuse in which the cause of death was regarded as being wholly or substantially attributed to amphetamine-class use in association with one or more forms of heart disease. These included cardiomegaly ($n = 8$), coronary artery disease ($n = 9$), fibrotic changes or conduction band defects ($n = 2$), left ventricular hypertrophy ($n = 1$), hypertrophic cardiomyopathy ($n = 1$), or presence of inflammatory infiltrates ($n = 1$). Methamphetamine was present in 17 of these cases and was frequently associated with smaller amounts of amphetamine as probable metabolite. Amphetamine (0.2 mg/L) in the absence of MA was found in one case. MDMA was detected in six cases, although all of these except one also had MA detected. The age range was 21–50, median 40 years. There were five females.

The serotonin syndrome was reported in three cases (sub-category A3), all associated with moclobemide (MAO inhibitor) and MDMA, illustrating the risk associated with the concomitant use of MDMA and a serotonin-active drug (28). In these cases, the MDMA concentrations were 1.7, 1.0, and 2 mg/L, respectively. The moclobemide concentration in case 26 was consistent with therapeutic use (0.3 mg/L), but was elevated in the other cases (15 and 8.7 mg/L). This drug combination was also seen in case 16; however, a serotonin syndrome was not reported.

The fourth sub-category (A4) included three cases in which toxicity to amphetamine-class drugs alone was regarded as the cause of death. MDMA was found in one case at a concentration of 93 in combination with smaller amounts of MA and amphetamine. Methamphetamine was present in all category A4 cases with blood concentrations at 5.3, 0.2, and 0.4 mg/L together with a smaller amount of amphetamine as metabolite. Other findings in these three cases included nonspecific changes such as pulmonary edema and brain edema in one case. The third case was decomposed; hence, possible pathology findings may have been masked by putrefactive changes.

Comparisons of Blood Concentrations

Not unexpectedly there was a wide range of blood concentrations of all detected amphetamine-class drugs. In all of group A cases, the range of MA concentrations was 0.02–60 mg/L with a median of 0.25 mg/L. The concentration of MA was highest in the A2 sub-category (median 3 mg/L) (Table 3). There are increasing reports of MA associated deaths (9,11,18–20). In the most recent report, 13 of 32 cases of MA poisoning were diagnosed in the absence of significant natural disease. The postmortem concentrations of MA ranged from 0.6 to over 50 mg/L. Unfortunately, testing for the presence of other drugs was limited to a Triage screen in urine which presumably only targeted some selective drugs of abuse (9).

In another series of 146 MA positive cases, 52 deaths were caused by combined drug toxicity. There was substantial overlap in MA concentration between drug-associated cases and drug-caused deaths. Most MA deaths occurred with blood concentrations greater than 0.5 mg/L; however, some involved concentrations as low as 0.05 mg/L, most of which occurred in conjunction with other drugs or significant natural disease (27). These data are also supported by the postmortem findings in a series of deaths in San Francisco (11). Mean blood concentrations of MA (and amphetamine) were indistinguishable in cases where MA was related and unrelated to the cause of death.

TABLE 3—*Prevalence and concentration of amphetamines detected in blood samples of postmortem cases.*

	Group A2 $n = 19$			Group B $n = 96$			Group C $n = 42$		
Drug	Number of Cases	Blood Concentration Range	Median Concentration	Number of Cases	Blood Concentration Range	Median Concentration	Number of Cases	Blood Concentration Range	Median Concentration
MA	17	0.02–60	0.3	87	0.01–9.8	0.2	38	0.02–2.0	0.28
Amphetamine	11	0.02–0.6	0.06	42	0.02–0.8	0.11	11	0.02–0.4	0.02
MDMA	5	0.5–2.6	0.3	11	0.03–3.5	0.05	10	0.03–2.0	1.03
MDA	2	0.02–0.1	0.06	6	0.1–0.2	0.1	3	0.03–0.1	0.1
MDEA	–	–	–	–	–	–	1	0.1	0.1

All concentrations in mg/L.

MA, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine; MDEA, 3,4-methylenedioxyethylamphetamine.

The concentration range for MDMA in group A cases was 0.05–93 mg/L, median 1 mg/L. This was also higher than the MDMA concentrations in both groups B & C (Table 3). The median concentration of MDMA in the A3 sub-category was 1.7 mg/L; however, the MDMA case in category A4 demonstrated the highest concentration (93 mg/L).

