Coronary Artery Spasm Induced by Intravenous Epinephrine Overdose

STEVEN B. KARCH, MD

A 27-year-old man was accidentally given 2 mg intravenous epinephrine instead of 2 mg naloxone. He immediately developed chest pain, nausea, and diaphoresis. An ECG taken shortly after the epinephrine administration showed widespread ischemia. Forty-five minutes later the tracing still showed an early repolarization pattern, but ST elevation was less marked and the patient was asymptomatic. Serum potassium was 3.2 mEq/L and serum catecholamines, drawn approximately 20 minutes after the epinephrine administration, were 10 times normal (dopamine, 173 ng/L; epinephrine, 1,628 ng/L; norepinephrine, 1,972 ng/L). There are seven other reports of intravenous epinephrine overdose in the English literature. Two of the previously reported cases had 12-lead ECGs within the first hour. In both there was evidence of transient ischemia similar to that observed in this case. Most of the patients had symptoms consistent with angina, and several developed pulmonary edema. These findings suggest that, in humans, large intravenous doses of epinephrine are likely to produce coronary artery spasm and may decrease coronary artery perfusion. (Am J Emerg Med 1989;7:485-488. © 1989 by W.B. Saunders Company.)

Accidential overdose with epinephrine is an uncommon event, fewer than 40 cases having been reported in the last 50 years. In only seven of these cases was the epinephrine given intravenously.[1-6] The case reported here is of particular interest because catecholamines were measured. The case is also of interest because the amount of epinephrine given was in the range which some experimenters feel is necessary for successful cardiac resuscitation.[7,8]

CASE REPORT

A 27-year-old man was transported to the emergency department by paramedics. Following an argument with a friend he had pushed his hand through a plate glass window in anger. When the paramedics arrived he was bleeding profusely from a right forearm laceration and was quite agitated. The base station was contacted and a combination of valium, 5 mg, 50% dextrose, 50 cc, and narcan, 2 mg, was ordered. By mistake, 2 cc of 1:1,000 epinephrine (2 mg) was administered. The patient immediately became even more agitated and had to be restrained in order to be transported. Enroute to the hospital he began to complain of nausea and chest pain. On arrival in the emergency department he was still quite agitated, but was also diaphoretic and pale. His pulse was 140 beats/min and his BP was 86/46 mmHg. Except for the laceration, there were no physical findings of note. An ECG (Fig 1) demonstrateed a rate of 115/min with diffuse ST elevation. Laboratory tests done on specimens drawn shortly after arrival in the emergency department included a WBC count of 7,900 cells/μL and a hemoglobin of 12.8 g. The differential had 71 polys, 16 lymphs, 11 monocytes, 1 basophil and 1 eosinophil; there were no band forms. The electrolytes were abnormal with a sodium of 127 mEq/L, a potassium of 3.2 mEq/L, a chloride of 113 mEq/L and a CO_2 of 16 mEq/L. Glucose was 129 mg/dL, BUN was 10 mg/dL, and creatinine was 1.1 mg/dL. Cardiac enzymes were not ordered.

The patient received 5 mg intravenous haloperidol and 2 L lactated ringers with 40 mEq potassium chloride added. He was given plain lidocaine as a local anesthetic and his laceration was repaired. By that time he had calmed down considerably and was no longer complaining of chest pain or nausea. A repeat ECG about 45 minutes after the first tracing was still abnormal, but the ST elevation was much less marked and the remaining abnormalities consisted mainly of early repolarization (Fig 2). The patient was observed for another hour and was then discharged. The repolarization changes still persisted on the ECG, but the patient denied all symptoms and wanted to go home. He has since been lost to follow-up.

Serum catecholamines were not initially ordered, but the following morning a refrigerated specimen of heparinized blood from the patient, stored at 4°C, was found and submitted for analysis. Measurements were performed at an outside reference laboratory using the single isotope derivative radioenzymatic method.[1] Dopamine was 173 ng/L, epinephrine was 1,628 ng/L, and norepinephrine was 1,972 ng/L.

