Drug and Alcohol Dependence 150 (2015) 1–13

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Review

Treatment of toxicity from amphetamines, related derivatives, and analogues: A systematic clinical review☆

John R. Richards[a,*], Timothy E. Albertson[b,c], Robert W. Derlet[a], Richard A. Lange[d], Kent R. Olson[e,f], B. Zane Horowitz[g]

[a] Department of Emergency Medicine, University of California Davis Medical Center, Sacramento, CA, United States
[b] Department of Internal Medicine, Divisions of Toxicology, Pulmonary and Critical Care, University of California Davis Medical Center, Sacramento, CA, United States
[c] Northern California VA Medical System, Sacramento, CA, United States
[d] Department of Medicine, Division of Cardiology, University of Texas Health Sciences Center, San Antonio, TX, United States
[e] Department of Medicine, University of California, San Francisco, CA, United States
[f] Department of Clinical Pharmacy, University of California, San Francisco, California Poison Control System, San Francisco Division, San Francisco, CA, United States
[g] Department of Emergency Medicine, Oregon Health Sciences University, Oregon Poison Center, Portland, OR, United States

ARTICLE INFO

Article history:
Received 6 November 2014
Received in revised form
24 December 2014
Accepted 28 January 2015
Available online 18 February 2015

Keywords:
Amphetamines
Agitation
Beta-blockers
Hypertension
Tachycardia
Sedation

ABSTRACT

Background: Overdose of amphetamine, related derivatives, and analogues (ARDA) continues to be a serious worldwide health problem. Patients frequently present to the hospital and require treatment for agitation, psychosis, and hyperadrenegic symptoms leading to pathologic sequelae and mortality.
Objective: To review the pharmacologic treatment of agitation, psychosis, and the hyperadrenergic state resulting from ARDA toxicity.
Methods: MEDLINE, PsycINFO, and the Cochrane Library were searched from inception to September 2014. Articles on pharmacologic treatment of ARDA-induced agitation, psychosis, and hyperadrenergic symptoms were selected. Evidence was graded using Oxford CEBM. Treatment recommendations were compared to current ACCF/AHA guidelines.
Results: The search resulted in 6082 articles with 81 eligible treatment involving 835 human subjects. There were 6 high-quality studies supporting the use of antipsychotics and benzodiazepines for control of agitation and psychosis. There were several case reports detailing the successful use of dexmedetomidine for this indication. There were 9 high-quality studies reporting the overall safety and efficacy of β-blockers for control of hypertension and tachycardia associated with ARDA. There were 3 high-quality studies of calcium channel blockers. There were 2 level I studies of α-blockers and a small number of case reports for nitric oxide-mediated vasodilators.
Conclusions: High-quality evidence for pharmacologic treatment of overdose from ARDA is limited but can help guide management of acute agitation, psychosis, tachycardia, and hypertension. The use of butyrophenone and later-generation antipsychotics, benzodiazepines, and β-blockers is recommended based on existing evidence. Future randomized prospective trials are needed to evaluate new agents and further define treatment of these patients.

Contents

☆ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

* Corresponding author at: Department of Emergency Medicine, PSSB 2100, U.C. Davis Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817, United States. Tel.: +1 916 734 1537; fax: +1 916 734 7950.
E-mail address: jrrichards@ucdavis.edu (J.R. Richards).

http://dx.doi.org/10.1016/j.drugalcdep.2015.01.040
0376-8716/

1. Introduction

The accidental or intentional overdose and abuse of over-the-counter, prescribed, and illicit amphetamine, its related derivatives, and analogues (ARDA) such as ephedrine, pseudoephedrine, methylphenidate, lisdexamfetamine, methamphetamine, cathinone ("khat") and derivatives ("bath salts"), and 3,4-methylenedioxy-N-methylamphetamine (MDMA or "ecstasy") is a growing problem. Based on the most recent United Nations World Drug Report (2012), there are an estimated 50 million ongoing users worldwide, which surpasses heroin and cocaine use combined. This does not include frequent use of naturally occurring compounds such as cathinone from the khat plant (*Catha edulis*) used in the horn of Africa and Middle East, and ephedrine and pseudoephedrine from *Ephedra sinica*, which are commonly ingested by inhabitants of East Asia.

