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Amphetamine Toxicity among Drug Abusers: An Observational Study.

[1]Dr Husnain Arshad Cheema,[2]Muhammad Hassan Rafique,[3]Dr Chaudhry Hamza Sarwar

[1]MBBS,Allama Iqbal Medical College,Lahore.

[2]MBBS,FMH College of Medicine And Dentistry,Lahore.

[3]MO, BHU Hanjra,Gujrat.

Corresponding Author: Dr Husnain Arshad Cheema**,** MBBS, Allama Iqbal Medical College, Lahore.

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Introduction

Amphetamines and cocaine are among the most significant central nervous system (CNS) stimulant drugs of abuse (l). At the present time, the prevalence of patients presenting to most EDs as a result of cocaine intoxication is higher than those with amphetamine intoxication. However, at our institution toxicity from amphetamines approximates cocaine in frequency. Amphetamines were first used clinically in the 1930s as stimulants and gained wide recognition during the Second World War (2). The addictive potential and medical danger were not fully realized until epidemic usage of the drug became prevalent after World War II, especially in Japan. The drug continued to be abused during the 1960s as a euphoriant and mood altering drug. The legitimate use of amphetamines for treatment of narcolepsy and attention deficit disorders in children has been overshadowed by the vast abuse of this drug. Despite the prevalence of other stimulants, amphetamines have continued to be a significant drug of abuse. Some studies have estimated that as many as 15 million people may have used amphetamines illicitly (3). Patients who are intoxicated with amphetamines frequently present to EDs. Patients were included in this study if intoxicated from amphetamines, and there was toxicological evidence of the presence of amphetamine or methamphetamine. Cases were excluded if no amphetamines were found on toxicological analysis. We excluded 20 patients who admitted to amphetamine use but did not have toxicology screens submitted. Each patient was categorized by chief complaint. All patients had urine submitted for toxicologic analysis by thin layer chromatography capable of detecting amphetamine, atropine, benzodiazepine (class), codeine, diphenhydramine, methamphetamine, meperidine, methadone, morphine, pentazotine, phencyclidine, propoxyphene, strychnine, phenothiazines (class), and tricyclic antidepressants (class). Additionally, patients had serum alcohol levels, and acid, neutral, and base drug determinations by gas chromatrography.

A total of 127 patients were evaluated for the toxic effects of amphetamines during the six-month study period. In the same period, over 18,510 patients were seen in the ED at this hospital, and 704 were treated for overdoses or toxic effects of drugs. Vital signs and demographic data are presented in Table 1 and Table 2.

Major symptoms

The most commonly reported symptom was altered mental status. This included agitation (21%)) hallucinations (7 %), suicidal ideation (12%), delusions (5%), and confusion (6%). Symptoms of agitation varied widely and included patients who were screaming loudly, belligerent, moaning, moving uncontrollably, aggressive,

or hyperactive. Thirteen cases were brought to the ED after being found unresponsive in the field. In four of these cases benzodiazepines were found on toxicology screens, two cases had high alcohol levels, and three cases awoke with naloxone. However, in four cases no cause for unconsciousness could be found. All of these patients used amphetamine intravenously just prior to collapsing; none responded to naloxone, and none had a history of a seizure disorder. Other symptoms included chest pain, palpitations, headaches, seizures, and abdominal pain. The type of amphetamine was analyzed in all cases. Laboratory analysis showed that 37% of the patients had taken either methamphetamine or amphetamine alone, and in the remaining 26% both drugs were used in combination. Route of administration of the drug was by intravenous injection (IV) in 35%, oral ingestion in 14%, nasal "snorting" in 10%; the mode of ingestion was unknown in 41%. Most patients received no specific treatment. Twenty-five percent received intravenous fluids and 13% received activated charcoal with either sorbitol or magnesium citrate. Eight patients (6%) received haloperidol, and five patients (4%) were given diazepam to control agitation. Clinically, patients appeared to respond equally well to either drug. Cardiac monitoring was employed for 32% of the cases, with no significant findings other than sinus tachycardia.

