Drug and Alcohol Dependence 179 (2017) 174–179

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Prevalence and nature of cardiovascular disease in methamphetamine-related death: A national study

Shane Darke[a,*], Johan Duflou[a,b], Sharlene Kaye[a,c]

[a] National Drug and Alcohol Research Centre, University of New South Wales, NSW, 2052, Australia
[b] Sydney Medical School, University of Sydney, NSW, Australia
[c] Justice Health and Forensic Mental Health Network, NSW Justice Health, NSW Australia

ARTICLE INFO

Keywords:
Methamphetamine
Mortality
Disease
Cardiovascular
Heart

ABSTRACT

Background: Methamphetamine dependence is a major public health problem. This study examined the nature, and extent, of cardiovascular disease amongst cases of methamphetamine-related death in Australia, 2009–2015.
Methods: Analysis of 894 cases of methamphetamine-related death with full autopsy reports retrieved from the National Coronial Information System.
Results: The mean age was 37.9 yrs (range 15–69 yrs) and 78.5% were male. A quarter (26.3%) of cases had enlarged hearts and left ventricular hypertrophy was diagnosed in 18.9%. Severe coronary artery disease was present in 19.0%, the left coronary artery being the vessel most frequently stenosed (16.6%). Replacement fibrosis (evidence of earlier ischaemic events) in the heart muscle was observed in 19.8% of cases, and cardiomyopathy was diagnosed in 5.5%. Histological evidence of hypertension was observed in 32.7% of cases. With the exception of cardiomyopathy, equally common amongst both sexes, cardiovascular disease was more common amongst males, and those aged > 35yrs. Clinically significant levels of cardiovascular disease were also observed amongst cases where the cause of death was not attributed to cardiovascular disease: cardiomegaly (19.3%), left ventricular hypertrophy (14.6%), severe coronary artery disease (9.4%), replacement fibrosis (14.4%), cardiomyopathy (3.3%).
Conclusions: Cardiovascular disease was highly prevalent, despite the relatively young age of cases. With methamphetamine use increasing rapidly in major regions, cardiovascular disease and cardiovascular-related death will likely increase amongst methamphetamine users.

1. Introduction

There are an estimated 35 million stimulant users worldwide, and recent years have seen large increases in production, seizures and use (Degenhardt et al., 2013). In particular, the use of high potency crystal methamphetamine has become a major public health problem, most notably in the Pacific rim (North America, East/Southeast Asia, Oceania) (Degenhardt and Hall, 2012; Degenhardt et al., 2013; United Nations Office on Drugs and Crime, 2016), and the drug is frequently injected (Degenhardt and Hall, 2012; Degenhardt et al., 2013; McKetin et al., 2012). Dependent methamphetamine use carries an array of medical consequences, with the physical health of dependent users being poorer than that of the general population, and the mortality rate elevated 3–6 times (Callaghan et al., 2012; Darke et al., 2008; Degenhardt and Hall, 2012; Marshall and Werb, 2010; Singleton et al., 2009).

The predominant health concern relating to methamphetamine dependence is cardiovascular disease (Huang et al., 2016; Karch, 2009, Kaye et al., 2007; Moon et al., 2015). Methamphetamine stimulates the release of endogenous catecholamines (dopamine and noradrenaline) and has both α- and β-adrenergic agonist effects, causing elevated heart rate and blood pressure (Huang et al., 2016; Karch, 2009, Kaye et al., 2007). High catecholamine levels are known to be cardiotoxic, causing vasoconstriction, vasospasm, tachycardia and hypertension (Karch, 2009). Sympathomimetic use has also been shown to result in myocardial remodelling, with changes to myocyte morphology, the collagen network that support myocytes, and the ion channels that penetrate them (Karch, 2009). Catecholamines, whether endogenous or exogenous, have also been shown to activate calmodulin with resultant myocyte hypertrophy. The most prominent consequences of myocardial remodelling are left ventricular hypertrophy and interstitial fibrosis, with or without lymphocytic infiltrates, and the effect of these changes is a propensity to cardiac arrhythmia.

Consistent with these pathologies, case control studies report higher

* Corresponding author.
E-mail address: s.darke@unsw.edu.au (S. Darke).

http://dx.doi.org/10.1016/j.drugalcdep.2017.07.001
Received 2 May 2017; Received in revised form 6 July 2017; Accepted 6 July 2017
Available online 01 August 2017
0376-8716/

levels of cardiovascular disease amongst methamphetamine users compared to matched controls (Huang et al., 2016; Karch et al., 1999; Yeo et al., 2007), and regular users report frequently report symptoms of cardiovascular disease such as chest pains and palpitations (Darke et al., 2010). Case reports have associated methamphetamine with a range of cardiovascular disease indicative of systemic hypertension, including cardiomegaly (enlargement of the heart), left ventricular hypertrophy, accelerated atherosclerotic coronary artery disease, ischaemic heart disease, hypertensive heart disease, replacement fibrosis (indicating previous ischaemia) dilated cardiomyopathy, arrhythmias and aortic dissection (Karch, 2009; Kaye et al., 2007; Neeki et al., 2016; Voskoboinik et al., 2016).