In the United States, there were greater than 150,000 emergency department visits for toxicity from ARDA in 2011 based on data from the Substance Abuse and Mental Health Services Administration (SAMHSA, 2011). The Drug Enforcement Agency estimates there were 439,000 past-month methamphetamine users in 2011 (USDOJ, 2013). The number of first-time methamphetamine users ages 12 and older was 133,000 in 2011, which represents an increase from 97,000 in 2008 (SAMHSA, 2012). In 2011, 11% of children 4–17 years old (6.4 million) had at some point in their lives been diagnosed with attention deficit hyperactivity disorder (ADHD), and 3.5 million were taking ADHD medication (Visser et al., 2014). Illicit use of these prescribed medications among young adults without ADHD and of designer synthetic cathinones such as "bath salts" is also an increasing problem (Garnier et al., 2010; Lakhan and Kirchgessner, 2012; Wood, 2013). Over-the-counter decongestants and herbal products targeting weight loss may contain pseudoephedrine, ephedrine, and phenylpropanolamine and have been associated with morbidity and mortality even when taken at correct dosage (Gunn et al., 2001).

These patients frequently present to the emergency department for acute care and consume hospital resources at a higher than normal rate, including emergency, psychiatric, trauma, intensive care unit, and telemetry services (Cloutier et al., 2013; Hendrickson et al., 2008; Richards et al., 1999a; Swanson et al., 2007). Furthermore, they are rarely forthcoming about their illicit drug use, and treating clinicians must consider a wide spectrum of diagnoses during the initial face-to-face evaluation, such as acute psychosis, thyrotoxicosis, sepsis, pheochromocytoma, anticholinergic toxicity, alcohol, benzodiazepine and opioid withdrawals, serotonin and neuroleptic malignant syndromes, and intracranial hemorrhage. Debate exists regarding the best "antidote" and method of treating acute intoxication or overdose. Therefore inconsistencies may occur among different physicians, specialties, and regional hospitals in their approach to the ARDA-intoxicated patient.

Amphetamine, its related derivatives, and analogues increase concentrations of norepinephrine, dopamine, and serotonin through multiple mechanisms and are amphipathic molecules which can cross the blood–brain barrier and placenta (Panenka et al., 2013). Blockade of plasmalemmal and vesicular transporters results in elevated levels of monoamines in the cytoplasm and synapse, respectively, and also cause reverse transport of cytoplasmic monoamines across the cell membrane of the presynaptic neuron into the synaptic space. These drugs also disrupt vesicular storage of monoamines and inhibit the degradative enzymes monoamine oxidase A and B. The net effect is a precipitous rise in central nervous system (CNS) and serum catecholamines with sudden and unpredictable increase in heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP; Fleckenstein et al., 2007). All ARDA have this potential hyperadrenergic effect, but with varying degrees based on the specific ARDA, route of administration, patient tolerance, and pharmacogenetics (de la Torre et al., 2012). Patients abusing ARDA may have serious consequences from this hyperadrenergic state.

Control of agitation and the hyperadrenergic state are top priorities to prevent acute coronary syndrome (ACS), stroke, pulmonary hypertension, acute heart and renal failure, and fetal/maternal morbidity and mortality (Ali et al., 2011; Bingham et al., 1998; Davis and Swalwell, 1994; Hawley et al., 2013; Johnson and Berenson, 1991; Kaye et al., 2007; Richards et al., 1999b; Stewart and Meeker, 1997; Sutamtewagul et al., 2014; Thompson, 2008; Turnipseed et al., 2003; Westover et al., 2007; Won et al., 2013). The half-lives of ARDA are several hours and vary with route of administration, increasing the potential for pathologic sequelae (Mendelson et al., 2006). The purpose of this review is to determine the current best evidence for treatment of (1) agitation/psychosis, and (2) the hyperadrenergic state caused by toxicity from ARDA, and any treatment-related adverse events.

2. Methods

All human trials, case series, or case reports of pharmacologic treatment of ARDA-related agitation, psychosis, and