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Cardiomyopathy Due to Ingestion of Adderall

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A patient is described who developed cardiomyopathy after receiving a therapeutic course of dextroamphetamine/amphetamine. The patient's cardiac function deteriorated to the point of heart failure, necessitating a heart transplantation. Cardiomyopathy associated with amphetamine use is a serious and potentially lethal condition. With early diagnosis, identification of the cause, and treatment, cardiomyopathy may be reversible. The dangers of therapeutic use of amphetamines are discussed, as well as problems and assumptions associated with U.S. Food and Drug Administration monitoring and removal from the market of harmful substances.

Keywords: Adderall, Ritalin, dextroamphetamine, amphetamine, cardiomyopathy

INTRODUCTION

Amphetamines are noncatecholamine sympathomimetic amines with CNS stimulant activity.[1] As prescription drugs, they are prescribed widely for attention deficit and hyperactivity disorders.[2] Of the number of adverse effects that are associated with amphetamines, one that can occur, sometimes with devastating results, is cardiovascular toxicity.[3] I describe a case of cardiomyopathy leading to a heart transplantation which was causally related to the prescription drug Adderall.

METHODS

The basis of this case report was a thorough review of the medical records, a medical history and physical examination after the heart transplantation had occurred, and a search of the current medical literature using Medline. A determination of causal relatedness between the consumption of Adderall (Shire Pharmaceuticals, Wayne, PA) and the development of cardiomyopathy was made by means of universally accepted algorithms,[4] as described.

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Case report

The patient was a 34-year-old Caucasian man with a medical history of asthma, obesity, irritable bowel syndrome, and genital herpes. He was given a diagnosis of attention deficit disorder and was prescribed and ingested Adderall (dextroamphetamine/amphetamine) for approximately a 2-year period.

Adderall was started initially at 20 mg daily. Two months later the dosage of Adderall was increased to 40 mg a day, and Prozac, 20 mg, was added as a mood stabilizer. Seven months later the Adderall dosage was again increased to 40 mg in the morning and 20 mg at night, as well as an increase in Prozac to 40 mg each day. The next month, the dose of Adderall was again increased, to 80 mg—three 20-mg tablets in the morning and one tablet in the evening—because the patient was still having problems with completing tasks. On the higher dose of Adderall, the patient experienced increased hyperactivity and irritability, and in response to these symptoms his neurologist recommended counseling; the Adderall and Prozac regimens were continued.

Two months later, the patient developed symptoms of abdominal pain, vomiting, and cough lasting for a month. He sought medical attention through his primary care physician with complaints of coughing (worst at night), chills, fatigue, tightness in the chest, and shortness of breath after climbing steps. On presentation, his pulse was 120 and his respiratory rate was 26. According to the patient, he vomited two to three times per day; his face and ankles were severely

swollen; he had chest tightness, fatigue, chills, and diarrhea. A chest x-ray showed a left-upper-lobe infiltrate and cardiomegaly, and he was diagnosed with pneumonia. On this same day, the patient required admission to the hospital and was evaluated for increasing shortness of breath, dyspnea with exertion, and a nonproductive cough of several weeks' duration. His cardiac examination showed a regular rhythm and S3 gallop, a pulse between 90 and 100, and a blood pressure of 196/50. He was assessed as possibly having a viral cardiomyopathy and mild congestive heart failure. An echocardiographic/cardiac Doppler examination confirmed a severely depressed ejection fraction of approximately 20%; and he developed a right popliteal occlusion secondary to a left ventricle thrombus. Soon after, the patient underwent a successful emergent cardiac transplant followed by cardiac rehabilitation.

Microscopic examination of heart tissue showed (1) focally severe coronary atherosclerosis: estimated maximum stenosis of 98%, proximal right coronary artery; (2) cardiomyopathy, mild cardiomegaly with biventricular myocyte hypertrophy, and focal biventricular endocardial and interstitial fibrosis; (3) mild focal nonspecific interstitial myocarditis suggestive of hypersensitivity; and (4) fatty infiltration of the right ventricular myocardium.

The pathologist noted that the contribution of coronary artery atherosclerosis to the development of cardiomyopathy in this case was uncertain.

DISCUSSION

Adderall, a combination of amphetamine and dextroamphetamine, is used to treat attention-deficit/hyperactivity disorder (ADHD) and narcolepsy. According to the manufacturer's prescribing information, "Isolated reports of cardiomyopathy have been associated with chronic amphetamine administration."[2] Relevant cardiovascular adverse reactions reported for Adderall include: palpitation, tachycardia, elevation of blood pressure, and isolated occurrences of cardiomyopathy associated with chronic amphetamine use.[2]

Although the patient was diagnosed during hospitalization with a viral cardiomyopathy, usually an infiltration of lymphocytes and plasma cells in the interstitial space (between muscle fibers) is seen later in the course of viral myocarditis. Furthermore, the nuclei and cross-striations of the cytoplasm typically are well preserved in viral cardiomyopathy. The standard (Dallas) microscopic criteria for viral myocarditis require the presence of necrotic myocytes along with lymphocyte infiltration, findings that were not present in this patient's heart pathology report.