Table 1 : Patient's Vital Signs

	Number	Percent
Male	82	65
Female	45	35
Age		
Less than 20	6	5
20-29	52	41
30 and older	69	54
Pulse		
<100/min	54	43
>100/min	73	57
Respirations		
<20/min	79	62
>20/min	48	38
Blood pressure		
<140/90 mmHg	84	66
>140/90 mmHg	43	34

Table 2. Major Symptoms

	Number	Percent
Altered Mental Status		
Agitation	27	22
Suicidal ideation	15	12
Hallucinations	9	7
Delusions	7	5
Confusion	8	6
Despondent affect	7	5
SUBTOTAL Altered Mental Status	73	57
Found unresponsive	13	10
Chest pain	11	9
Weakness and lethargy	7	5
Seizures	4	3
Headache	5	4
Palpitations	4	3
Abdominal pain	5	4
Rash	1	1
Dyspnea	1	1
Leg pain	1	1
Paresthesias	2	2
TOTAL	127	100

Forty-nine percent of the patients were referred for psychiatric evaluation. All of these patients had been were alcohol holds by police or hospital psychiatric workers because their altered mental status rendered them gravely disabled or a threat to others. Thirty-four percent of the patients went home after leaving the ED; four percent were incarcerated for possession of illegal substances.

The details of patients requiring hospital admission to the medical services are six patients were admitted for continued observation, as their mental status did not clear in the ED. Two patients who had been found unresponsive and who continued to be lethargic after arousal in the ED

were admitted. Despite admission work-up that included computed tomographic scans, lumbar punctures, and electroencephalograms, no clues as to the etiology of their unconscious episode were found. Two patients had significant orthostatic hypotension and required large amounts of fluid to correct this deficit. No clear etiology for this could be found. Another two patients who presented to the ED with confusion and agitation were IV users found to have fevers and admitted for antibiotic therapy. One of these patients signed out against medical advice within 10 hours; the other was treated for a suspected IV site cellulitis. A final patient developed epigastric pain and hematemesis following IV amphetamine use.

Discussion

Amphetamines are CNS stimulants that can induce euphoria, increase alertness, intensify emotions, alter self-esteem, and increase libido. In toxic doses, amphetamines induce unpleasurable CNS symptoms such as agitation, anxiety, hallucinations, delirium, and seizures. Toxic doses can also induce cardiovascular symptoms such as chest pain, palpitations, or dyspnea. The major toxic effects seen in this study appear to be secondary to excessive amounts of drug used (6). Because amphetamines are purchased illicitly and may be mixed with both inert and other toxic substances, the exact dose necessary to produce symptoms is unclear. Clinical observation of toxic effects is more relevant than an estimate of ingested dose since response to a given dose is variable. Tachyphylaxis occurs with amphetamines, and chronic users will tolerate higher doses with less symptomatology. Fatalities have been reported following ingestions as low as 1.5 mg/kg of methamphetamine whereas chronic abusers who develop tolerance to the drug may use as much as 5,000 to 15,000 mg per day (7). The vast majority of patients presented solely as a result of amphetamine or methamphetamine intoxication. Other stimulants such as phenylpropanolamine, ephedrine, or pseudoephedrine have been described as being used to adulterate amphetamines. However, on laboratory analysis these drugs were found in only eight of our patients. This may be the result of ever-increasing illicit laboratories that can manufacture amphetamines cheaply in mass quantities. Unfortunately, some of these clandestine chemists occasionally produce “designer” stimulants with toxicity of their own. One example of these amphetamine analogs is methylenedioxymetamphetamine (MDMA) (8). The toxicologic screen may not detect many of the new cogeners, like MDMA, which may produce symptoms indistinguishable from amphetamines (9, 10). The symptoms produced by cocaine and amphetamines are similar and may be difficult to differentiate clinically (11). Both animal and human studies support these observations. The sole distinguishing clinical feature may be the longer half-life of amphetamines, which may be up to eight times longer than cocaine (12). One might expect some of the street amphetamines to have been mixed with cocaine. However, only nine patients in our series were found to have cocaine in addition to amphetamines. A recent report on cocaine intoxication found that only 7% of patients presenting as a result of cocaine also had used amphetamines concurrently (13). CNS symptoms were the most common chief complaint seen in this study, and include agitation, confusion, delusions, hallucinations, and suicidal ideation. Fifty-seven percent of the patients had an altered mental status. Nearly all of these patients were referred to a psychiatric center or service on discharge from the ED. Several studies have demonstrated that amphetamines can both induce an acute toxic psychosis in previously normal persons as well as precipitate a psychotic episode in those with psychiatric illness (14). One large study found that most amphetamine addicts had