Despite the association of methamphetamine use with mortality and cardiovascular disease, there are few case series of methamphetamine-related death (Karch et al., 1999; Kaye et al., 2008; Logan et al., 1998; Zhu et al., 2000), and none that have specifically focused on cardiovascular disease. Indeed, the only study of fatalities to compare cardiovascular disease of methamphetamine-related death with deaths unrelated to methamphetamine was that of Karch et al. (1999), who reported heavier heart weights and higher levels of coronary artery disease amongst methamphetamine cases.

With recent increases in the use of high potency crystal methamphetamine, cardiovascular disease related to the drug may become a major public health problem. The current study examined cardiovascular disease amongst methamphetamine-related death in Australia over the period 2009–2015. A number of questions arise that may improve our understanding of the nature, and extent, of cardiovascular disease amongst methamphetamine users. What are the levels of clinically significant cardiovascular disease amongst such cases? How does such disease relate to demographic characteristics? How does cardiovascular disease relate to cause of death? What is the nature, and prevalence, of cardiovascular disease amongst cases of methamphetamine-related death that were *not* attributed to cardiovascular disease? Specifically, the study aimed to:

1. Determine the prevalence and nature of cardiovascular disease amongst all-cause methamphetamine-related death;
2. Determine the demographic correlates of cardiovascular disease; and
3. Determine the prevalence and nature of cardiovascular disease by cause of death.

2. Methods

2.1. National Coronial Information System

The National Coronial Information System (NCIS) is a database provided by the coroners' courts in each Australian jurisdiction. A complete NCIS case file includes demographics, a police narrative of circumstances, autopsy report, toxicology report and the coronial finding (which concludes whether the death was accidental, suicide or homicide, and confirms the cause of death). Cause of death is ascertained by a forensic pathologist and noted on the autopsy and coroner's report. The forensic pathologist may report on: i.) the direct cause of death, ii.) the antecedent cause, and iii.) other significant conditions associated with the death.

In Australia, the criteria for reporting a death vary between jurisdictions. In general, a death is reportable to a coroner where: the person died unexpectedly and the cause of death is unknown; the person died in a violent and unnatural cause; the person died during or as a result of an anaesthetic; the person was 'held in care' or in custody immediately before they died; a medical practitioner has been unable to issue a death certificate stating the cause of death; or the identity of the decedent is unknown. Ethical approval was received from the NCIS and University of New South Wales Ethics Committees.

2.2. Case identification

All cases of methamphetamine-related death occurring between 1/1/2009-31/12/2015 were identified and inspected. Searches were conducted on codes for "Cause of Death" and by "Object or Substance Producing Injury". Due to the fact that methamphetamine may be present in the urine for up to 24 h after consumption (Karch, 2009), and not reflect recent use, cases in which methamphetamine (or its primary metabolite amphetamine) was detected solely in urine were excluded, as were cases where the presence of amphetamine was attributable to prescribed dexamphetamine. For the purposes of this study of cardiovascular disease, data was reported only on cases where complete autopsies were conducted and the full report was available.

2.3. Measures

Information was collected on age, marital status, employment, drug use history, circumstances of death and suicidal intent. Cause of death was classified as: i.) Natural disease (cardiovascular) with contributing methamphetamine effect, ii.) Natural disease (non-cardiovascular) with contributing methamphetamine effect, iii.) Accidental drug toxicity, iv.) Accident, v.) Suicide, and vi.) Homicide.

Standardised forensic autopsies involve examination of all major organs, with representative specimens of tissue are sampled from all major organs during the autopsy for microscopy. Data relating to cardiovascular disease were collected on heart weight, cardiomegaly (enlarged heart), ventricular hypertrophy (thickening of the left ventricle wall), cardiomyopathy, severe coronary artery atherosclerosis (defined as $\geq$75% cross-sectional area stenosis of the artery), replacement fibrosis, interstitial fibrosis, cardiac valve disease, inflammatory heart disease (myocarditis, endocarditis) and histological evidence of hypertension (myocyte hypertrophy, perivascular fibrosis). Cardiomegaly was determined by a heart weight exceeding the 95th percentile of normal weight ranges stratified by sex, height and weight (Kitzman et al., 1988).

Toxicological data were reported for methamphetamine, other psychostimulants, hypnosedatives, alcohol, opioids, cannabis (Δ-9-THC), antidepressants and antipsychotics. In cases of hospitalisation prior to death, antemortem blood samples taken on, or near, admission to hospital were reported, and drugs administered by medical staff excluded. All autopsy blood samples were taken peripherally (femoral or subclavian vessels).

2.4. Statistical analyses

For normally distributed variables mean, standard deviation (SD) and range were presented. Where not normally distributed, median and range were presented. T-tests were used for group comparisons of normally distributed data, otherwise the Mann Whitney *U* test was used. Odds Ratios (OR) and 95% confidence intervals (CI) calculated for proportions. For the purposes of presentation and analysis, age was stratified those aged $\leq$35yrs and those aged > 35yrs. All analyses were conducted using IBM SPSS Statistics v. 23.0 (IBM, 2015).

3. Results

3.1. Case characteristics

There were 1649 cases identified, full details of which are reported elsewhere (Darke et al., 2017). Briefly, the mean age of cases was 36.9 (9.7, 14–69yrs), 78.4% were male, 33.6% were employed, 28.9% in married/defacto relationships, and 55.8% had histories (or the cutaneous stigmata) of injecting drug use. There were 894 cases in which full autopsies were conducted and the full report was available. In a further 473 cases an autopsy was performed, but only summary data were available, while in 287 cases no internal autopsy was conducted.