Many of the symptoms associated with and attributed to a viral syndrome in this patient are more reasonably related to a combination of his underlying cardiomyopathy, his irritable bowel syndrome, and symptoms of Adderall toxicity or overdose, including GI disturbances, such as diarrhea. Chronic Adderall intoxication, as in the case of this patient, can lead to irritability, hyperactivity, and personality changes. An overdose of Adderall may cause rapid respiration, nausea and vomiting, fatigue, and abdominal cramps.

Alternative etiologies for cardiomyopathy[3] that were considered but ruled out by history, examination, and testing included (1) alcoholism or use of other drugs; (2) heavy metals, emetine, doxorubicin, cocaine, methamphetamine, or cobalt; (3) human immunodeficiency virus and other infections: viral endocarditis/myocarditis, parasites, protozoa, and Chagas disease; (4) high-output states such as anemia, thyrotoxicosis, and pregnancy; (5) collagen vascular disease; (6) glycogen storage disease; (7) thiamine deficiency and zinc deficiency; (8) hypophosphatemia, hypokalemia, or hypocalcemia; (9) amyloidosis; and (10) neuromuscular disorders. The only cause of cardiomyopathy that was consistent with this patient's medical history was amphetamine use. It is reasonable to conclude in retrospect that many of the signs and symptoms that may have been attributed to a viral-like illness were, in fact, early signs of amphetamine toxicity or overdose, or signs of cardiac failure from amphetamine.

Clinical pharmacology

Amphetamines exert their pharmacologic action[1] by blocking the reuptake of norepinephrine and dopamine into presynaptic neurons, increasing the release of these monoamines into the extraneuronal space. Dextroamphetamine, the eutomer of amphetamine, acts peripherally by release and reuptake inhibition of the monoamine neurotransmitters acetylcholine and histamine but not glutamate. The activity of dextroamphetamine at the vesicular monoamine transporter (VMAT2) is vital to the neurotransmitter release process.

Amphetamines release stores of norepinephrine and dopamine from nerve endings by converting the respective molecular transporters into open channels. Amphetamines also release stores of serotonin from synaptic vesicles. Like methylphenidate (Ritalin), amphetamines prevent the monoamine transporters for dopamine and norepinephrine from recycling them (reuptake inhibition). This leads to increased amounts of dopamine and norepinephrine in the synaptic clefts. These combined effects rapidly increase the concentrations of the respective neurotransmitters in the synaptic

cleft, promoting nerve impulse transmission in neurons that have those receptors.

Short-term physiological effects of amphetamines[1,2] can include decreased appetite; increased stamina and physical energy; increased sexual drive/response; involuntary bodily movements; hyperhidrosis; hyperactivity; jitteriness; nausea; itchy, blotchy, or greasy skin; tachycardia; irregular heart rate; hypertension; and headaches. Fatigue can often follow the dose's period of effectiveness.

Long-term abuse or overdose effects of amphetamines can include tremor, restlessness, changed sleep patterns, anxiety and increase in pre-existing anxiety, poor skin condition, hyperreflexia, tachypnea, gastrointestinal narrowing, and weakened immune system. Fatigue and depression can follow the excitement stage. Erectile dysfunction, heart problems, stroke, and liver, kidney, and lung damage can result from prolonged use. When snorted, amphetamine can lead to a deterioration of the lining of the nostrils.

Short-term psychological effects can include alertness, euphoria, increased concentration, rapid talking, increased confidence, increased social responsiveness, nystagmus, hallucinations, and loss of REM sleep the night after use. Long-term psychological effects can include insomnia, mental states resembling schizophrenia, aggressiveness (not associated with schizophrenia), addiction or dependence with accompanying withdrawal symptoms, irritability, confusion, and panic. Chronic and/or extensively continuous use can lead to amphetamine psychosis, which causes delusions and paranoia, but this is uncommon when the drug is taken within common prescriptive guidelines. Amphetamine can be highly psychologically addictive, and with chronic use, tolerance develops very quickly. Although not physiologically threatening, withdrawal can be an unpleasant experience (including paranoia, depression, difficult breathing, dysphoria, gastric fluctuations and/or pain, and lethargy). This commonly leads chronic users to re-dose amphetamine frequently, explaining tolerance and increasing the possibility of addiction.

Cardiomyopathy from amphetamines

A number of case reports[5–9] and discussions in the medical literature[1,3] document the ability of amphetamine drugs to cause cardiomyopathy. The prescribing information for Adderall notes that "Isolated reports of cardiomyopathy have been associated with chronic amphetamine administration."[2] Relevant cardiovascular adverse reactions reported for Adderall include palpitation, tachycardia, elevation of blood pressure, and isolated occurrences of cardiomyopathy associated with chronic amphetamine use. This would point to several potential mechanisms of action for amphetamine-associated cardiomyopathy.

Table 1. Number of reported cases of cardiomyopathy and other adverse events due to Adderall and Ritalin through 2004.

Drug	Cardiomyopathy	All related terms
Adderall	8	677
Ritalin	11	963

A search of publicly available databases for adverse events related to Adderall and Ritalin indicated the reports listed in Table 1.

Physicians whose patients develop cardiomyopathy during treatment with amphetamines or who have an underlying cardiac disease or risk factors for cardiac disease should consider the potential contribution of amphetamines as part of their therapeutic decision-making process.

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