There were insufficient numbers for the other amphetamine-class substances to allow any worthwhile statistical comparison.

The higher average concentration of amphetamine-class drugs in group A cases (MLR: $n = 126$, $r = -0.367$, $p \leq 0.05$) compared to categories B and C may be linked to the higher usage of this class of drugs leading to an increased disposition to developing heart disease, particularly if sustained for a long period. The influence of individual susceptibility and tolerance as contributing factors was demonstrated by low postmortem blood concentrations (under 0.1 mg/L) in three cases 14, 21, and 22. These instances indicate that amphetamine-class deaths may be associated with postmortem blood amphetamine-class concentrations that are considerably lower than once thought (9). Category B cases involved more polydrug use than category A cases (MLR: $n = 125$, $r = 0.734$, $p \leq 0.05$) and significantly younger users ($n = 125$, $r = -0.242$, $p \leq 0.05$).

Typically, intravenous administration was most common in MA users whilst oral administration was most common in MDMA users. Compared with intravenous administration, the blood amphetamine-class drug concentration tended to be higher when other routes of administration were used ($p < 0.05$). Metabolite concentrations were considered in all cases, particularly the active metabolites amphetamine and MDA. However, in all cases where amphetamine-class metabolites were detected, metabolite concentrations were considerably lower than the parent drug and thus were regarded as having a lesser contribution to the cause of death.

The amphetamine-class concentrations in category C cases represented the typical postmortem amphetamine-class concentrations in people who abuse the stimulants but have died from other causes. The average concentrations in categories B and C were similar, suggesting that people die from amphetamine-class drug co-intoxications at the same concentrations as people who die from physical injury during amphetamine-class drug abuse (Table 3).

The postmortem interval and its influence on drug redistribution were acknowledged when assessing cases. Time lapsed between death and autopsy ranged from 1 to 5 days (median 3 days) excepting case 2 where the deceased was located an estimated 8 days after death. This interval would certainly have affected postmortem drug concentrations to some degree (24); however, considering the key finding of the study was advanced natural disease due to chronic amphetamine-class administration as opposed to a fatal acute poisoning, the duration of amphetamine-class use was of more significance than the postmortem drug concentration.

Pathology Findings

Excessive catecholamine activity and increased vasoconstriction in the periphery produces hypertension, tachycardia, arrhythmia, cardiac hypertrophy, myocardial ischemia, and fibrosis, predisposing individuals with borderline cardiac function or coronary artery atherosclerosis to a fatal cardiac episode such as myocardial infarction or ventricular arrhythmia (12,13). In a study from Japan, four of the 15 MA cases attributed directly to MA toxicity had blood concentrations ranging from 3.4 to 25 mg/L; however, these cases involved no other drugs or natural disease. There were two further cases in which death occurred from cerebral hemorrhage and myocardial infarction. Again, the conduct of toxicology testing for other drugs was limited; hence, the involvement of other drugs in these cases cannot be excluded. Common complications to MA use reported in this publication included cardiac and cardiovascular disease, cerebral perivasculitis, and liver cirrhosis/interstitial hepatitis (20). Similarly in a recent report, MA use was strongly associated with coronary artery disease and subarachnoid hemorrhage (11).

Almost all cases of group A had pre-existing cardiovascular disease, which strongly supports that amphetamine-class drugs cause or exacerbate the effects of heart disease (11). Heart disease predictably increased with age (MLR: $n = 126$, $r = 0.25$, $p \leq 0.05$); however, this was not restricted to older individuals—it was evident across all ages (as young as 19 years), demonstrating the harmful co-associations of heart disease with amphetamine-class drugs from young adult years. Compared to category A cases heart disease was significantly less prevalent in category B cases with the polydrug users (MLR: $n = 126$, $r = -0.54$, $p \leq 0.05$), and infrequent in the trauma group (category C).

As reported in the literature, a single, high dose has the potential to result in a serious cardiac event (12). However, considering the absence of a dose–response relationship (with amphetamine-class concentrations in the cases ranging from "normal" through to "fatal") (29), and the high prevalence of long-term users, it is most likely that prolonged and intermittent abuse of amphetamine-class drugs caused heart disease, rather than a single dose. Although this type of study can never prove that long-term amphetamine-class use necessarily caused or even accelerated the development of heart disease, the association seen repeatedly in descriptive studies does suggest a causal role for amphetamine-class drugs.

