Abnormal Serum Creatine Kinase and MB Fraction Following an Amitriptyline Overdose

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Widespread use of tricyclic antidepressants in clinical practice has led to extensive knowledge of their therapeutic and toxic effects. Foremost among the toxic effects is cardiotoxocity, particularly in acute overdoses as seen in adult suicide attempts. Cardiac effects include arrhythmia, both supraventricular and ventricular; prolongation of conductivity, especially seen in QRS and QT segments; hypotension; and decreased myocardial contractility.[1]

Herein is described a case of likely cardiac toxicity following an overdose of amitriptyline with a suggested mechanism that would account for the release of cardiac enzymes into the peripheral blood.

CASE REPORT

A 41-year-old woman was brought to the emergency room in a comatose condition. Her vital signs were pulse of 120 beats per minute, blood pressure of 150/100 mmHg, temperature 35.9°C (96.6°F) and respiration 16 per minute.

The patient's physical examination was normal, except for coma and lack of response to painful stimuli. There were no signs of trauma. The complete blood count, electrolytes, prothrombin time, and partial thromboplastin time were normal. Urinalysis was normal except for a positive ketone test; arterial blood gas results were pH 7.31, carbon dioxide pressure (PCO_2) 43 mmHg, oxygen pressure (PO_2) 130 mmHg, and bicarbonate 21 mmol/L. Her family reported the patient had been taking amitriptyline for monopolar depression, and the initial impression was coma owing to a massive overdose of this drug. The first electrocardiogram (ECG) showed a sinus tachycardia of 120 beats per minute, PR interval of 0.20 sec, QRS interval of 0.08 sec, and a prolonged QT interval of 0.34 sec, findings that were consistent with tricyclic antidepressant poisoning. A computerized tomography scan of the head was normal. She was treated with gastric lavage and activated charcoal but did not require physostigmine.

The patient was transferred to the medical intensive care unit for monitoring. Within four hours, she was arousable by verbal stimuli; she became alert and oriented, and her tachycardia resolved within 20 hours after admission. She had no hypotension at any time. ECGs were obtained for four days, which showed no signs of myocardial infarction or ischemia. The PR, QRS, and QT prolongation resolved within 48 hours. Because the origin of the patient's coma was not decipherable at the time of arrival in the emergency room, serum cardiac enzymes had been ordered. She showed marked elevation of the serum creatine kinase (CK) and of the MB fraction, a finding compatible with myocardial damage. The lactate dehydrogenase and its isoenzymes remained normal throughout her hospitalization. The temporal sequence of the serum enzyme abnormalities are shown in Table 1. On day 6, her creatine kinase and CK-MB fraction had returned to normal. Agarose gel electrophoresis, a widely used and accurate technique, had been used to determine creatine kinase isoenzymes.[2]

The serum amitriptyline concentration in blood collected on admission was 2.00 mg/L (toxic at greater than 0.50 mg/L), and the active metabolite, nortriptyline, was 0.43 mg/L (toxic at greater than 0.50 mg/L). After recovering, the patient acknowledged the overdose, but was unable to recall how many tablets she had taken. She denied any history of a previous cardiac disorder and denied any cardiac symptoms. An extensive cardiac evaluation included an M-mode and two-dimensional echocardiogram, and a 24-hour Holter ECG recording; all these were within normal limits. Because of the possibility that the abnormal creatine kinase and CK-MB values represented myocardial

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TABLE 1. TEMPORAL CHANGES OF SERUM ENZYMES IN PATIENT

Day	Time (hours)	Serum Creatine Kinase (CK) (U/L)	Serum CK-MB Fraction (% of CK)	Serum Lactate Dehydrogenase (U/L)
1	1100	220	3.8	—
1	2000	153	5.3	58
2	1430	182	4.4	—
2	2000	158	5.2	107
3	800	106	3.9	85
6	900	9	None	—

Reference ranges, creatine kinase; 0-95 U/L; lactate dehydrogenase; 49-110 U/L

damage, cardiac catheterization was performed at eight days after admission, which showed normal left ventricular function, no evidence of dyskinesis, and coronary arteries free of any obstructive lesions.