DISCUSSION

The first case of intravenous epinephrine overdose was reported in 1969. Novey and Meleyco described what happened after a patient with an allergic reaction to contrast medium was accidentally given 30 mg epinephrine intravenously. The patient developed congestive heart failure, pulmonary edema, and renal shutdown, but survived. Initial blood sugar and elec-

From the Department of Emergency Medicine, University Medical Center, Las Vegas.

Manuscript received August 9, 1988; revision accepted November 18, 1988.

Reprints not available.

Key Words: Epinephrine, overdose, coronary artery spasm.

0735-6757/89/0705-0007$5.00/0

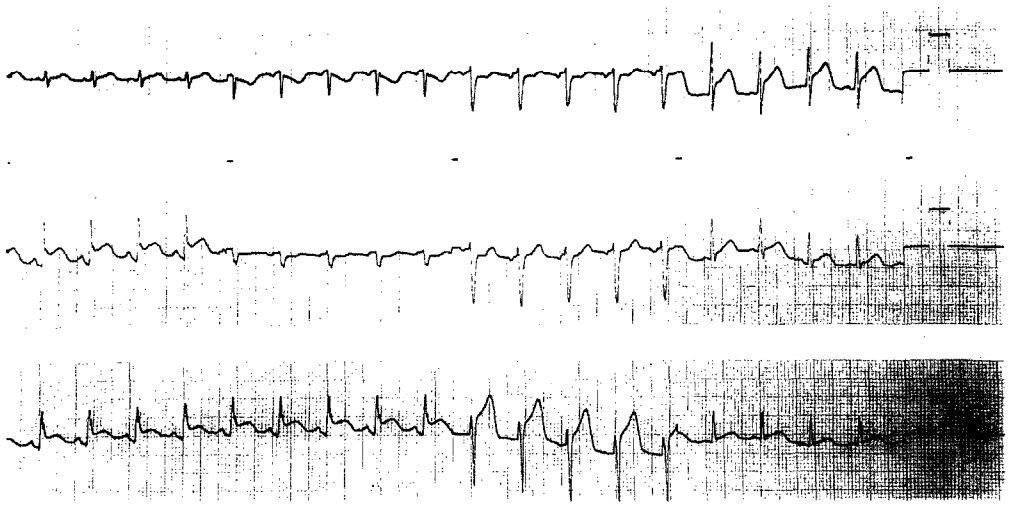

FIGURE 1. Initial ECG obtained immediately upon arrival in the emergency department. There is sinus tachycardial and diffuse ST elevation.

trolytes were not measured and an ECG done two hours after the onset of symptoms showed only sinus tachycardia.[2] In 1983, Horak et al administered 0.3 mg intravenous epinephrine, along with betamethasone and promethazine, to a young woman with an allergic reaction to penicillin. Almost immediately she developed chest pain, nausea, and diaphoresis. Her ECG showed changes consistent with extensive anterolateral ischemia. Both the chest pain and the ECG abnormalities were relieved when the patient was treated with sublingual and intravenous nitroglycerine.[3] In 1985 Kurachek and Rockoff described a case in which a 13-month-old child received racemic epinephrine intravenously instead of by nebulization. The total dose of L-epinephrine was roughly 0.325 mg. The child developed pulmonary edema but survived. ECG findings, blood sugar, and electrolytes were not mentioned in the report.[4] Another child who accidentally received racemic epinephrine was reported by Levine et al. A neonate received between 0.25 and 0.50 mg racemic epinephrine through an umbilical artery catheter. The patient developed peripheral vasoconstriction, tachycardia, hypertension, and anuria. A renal scan showed markedly diminished renal perfusion, presumably from spasm caused by the epinephrine which had entered the aorta below the renal arteries.[5] In 1987, Hall, Kulig, and Rumack reported the case of an intravenous polydrug abuser who injected himself with approximately 1 mg of epinephrine from an aerosol nebulizer. He immediately developed chest pain, pallor, and diaphoresis. His ECG showed ischemic changes in the precordial leads, but these changes cleared during overnight observation. Hypokalemia and hyperglycemia were also present.[6] There is one other report in the literature of two patients with penicillin-induced anaphylaxis.[9] Each patient received an intranvenous dose of 0.5 mg epinephrine. Both patients developed ventricular tachycardia, one in conjunction with an idioventricular rhythm. Both patients had uneventful recoveries after treatment with

FIGURE 2. ECG obtained 45 minutes after the first tracing. Early repolarization pattern is present but ST abnormalities are much less marked.

lidocaine. Unfortunately, 12-lead ECGs either were not performed or were not reported.