It is well known that amphetamine-class drug-induced hypertension and spasm of the cerebral arteries potentially results in blood-vessel rupture, cerebral ischemia, and cerebral hemorrhage, particularly in individuals with cerebral vascular abnormalities such as an aneurysm or angioma (10,29). The seven cases involving hemorrhage and aneurysm in the group A cases provide evidence for this association, because in nonamphetamine-class users (particularly of a young age) cerebral hemorrhage and aneurysms are very rare (11,18). There was one case of cerebral hemorrhage in the other two categories (Group C). In contrast to cardiac disease, the duration of amphetamine-class use did not appear to be a major contributing factor in triggering a bleed—amphetamine-class-attributed hemorrhage and aneurysm ruptures more frequently occurred with earlier exposures rather than chronic damage. This is because these deaths typically occur in susceptible individuals with preexisting cerebral abnormalities such as aneurysm, and a minor rise in blood pressure from stimulant use can trigger a rupture or bleed. This also explains the incidence of younger deaths attributed to amphetamine-class drug-induced cerebral toxicity as these cases usually occur within the first few exposures (18).

Reports indicate that the high fever and metabolic disturbances provoked by amphetamine-class use (particularly MDMA) frequently cause serious liver damage (2); however, it is most interesting that no liver damage or acute liver failure was found in this study.

In Australia, amphetamine derivatives are pharmacotherapies for attention deficit disorders and narcolepsy. Indeed, year 2000 report indicates an average increase of dexamphetamine and methylphenidate consumption in Australia of 26% per year since 1984 (30). A number of recent reports also propose the involvement of these prescribed amphetamine-class drugs in disease and drug misuse (31–33). Although methylphenidate and dextroamphetamine are prescribed in Australia for treating narcolepsy and attention deficit disorders, there were no cases in the present study involving prescribed amphetamine use. All cases involved recreational use of illegal amphetamine derivatives, including case 13 who was a chronic MA user and thus the presence of amphetamine alone was

likely metabolite or derived from illicit amphetamine which is occasionally available in Australia.

Collectively, these data demonstrate that sudden death can occur through a fatal hemorrhage but the incidence of other amphetamine-class drug caused deaths is most uncommon unless there is significant heart disease, particularly an enlarged heart, contraction band defects, or coronary artery disease.

A number of methodological problems arose in the study which complicated the interpretation of the involvement of amphetamine-class drugs in causing death. In cases where medical or police reports were not entirely specific, witness statements were used to ascertain the relevant details. Although this information was probably accurate, witness statements are not always reliable. There were also cases where pertinent information could not be acquired (i.e., objection to autopsy) which negated the ability to obtain relevant pathology information. Furthermore, as is the case in many drug studies, the prevalence of polydrug use amongst amphetamine-class users made it difficult to distinguish between the effects of amphetamines and those of alcohol or other drugs.

Further research is required to investigate the long-term adverse consequences of amphetamines. Differences in individual susceptibility to amphetamine-class drug-induced toxicity mean that it is currently unrealistic to predict which users are most vulnerable to experience such effects (10). Further research is needed to identify and gather information on genes or metabolic enzymes which are responsible for causing toxicity. Additionally, further research is essential to explore in more detail the correlation between amphetamine-class use and pre-existing cardiac pathology, i.e., genetic linked arrhythmias including Long QT Syndrome.

Conclusions

It is noteworthy that in 5 years of death investigations in Victoria, there are remarkably few cases in which death was directly caused by acute or short-term amphetamine-class drug use in the absence of other contributing substances. There were six cases involving a blood vessel rupture and two to three cases of other causes not involving a bleed. This is about two deaths per year in a community that, unfortunately, is known for relatively high use of amphetamine-class drugs. There were at least three cases in which it was likely that a serotonin syndrome caused death in the presence of moclobemide and a number of cases of death caused by use of MDMA. However, there were 19 cases in which death occurred in the presence of amphetamine-class drugs and significant heart disease and possibly only one case which was caused by MA alone.

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