Case report

Severe lactic acidosis in a case of nitroprusside resistance

Marcello Mellino, M.D.
Daniel F. Phillips, M.D.

Department of Cardiology

Sodium nitroprusside (NP) has recently gained wide acceptance as a relatively safe agent to achieve controlled hypotension during surgery.[1] It is also effective in reducing ventricular afterload and preload in clinical conditions characterized by high left ventricular end-diastolic pressure, elevated mean arterial pressure, and acute myocardial ischemia.[2]

This drug offers the dual advantage of rapid onset of action and short half-life, which allows prompt cessation of its effect upon withdrawal and of a high rate of response with a high therapeutic index. The most dangerous aspect of NP therapy is cyanide toxicity,[3] which clinically presents with central nervous system depression, metabolic disturbances, and severe hypotension. It may lead to death if not promptly discovered and adequately treated.[4]

Suggestions have been made to monitor NP administration during both short and long infusions with thiocyanate blood levels in order to detect cyanide toxicity. Levels higher than 10 mg/dl correlate well with toxic levels of cyanide.[4] More recent studies recommend monitoring blood cyanide levels as a better indication of NP metabolism and of potentially lethal cyanide accumulation.[5] We report a case of severe lactic acidosis following ad-

ministration of NP to a patient who suffered an acute myocardial infarction complicated by persistent systemic hypertension and prolonged angina immediately after the acute event.

Case report

A 52-year-old white woman complained of sudden onset of severe, persistent, retrosternal chest pain radiating to both arms, accompanied by diaphoresis, dyspnea, lightheadedness, and nausea. She had had no previous episodes of chest pain nor notable cardiovascular symptoms except for mild dyspnea on exertion during the past year. She was found to have mild hypertension 3 years previously for which she was taking hydrochlorothiazide, 50 mg daily, with good control. She had smoked one pack of cigarettes a day for more than 30 years.

Physical examination showed an acutely ill, diaphoretic and mildly dyspneic woman. Her weight was 66 kg (145 pounds), blood pressure was 180/110 mm Hg, and the pulse rate was 72 beats/min and regular. There was no jugular venous distension. The lungs were clear. An examination of the heart revealed normal heart sounds without any S3 or S4 gallop or murmur. The peripheral pulses were normal. The abdominal examination was normal, and there were no neurologic abnormalities.

Laboratory findings were as follows: the electrocardiogram showed an acute anteroseptal myocardial infarction. A roentgenogram of the chest was normal. On admission, the serum cholesterol was 330 mg/dl; the blood urea nitrogen (BUN), 18 mg/dl; and the creatinine, 1.0 mg/dl. The electrolytes, complete blood count, and arterial blood gases were normal. A nonfasting blood sugar was 180 mg/dl with a subsequent fasting blood sugar of 100 mg/dl. The initial cardiac and hepatic enzyme levels were normal, but serial (CPK), lactic dehydrogenase (LDH), and serum glutamic oxaloacetic transaminase (SGOT) determinations confirmed the diagnosis of acute myocardial infarction. The CPK-MB band peaked at 39% on the second day, with a subsequent return to normal.

The patient was admitted to the coronary care unit with continuous chest pain unrelieved by nitroglycerin and morphine sulphate. A continuous intravenous infusion was started with 100 mg of NP in 250 cc, 5% dextrose in water at 10 microdrops per minute, equivalent to 66 μg/min or 1 μg/kg/min, in order to keep her mean blood pressure 75 to 85 mm Hg. Her mean blood pressure during the subsequent 34 hours remained constantly between 90 and 110 mm Hg in spite of progressively increasing doses of NP to 6.0 μg/kg/min. She received a total dose of 1093 mg of NP intravenously during a 34-hour period (mean, 32 mg/hr or 0.48 mg/kg/hr). After 32 hours of continuous intravenous infusion of NP, progressive, labored respirations with tachypnea devel-

Table. Biochemical data on admission and after 32 hours of continuous NP infusion: repeated determinations after abrupt withdrawal of NP