Similar complications have been reported after subcutaneous epinephrine. In 1986 Ferry et al described the case of a 43-year-old man who had a myocardial infarction 15 minutes after receiving 0.3 mg of sustained-dose epinephrine. When he was studied angiographically 1 month later, normal coronary arteries were found.[10]

The delay in processing refrigerated blood in the case reported here probably resulted in catechol readings that were falsely low. Previous studies have shown that plasma obtained from heparinized blood can be accurately assayed for catecholamines, though there is more loss of activity than in specimens that have been collected in mixtures of EGTA and reduced glutathione. Frozen specimens deteriorate at a rate of 5% a month, and this rate of deterioration increases as the temperature rises.[1] Supposing that half the activity was lost, the resultant blood levels would have still been less than half the level seen during cardiac arrest.[11] It is also unfortunate that toxicologic screening was not done. Some widely abused drugs, especially cocaine, as well as alcohol, tricyclic antidepressants, and even agitation, can increase serum catecholamines, though not to the levels found in this case.[12] The elevation in norepinephrine level may also have been the result of treatment with haloperidol. Haloperidol inhibits the dopamine$_2$ receptor, disrupting normal presynaptic inhibition of norepinephrine release.[13] Though the mechanism is not understood, it is nonetheless well known that a high level of epinephrine is associated with a high level of norepinephrine.[11] The high level of norepinephrine seen here could represent overflow from an intensely stimulated sympathetic nervous system, adrenomedullary release, or both.[14] The high levels are not the result of epinephrine breakdown because epinephrine is metabolized by catecholomethy transferase to metanepherine, which then acts as a substrate for monoamine oxidase.[14]

This patient also had ECG changes consistent with ischemia, as well as hyperglycemia, hypokalemia, and hypotension. Hypotension is a common finding in epinephrine overdose and occurs following an initial hypertensive response. Alpha stimulation initially produces increased peripheral resistance and hypertension. When circulating epinephrine levels drop back toward normal, alpha stimulation ceases but the more sensitive beta receptors continue to respond, and the result is peripheral dilation and hypotension.[14] In this particular case it is difficult to determine whether the observed relative hypotension was secondary to fluid loss or epinephrine effect. The patient's BP had returned to 110/70 mmHg in less than two hours, during which time he received nearly 3 L lactated ringers solution.

Reduced potassium in these patients is an example of stress hypokalemia. An intracellular shift in potassium is produced by catechol stimulation of Na-K ATPase.[15] Glucose elevation results from beta-mediated glucagon secretion, insulin inhibition, and increased glycogenolysis.[16] A possible explanation for the ischemic ECG changes is coronary artery spasm.

The sequence of events producing coronary artery spasm is poorly understood. Coronary spasm is generally thought to be the result of autonomic imbalance. Patients with Prinzmetal's angina, for instance, appear to have alterations in the autonomic nervous systems which produce repolarization abnormalities and QT prolongation before clinical evidence of spasm.[17] In animal studies, unilateral stellate ganglion stimulation also causes selective coronary spasm, QT prolongation, and increased coronary artery resistance.[18] Also in experimental animals, catechol infusions produce the same triad.[19] The catechol levels in our patient were higher than those known to produce spasm in experimental animals.

Physiological doses of epinephrine are thought to increase cardiac blood flow through a combination of effects. Indirect actions include increase in the duration of diastole, elevation of mean aortic pressure, and vasodilation occurring secondary to increased metabolic demand. Although the indirect effects of epinephrine on coronary vessels all favor vasodilation, there is some evidence for direct vasoconstrictive effects, and norepinephrine definitely has such an action.[20] Normally the direct action is of little importance compared to metabolically induced dilatation. The evidence available from the cases described here and in the literature suggests that when large doses of the drug are administered, the direct action of epinephrine on coronary arteries assumes much greater importance. It is unknown whether it produces the same result when it is administered during resuscitation. There are grounds for concern because the threshold for induction of coronary spasm is lowered by ischemia, hypoxia, and loss of autonomic control.[21] All of these conditions are present during cardiac arrest, and the possibility of epinephrine-induced coronary spasm merits further study.