DISCUSSION

In this case, an overdose of amitriptyline produced coma and led to the appearance of the "cardiac" enzyme CK-MB in serum in the absence of correlative evidence of myocardial damage. The dramatically increased serum concentrations of amitriptyline confirmed the conclusion of an overdose. Based on her history and the absence of any other toxic substances on her toxicology screening test, the patient was believed not to have taken other drugs or alcohol.

While the abnormal creatine kinase and CK-MB fraction suggested possible acute myocardial infarction, this condition was ruled out based on both laboratory and clinical grounds. Her serum lactic dehydrogenase was persistently normal (Table 1), and she showed no ECG changes compatible with infarction; the normal coronary arteries found at cardiac catheterization tended to rule out infarction. The origin of the increased creatine kinase and the CK-MB fraction required explanation; the changes of these tests over time mimicked what is commonly seen in patients with myocardial infarction.[2]

When the enzyme CK-MB was first described over a decade ago, the reports stated that its presence in the serum was nearly 100 percent specific for myocardial necrosis.[3-6] However, by the mid to late 1970s, improved methods for detecting CK-MB had been developed that permitted detection of creatine kinase at much lower activities. It was soon found that the serum of normal persons contains low activities of CK-MB, usually at less than 1 to 3 percent of the total creatine kinase.[2,7,8] The source of the serum CK-MB fraction may come from the turnover of normal myocardial cells or it may represent noncardiac sources.

As the ability to measure the enzyme CK-MB became more widespread and accurate, reports of its detection in a number of noncardiac disorders and cardiac disorders without apparent myocardial infarction began to appear in the literature.[9] These reports included both acute and chronic primary muscle disorders,[10-12] cardiac disorders without infarction,[13] and a variety of miscellaneous situations including marathon running,[14] Reye's syndrome,[15] the peripartum period,[16] and fetal distress.[17]

This patient had no clinical evidence or laboratory tests compatible with skeletal muscle as a source of her increased serum CK-MB. Whether her increased serum creatine kinase could have come from a cardiac source in the absence of acute myocardial necrosis has been a point of controversy among experts in the field. The widely held notion that an abnormal CK-MB fraction can be equated with myocardial infarction is incorrect.[9] If an abnormal CK-MB fraction does not imply myocardial injury, what does it mean? Varat and Mercer[18] described four patients without acute myocardial infarction but with chronic atrial fibrillation where the CK-MB fraction was elevated, but where the 24- to 48-hour peak pattern of enzyme abnormalities typical of acute myocardial infarction were absent. They concluded that the enzyme CK-MB had been released from myocardial cells without myocardial necrosis. Marmor et al[19] reported patients with

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unstable angina who had an elevated CK-MB fraction with a normal total creatine kinase level and no evidence of myocardial infarction. In a second report with similar findings, Marmor et al[20] performed stress ECGs, and found that the degree of increased CK-MB correlated well with the degree of ischemia noted during the stress ECGs. They concluded that myocardial ischemia alone could lead to the release of CK-MB from myocardial cells in the absence of irreversible injury. Actual leakage from myocardium without infarction was described by Chiong et al in 1974,[21] who found an increased serum creatine kinase in the coronary sinus of patients who had anginal attacks during atrial pacing. These authors concluded that transient ischemia had led to the release of creatine kinase from viable myocardial cells.

