Heart, Lung and Circulation (2016) **25,** 325–332
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.10.019

REVIEW

The Cardiac Complications of Methamphetamines

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Received 27 August 2015; received in revised form 26 October 2015; accepted 31 October 2015; online published-ahead-of-print 28 November 2015

Methamphetamines are increasingly popular drugs of abuse in Australia, and are rising in purity. The rising popularity and purity of methamphetamines has notably increased demands upon Australian medical services.

Methamphetamines are sympathomimetic amines with a range of adverse effects upon multiple organ systems. Cardiovascular complications are the second leading cause of death in methamphetamine abusers, and there appears to be a high prevalence of cardiac pathology. Cardiovascular pathology frequently seen in methamphetamine abusers includes hypertension, aortic dissection, acute coronary syndromes, pulmonary arterial hypertension and methamphetamine-associated cardiomyopathy.

The rising prevalence of methamphetamine abuse is likely to increase the burden of cardiovascular pathology in Australians. A National Parliamentary Enquiry was opened in March 2015 to address concerns regarding the medical and social impacts of methamphetamine abuse. From April 2015, a National 'Ice Taskforce' was also created in parallel.

Reversal of cardiac pathology appears to be achievable with abstinence from methamphetamines and initiation of appropriate treatment.

It is key to appreciate that the pathogenesis of methamphetamine-induced cardiac complications arises as a result of the specific toxic effects of methamphetamines. Clinical management is hence individualised; suggested management approaches for methamphetamine-induced cardiac complications are detailed within this article.

Keywords Methamphetamines • Cardiomyopathy • Pulmonary hypertension • Hypertension • Toxicology

Introduction

Amphetamine-type stimulants are now the second most consumed illicit drugs globally after cannabis [1]. In Australia, annual expenditure on methamphetamines by drug users is estimated to exceed $1 billion and is rising [2]. From March 2015, a parliamentary enquiry opened to address national concerns regarding the epidemic of methamphetamine abuse.

The last peak of methamphetamine production and consumption in Australia occurred in 2005-6, and most publications regarding medical complications of methamphetamines date from this era [3,4]. However, a key difference of this 'new peak' of methamphetamine popularity is the dramatically increased purity of methamphetamines. Mean purity of methamphetamines in Australia has risen from 16% in 2006 to 61% in 2013 [2].

Consequent to both rising popularity and purity, there is an escalating demand on medical services to assist with methamphetamine-related medical complications. From 2011/12 - 2012/13, there was an 88% increase in methamphetamine-related ambulance callouts in metropolitan

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Melbourne and a 109% increase in rural Victoria [5]. Methamphetamines are now the second most common culprit after opioids for drug-related hospital attendances. Methamphetamine-related mortality has also doubled from 2001 to 2009 [6]. Cardiac complications of methamphetamines play a significant role in escalating methamphetamine-related morbidity.

Physiology

Methamphetamines are sympathomimetic amines that may be smoked, injected, ingested or inhaled. They increase intra-synaptic levels of monoamines (serotonin, noradrenaline, dopamine) via multiple mechanisms, including displacement from cytoplasmic vesicles and inhibition of both reuptake and degradation. Elevated intra-synaptic monoamine levels create hallucinogenic, anorexigenic, euphoric and stimulant effects [7]. There are multiple medical complications of methamphetamine abuse, encompassing neurological, psychiatric, metabolic, gastrointestinal and cardiovascular sequelae [3].

Cardiovascular complications (Table 1) are particularly problematic and include malignant hypertension, aortic dissection, myocardial infarction, pulmonary hypertension and methamphetamine-associated cardiomyopathy. In a series of 371 Australian coronial cases of methamphetamine-related deaths [8], cardiovascular complications were the leading direct cause of death after drug toxicity / overdose, responsible for death in 14% of cases. Fifty-four per cent of the cohort exhibited cardiovascular pathology; in a group with a mean age of 32 years and predominantly male (78%), this was significantly above predicted baseline prevalence of cardiovascular disease. Notably, this data from 2008 precedes the current rise in methamphetamine purity.

Table 1 Cardiac complications of methamphetamines

Methamphetamine effect	Cardiac outcome
Tachycardia, hypertension	Malignant hypertension Coronary vasospasm Acute myocardial infarction Aortic dissection
Myocardial toxicity	Malignant arrhythmias Methamphetamine associated cardiomyopathy
Pulmonary arterial hypertension	Right heart failure
Neurotransmitter depletion	Dysrhythmias Sudden cardiac arrest
Intravenous drug injection	Infectious endocarditis

The cardiac complications of methamphetamines are hypothesised to arise from a variety of mechanisms. In animal studies, administration of methamphetamine to rats causes hypertension, tachycardia and myocardial toxicity with cellular death, fibrosis and contraction band necrosis [9]. In human autopsy specimens, severe interstitial fibrosis and scar formation has been documented [10]. Physiological pathways implicated include catecholamine surges acutely during methamphetamine intoxication with contingent hypertensive crises, longer-term upregulation of the sympathetic axis, and myocardial toxicity with impaired cellular metabolism. Depending on which process predominates, different patterns of pathology may develop, particularly in the case of methamphetamine-associated cardiomyopathy (Table 2).

Co-ingestion of methamphetamine with other illicit drugs, for example cocaine, may acutely heighten the risks of cardiac toxicity, either by direct additive toxic effect or drug-drug interactions leading to potentiation and prolongation of drug efficacy. Prior chronic use of cardiotoxic drugs causing cardiomyopathy may further potentiate cardiac impact of methamphetamines.

What is Unique about Methamphetamine-associated Cardiac Complications and their Management?

Hypertension

It is key to recognise that methamphetamine-induced hypertension and tachycardia are due to a hyperadrenergic state, analogous to phaeochromocytoma or autonomic dysfunction (Table 3). This hyperadrenergic state stimulates both α-adrenoreceptors (mediating peripheral vasoconstriction) and β2-adrenoreceptors (mediating peripheral vasodilation). Consequently, in treating patients with hypertension and tachycardia it is important to achieve blockade of both α-and β-adrenoreceptors. Otherwise, paradoxical worsening of hypertension may occur due to unopposed α-mediated vasoconstriction [19].

In the acute setting, sedation reduces the intra-synaptic catecholamine surge, acting centrally to relieve hypertension. If hypertension persists after appropriate sedation, cerebral imaging should be arranged to exclude intracranial bleeding. Medical therapy of hypertension should avoid β-antagonists. Appropriate first-line anti-hypertensives include nitrate therapy and α-antagonists such as phentolamine [20]. There are currently no evidence-based recommendations in the context of methamphetamine-induced hypertension, but the literature on phaeochromocytoma suggests that 14 days of α-antagonist therapy is adequate to facilitate safe introduction of β-antagonists [21].

In the longer-term, it may be preferable to choose a β-antagonist with partial α-antagonism such as carvedilol or labetalol to ensure ongoing α-adrenoreceptor suppression. Calcium channel blockers have also been effective in blunting