REFERENCES

1. Johnson GA, Kupiecki RM, Baker CA: Single isotope derivate (radio-enzymatic methods in the measurements of catecholamines. Metabolism 1980;29:1106-1113 (suppl 1)
2. Novey HS, Meleyco LN: Alarming reaction after intravenous administration of 30 ml of epinephrine. JAMA 1969;207:2435-2436
3. Horak A, Raine R, Opie LH, et al: Severe myocardial ischaemia induced by intravenous adrenaline. Br Med J 1983;286:519
4. Kurachek SC, Rockoff MA: Inadvertent intravenous admin-

istration of racemic epinephrine. JAMA 1985;253:1441-1442
5. Levine DH, Levkoff AH, Pappu K, et al: Renal failure and other serious sequelae of epinephrine toxicity in neonates. South Med J 1985;78:874-876
6. Hall AH, Kulig KW, Rumack BH: Intravenous epinephrine abuse. Am J Emerg Med 1987;5:64-65
7. Koscove EM, Paradis NA: Successful resuscitation from cardiac arrest using high-dose epinephrine therapy, report of two cases. JAMA 1988;259:3031
8. Brown CG, Werman HA, Davis EA, et al: Comparative effect of graded doses of epinephrine on regional brain blood flow during CPR in a swine model. Ann Emerg Med 1986;15:1138-1144
9. Sullivan TJ: Cardiac disorders in penicillin-induced anaphylaxis: Association with intravenous epinephrine therapy. JAMA 1982;248:2161-2162
10. Ferry DR, Henry RL, Kern MJ: Epinephrine-induced myocardial infarction in a patient with angiographically normal coronary arteries. Am Heart J 1986;111:193-195
11. Worstman J, Frank S, Cryer PE: Adrenomedullary response to maximal stress in humans. Am J Med 1984;77:779-784
12. Karch SB: Serum catecholamines in acutely intoxicated cocaine users with cardiac symptoms. Ann Emerg Med 1987;16:481
13. Mercuro G, Gessa GM, Rivano CA, et al: Evidence for a dopaminergic control of sympthoadrenal catecholamine release. Am J Cardiol 1988;62:827-828
14. Weiner N: Norepinephrine, epinephrine, and the sympathetic amines. *In* Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacologic Basis of Therapeutics (ed 7). New York, Macmillan, 1985, pp 145-180
15. Carter BT: Subcutaneous epinephrine excess. Anesth Analg 1971;50:175-178
16. Brown MJ: Hypokalemia from beta$_2$-receptor stimulation by circulating epinephrine. Am J Cardiol 1985;56:3D-10D
17. Clutter WE, Bier DM, Shah SD, et al: Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest 1980;66:94-101
18. Ricci DR, Orlick AE, Cipriano PR, et al: Altered adrenergic activity in coronary arterial spasm: Insight into mechanism based on a study of coronary hemodynamics and the electrocardiogram. Am J Cardiol 1979;43:1073-1079
19. Randal WC, Armor JA, Geis WP, et al: Regional cardiac distribution of the sympathetic nerves. Fed Proc 1972; 21:1199-1208
20. VanCiters RL, Wagner BM, Rushmer RF: Architecture of small arteries during vasoconstriction. Circ Res 1962;10:668-675
21. Parratt JR: Effects of adrenergic activators and inhibitors on the coronary circulation. *In* Szerkeres L (ed): Handbook of Experimental Pharmacology, vol 54, part 2. Berlin, Springer Verlag, 1981, pp 737-757
22. Sheperd JT, Van Houthe PM: Spasm of the coronary arteries: Causes and consequences (the scientists viewpoint). Mayo Clin Proc 1985;60:33-46