Support for the concept that enzymes can be released from myocardial cells in the absence of necrosis comes from extensive research with animals. Studies using myocardial cells from rat,[22] guinea pig,[23] and rabbit[24] have shown that significant leakage of creatine kinase and other enzymes occurs from myocardial cells in the absence of irreversible damage. Isolated myocardial cells from the various species were subjected to a period of hypoxia; oxygenation was restored before the cells were irreversibly damaged. Consistently, these studies have shown that nonfatal hypoxic insult causes the cells to leak significant amounts of creatine kinase and other cytoplasmic enzymes. These reports cast doubt on the premise that only irreversible myocardial cell damage results in enzyme release.[23] Piper et al[25] used electron microscopy to demonstrate changes in the myocardial cell membrane of isolated rat myocardial cells subjected to reversible anoxia. They felt that the enzyme release correlated with the depletion of energy reserves owing to hypoxic insult. All of these studies support the hypothesis that the myocardial cell membrane permeability can be altered enough by short-term hypoxia to allow escape of CK-MB without having myocardial cell necrosis.

Sufficient data exist to support a hypothesis that the high concentration of amitriptyline produced a transient change in myocardial and skeletal muscle membrane permeability sufficient to cause the serum enzyme abnormalities that were observed.[26] There have been no previous reports of abnormal serum CK-MB enzyme activities following a tricyclic overdose. Being lipophilic agents, tricyclic antidepressants are bound to myocardial and other tissues. Amitriptyline, and its active metabolite, nortriptyline, have been found to be bound to myocardium, both in human and animal studies.[27,28] The drug binding has been correlated with amitriptyline's significant cardiac toxicity.[29]

When rats are given imipramine, a tricyclic antidepressant very similar in structure to amitrip-

tyline, their skeletal muscle cells become "leaky," and cytoplasmic enzymes such as creatine kinase are released.[30] This leakage is due to alteration of the myocardial cell membrane by the tricyclic agent.

It is most likely that the same phenomenon occurred in this patient. The release of creatine kinase and CK-MB was caused by the toxic effect of amitriptyline on the cell membranes of myocardium and skeletal muscle. The presence of abnormal activities of CK-MB in serum in the amounts that were observed would indicate direct involvements of the myocardial cells and leakage of enzymes from these cells.

Amitriptyline and nortriptyline have a marked affinity for the myocardium, with drug concentrations in this tissue that are typically five times that in serum.[27] Apparently the drug triggers the release of creatine kinase and CK-MB from myocardial cells, as was observed in this patient. Myocardial cell necrosis was believed to have been absent in this case; the changes in cell membrane permeability were transient.

It is important that this hypothesis be kept in a proper perspective. Its purpose is to inform clinicians about the various factors that can affect CK-MB activities in the clinical setting and to stimulate thought and interest into evaluating other factors, as yet unknown, that may affect this most useful test. It must be remembered that in a clinical situation where acute cardiac necrosis is likely or even possible, that CK-MB is still widely regarded as a highly sensitive and extremely specific indicator of myocardial cell necrosis.