a diagnosis of some psychiatric problem before addiction (15). A choreoathetoid disorder can also be induced by amphetamines (15). Of the patients in our series, 10% were either unconscious at presentation or had been found unresponsive. In all but four of these, unresponsiveness could be explained by drugs. In these four, the etiology of the unresponsiveness episode could be a result of a seizure, hypotension, a reaction to a contaminant, or an undescribed effect of intravenous amphetamine. One author states that the unconscious patient who has taken amphetamine overdose "has usually suffered a cerebral hemorrhage caused by hypertension, seizure, or hyperpyrexia" (16). Other problems that have been described but were not seen in this series are stroke due to hemorrhage or vasospasm, and cerebral vasculitis (17). Amphetamines were used IV in 33% of our cases; however, few complications were seen. The problems associated with intravenous amphetamine abuse include hepatitis, bacterial endocarditis, anaphylaxis, pulmonary angiothrombotic granulomatosis, and necrotizing angiitis. Two cases of acute cardiomyopathy after intravenous injection of amphetamine have been described (18). Hepatocellular injury was reported in a 19-year-old woman who regularly abused methylphenidate intravenously (19). The cardiovascular toxicity of amphetamines has been well publicized. Atria1 and ventricular dysrhythmias and myocardial ischemia have also been described as a result of amphetamine toxicity (20). Chest pain was seen in 9% of our cases, and although no ECG changes were seen, a cardiac etiology cannot be excluded. One-third of our patients presented with hypertension, but none required treatment with antihypertensive agents. In addition to its alphaadrenergic effects, amphetamines also inhibit monoamine oxidase activity (21). Therefore, when treating a hypertensive crisis, consideration should be given to an anti-alpha agent such as phentolamine. In theory, less severe cases could be treated with chlorpromazine, which has sedative as well as anti-alpha actions (22). However, animal models have shown that haloperidol is superior to chlorpromazine in antagonizing amphetamine toxicity (23). Despite amphetamines' ability to induce significant CNS and cardiovascular stimulation, relatively few of our patients required treatment. Only 10% of those patients presenting to the ED required pharmacologic intervention for their agitation. At our institution, there is no protocol for treating amphetamine agitation, and the ED physician determines when and what to treat with. Generally, patients are not treated for agitation unless they could harm themselves while jerking or tearing at their restraints. Eight such patients were treated with haloperidol, while five such patients were treated with diazepam. All responded to treatment by either drug. Amphetamines enhance the release of dopamine at specific central neurotransmission sites and inhibit dopamine re-uptake (24). Animal studies suggest that haloperidol blocks the toxic effects of amphetamines in the CNS by competitively antagonizing the dopamine receptors at specific sites (25). Diazepam, a benzodiazepine that augments gam ma-aminobutyric acid (GABA) neurotransmission, clinically raises seizure thresholds and produces a sedative effect (26). The five cases treated with diazepam in this series responded well. The mechanism of diazepam in reducing amphetamine psychosis is unclear. One speculated mechanism is that by increasing GABA modulation, activity of dopaminergic pathways may decrease. Diazepam is highly effective in antagonizing the stimulant toxic effects of cocaine in animals (Derlet R, Albertson TE: Diazepam in the prevention of seizures and death in cocaine intoxicated rats. However, the mechanism of this protective effect has not been fully elucidated. Most cases of amphetamine

toxicity seen in our ED were managed conservatively. Almost half required absolutely no treatment beyond confirmation of the diagnosis and observation until medically clear for discharge. Only 10% of the patients required admission, and those who were hospitalized were generally discharged within two days. Vital signs have been said to be an indicator of severity of intoxication, with temperature above 40 degrees centigrade being an especially poor prognostic sign. In our series, there was no significant difference in vital signs between those admitted and those not admitted. No cases of hyperthermia were seen in this series. In conclusion, the majority of patients seen as a result of amphetamine intoxication displayed marked changes in mental status. Most could be managed in the ED conservatively, and those requiring treatment for agitation responded equally well to either diazepam or haloperidol. Admission may be indicated to exclude myocardial infarction, angina, stroke, or sepsis.

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