	Admission	2:15 a.m.	3:00 a.m	4:00 a.m.	6:00 a.m.
pH	7.57	7.08	7.36	7.45	7.52
pCO_2, mm Hg	32	11	19	25	39
pO_2, mm Hg	58	126	80	68	76
HCO_3, mEq/L	29	3	10	17	31
Base excess, mEq/L	+9	−25	−12	−4	+9
Lactic acid (N = 10.5 − 22 mEq/L)	0	19.6	...	...	<2.0
Thiocyanate (N<10 mg/dl)	0	2.5	...	...	2.5
Na^+, mEq/L	138	123	...	...	135
K^+, mEq/L	4.1	3.6	...	...	3.7
Cl^-, mEq/L	98	92	...	...	94
CO_2, mEq/L	26	3	...	...	29
BUN, mg/dl	18	21	...	...	20

oped. She became restless and irritable and complained of nausea and vomited repeatedly. Her mental status rapidly deteriorated until she became unconscious, with fully dilated pupils, cold and clammy skin, and a peculiar pink mottled appearance. There were no focal neurological changes. The electrocardiogram showed frequent unifocal premature ventricular contractions, and her urinary output decreased.

Her blood gases were markedly abnormal (*Table*). She had evidence of severe lactic acidosis with inadequate respiratory compensation. A thiocyanate level was drawn and subsequently reported as 2.5 mg/dl (toxic level greater than 10 mg/dl). A second thiocyanate level 4 hours later was 2.5 mg/dl. The intravenous infusion of NP was discontinued abruptly, and she received two ampules of sodium bicarbonate intravenously. Over the following 45 minutes, she gradually improved, and in 3 hours, had regained full consciousness with complete disappearance of the previous symptoms. Her metabolic status returned to normal. Her mean blood pressure became normal and subsequently remained within normal limits without further treatment.

Discussion

This case illustrates that severe lactic acidosis can be a potentially lethal complication of NP therapy, as previously reported.[6] We believe that this has not received adequate emphasis in the abundant recently published reports on the various aspects of this drug.

The metabolic degeneration of NP consists of an initial nonenzymatic production of cyanide from the interaction of NP with hemoglobin producing methemoglobin and eventually cyanmethemoglobin from the further reaction of cyanide with methemoglobin. The cyanide released in the initial reaction may overwhelm this detoxifying mechanism; at the cellular level it is capable of inactivating the cytochrome oxidase, causing cellular hypoxia and possibly death. Rhodanase is an intramitochondrial enzyme particularly active in the liver and in the kidney, which is capable of detoxifying the cyanide with production of thiocyanate. The effectiveness of this enzyme depends on the availability of thiosulphate, which supplies necessary amounts of sulphur groups. Thiocyanate is eventually eliminated mostly unchanged via the kidneys.[7] Vitamin B_{12} also may play a role in the detoxification of excess cyanide with production of cyanocobalamin.

Detection of early evidence of cellular toxicity due to cyanide accumulation would be extremely important clinically. Early metabolic indicators include progressive acidosis, base deficit, and elevated, mixed venous oxygen tension, all of which indicate increased cellular anaerobic metabolism.[7]

The clinical incidence of lactic acidosis complicating the use of NP is unknown possibly because it is rarely suspected. Severe cyanide toxicity can develop with normal thiocyanate blood levels, possibly because of different metabolic steps that cyanide must go through before being transformed into the relatively nontoxic thiocyanate. Consequently, thiocyanate levels do not always reflect potentially toxic cyanide levels, and normal thiocyanate levels do not disprove the possibility of NP toxicity.[5]

This case most likely demonstrates resistance to NP, which has been rarely reported clinically, as evidenced by absent hypotensive response to progressively increasing doses.[4] The mechanism of development of resistance to NP is not fully understood. Some investigators have suggested that the elevated plasma renin activity associated with NP-induced hypotension could lead to increased renin-angiotensin release, with consequent vasoconstriction, which an-

tagonizes the hypotensive action of NP.[4] As a consequence, larger doses of NP are needed to achieve the desired hypotensive response.

A direct antagonizing effect of cyanide on smooth vascular muscles has also been suggested, with progressively less responsiveness to NP, also as a consequence of cellular hypoxia.[4]

Close metabolic monitoring should be instituted in patients receiving NP therapy particularly if resistance is suspected, because the development of lactic acidosis as an early manifestation of cyanide accumulation at a cellular level necessitates prompt withdrawal of NP and institution of adequate measures indicated for the treatment of NP toxicity.[4, 8]

References

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