References

1. Marshall JB, Forker AD: Cardiovascular effects of tricyclic antidepressant drugs: Therapeutic usage, overdose, and management of complications. Am Heart J 1982; 103:401-414
2. Lott JA, Stang JM: Serum enzymes and isoenzymes in the diagnosis and differential diagnosis of myocardial ischemia and necrosis. Clin Chem 1980; 26:1241-1250
3. Wagner GS, Roe CR, Limbird LE, et al: The importance of the identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. Circulation 1973; 47:263-269
4. Blomberg DJ, Kimber WD, Burke MD: Creatine kinase isoenzymes. Predictive value in the early diagnosis of acute myocardial infarction. Am J Med 1975; 59:464-469
5. Roberts R, Gowda KS, Ludbrook PA, et al: Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. Am J Cardiol 1975; 36:433-437
6. Galen RS, Reiffel JA, Gambino SR: Diagnosis of acute myocardial infarction. Relative efficiency of serum enzyme and isoenzyme measurements. JAMA 1975; 232:145-187
7. Shell WE, Kligerman M, Rorke MP, et al: Sensitivity and specificity of MB creatine kinase activity determined with column chromatography. Am J Cardiol 1979; 44:67-75
8. Roberts R, Henry PD, Witteeveen SAGJ, et al: Quantification of serum creatine phosphokinase isoenzyme activity. Am J Cardiol 1974; 33:650-654
9. Lott JA: Serum enzyme determinations in the diagnosis of acute myocardial infarction: An update. Human Pathol 1984; 15:706-716
10. Larca LJ, Coppola JT, Honig S: Creatine kinase MB isoenzyme in dermatomyositis: A noncardiac source. Ann Intern Med 1981; 94:341-343
11. Somer H, Dubowitz V, Donner M: Creatine kinase isoenzymes in neuromuscular diseases. J Neurol Sci 1976; 29:129-136
12. Silverman LM, Mendell JR, Sahenk Z, et al: Significance of creatine phosphokinase isoenzymes in Duchenne dystrophy. Neurology 1976; 26:561-564
13. Adornato BT, Engel WK: MB creatine phosphokinase isoenzyme elevation not diagnostic of myocardial infarction. Arch Intern Med 1977; 137:1089-1090
14. Kielblock AJ, Manjoo M, Booyens J, et al: CPK and LDH levels after ultra long-distance running. An analysis of isoenzyme profiles with special reference to indicators of myocardial damage. S Afr Med J 1979; 55:1061-1064
15. Roe CR, Schonberger LB, Gelbach SH, et al: Enzymatic alterations in Reye's syndrome. Pediatrics 1975; 55:119-126
16. McNeely MDD, Berris B, Papsin FR: Creatine kinase and its isoenzymes in the serum of women during pregnancy and the peripartum period. Clin Chem 1977; 23:1878-1880
17. Woolley B, Peevy KJ, Mendenhall HW, et al: Abnormal fetal heart rate patterns and percentage of creatine phosphokinase-2. Am J Obstet Gynecol 1983; 147:701-702
18. Varat MA, Mercer DW: Cardiac specific CPK isoenzyme in the diagnosis of acute myocardial infarction. Circulation 1975; 51:855-859
19. Marmor A, Kahana L, Alpan G, et al: Creatine kinase isoenzyme (CK-MB) in acute coronary ischemia. Am Heart J 1979; 97:574-577
20. Marmor A, Alpan G, Kreider S, et al: The MB isoenzyme of creatine kinase as an indicator of severity of myocardial ischemia. Lancet 1978; 1:812-814
21. Chiong A, West R, Parker JO: Myocardial balance of inorganic phosphate and enzymes in man. Circulation 1974; 44:283-290
22. Piper HM, Hutter JF, Spieckermann PG: Relation between enzyme release and metabolic changes in reversible anoxic injury of myocardial cells. Life Sci 1984; 35:127-134
23. Sakai K, Gebhard MM, Spieckermann PG, et al: Enzyme release resulting from total ischemia and reperfusion in the isolated, perfused guinea pig heart. J Mol Cell Cardiol 1975; 7:827-840
24. Nakanishi T, Young HH, Shimizu T, et al: The relationship between myocardial enzyme release and Ca^{2+} uptake during hypoxia and reoxygenation in the newborn and adult heart. J Mol Cell Cardiol 1984; 16:519-532
25. Piper HM, Schwartz P, Spahr R, et al: Early enzyme release from myocardial cells is not due to irreversible cell damage. J Mol Cell Cardiol 1984; 16:385-388
26. Bais R, Edwards JB: Creatine kinase. CRC Crit Rev Clin Lab Sci 1982; 16:291-335
27. Hebb JH, Caplan YH, Crooks CR, et al: Blood tissue concentrations of tricyclic antidepressant drugs in post mortem cases: Literature survey and a study of forty deaths. J Anal Toxicol 1982; 6:209-216
28. Cassano GB, Sjostrand SE, Hansson E: Distribution and fate of C^{14}-amitriptyline in mice and rats. Psychopharmacol 1965; 8:1-11
29. Elonen E: Correlation of the cardiotoxicity of tricyclic antidepressants to their membrane effects. Med Biol 1974; 52:415-423
30. Verrill HL, Pickard NA, Gruemer H-D: Mechanisms of cellular enzyme release. I. Alteration in membrane fluidity and permeability. Clin Chem 1977; 23:2219-2225