USE OF NALOXONE IN SEPTIC SHOCK

Jerome Canady, MD, Wydell Williams, MD, Ira Thompson, MD,
Gilford S. Vincent, MD, and Eddie Hoover, MD
Nashville, Tennessee

Experimental and clinical evidence show that endogenous opiates (endorphins) contribute to the pathophysiology of circulatory shock. The authors evaluated the effectiveness and safety of continuous infusion of naloxone in five septic patients with prolonged hypotension unresponsive to volume replacement and dopamine infusion. Naloxone (2 mg bolus) was intravenously administered and continued at 0.25 mg/hr for 24 to 48 hours. All five patients had significant increase in mean arterial pressure of between 20 and 30 mmHg ($P < 0.0012$). Cardiac index, systemic vascular resistance, and pulmonary arterial pressure were not significantly altered; however, there was a significant difference in pulmonary capillary wedge pressure ($P < 0.034$) and urinary output ($P < 0.0273$). Subjects did not experience side effects with naloxone. We conclude that continuous infusion of naloxone can reverse endorphin-mediated hypotension in septic shock patients.

Inotropic or vasoactive drugs have been used in noncardiogenic and cardiogenic shock. Levarterenol and isoproterenol are no longer first-line drugs of choice because they produce undesirable effects such as disturbed cardiac rate or rhythm, peripheral and renal vasoconstriction, and increased oxygen demand. The ideal agent should enhance cardiac contractility, maintain effective circulatory blood volume and renal blood flow, but not induce or aggravate arrhythmias, significantly increase heart rate, or produce extreme variation in aortic blood pressure.[1]

Dopamine, a potent sympathomimetic, is the immediate precursor of norepinephrine and epinephrine.[2] It is a selective β_1-agonist, has dopaminergic renovascular receptor action, and is a direct coronary vasoconstrictor.[3-5] At low doses it increases glomerular filtration rate, sodium excretion, renal blood flow, contractile force of the heart (with minimum changes in the heart rate), and systolic blood pressure. High doses increase heart rate and total peripheral resistance and produce renal vasoconstriction by α-agonist activity. Dopamine is used in patients with low blood pressure, low or normal systemic vascular resistance, and oliguria; the drug is effective in patients with cardiogenic or septic shock.[6-8]

Dobutamine is structurally similar to dopamine, with the exception of an aromatic substitute for hydrogen on the amino group. It selectively increases myocardial contractility with minimum changes in heart rate. Sinus node automaticity and atrial ventricular node conduction velocity are enhanced[9]; the drug has no direct effect on coronary vascular tone.[1,10-13] Dobutamine is used effectively in patients with severe congestive heart failure[14-16] and after coronary bypass surgery in combination with nitroglycerin.[17]

Endorphins are elevated in shock,[18-20] and naloxone, an opioid receptor antagonist, may reverse this hypotension.[21] There are at least five groups of naturally occur-

From the Meharry Medical College Department of Surgery, Nashville, Tennessee. Presented at the Drew-Walker Forum at the 93rd Annual Convention and Scientific Assembly of the National Medical Association, Los Angeles, California, July 30-August 3, 1988. Requests for reprints should be addressed to Dr. Gilford S. Vincent, Department of Surgery, Meharry Medical College, 1005 D.B. Todd Boulevard, Nashville, TN 37208.

TABLE 1. PROFILE OF STUDY GROUP

Patient	Age/Sex	Primary Diagnosis	Infection	Vasoactive Pressors (μg/kg/min)	Outcome
1	62/M	Fecal peritonitis	*Klebsiella pneumoniae*	Dopamine (15) Phenylephrine	Survived
2	75/M	Gangrene of the leg	*Pseudomonas aeruginosa*	Dopamine (12)	Died
3	76/M	Ruptured abdominal aortic aneurysm, gangrene of the leg	*Staphylococcus aureus*	Dopamine (15)	Died
4	65/F	Urosepsis, infected decubiti	*Escherichia coli*	Dopamine (14)	Died
5	70/M	Ruptured abdominal aortic aneurysm	*Pseudomonas aeruginosa*	Dopamine (15)	Died

TABLE 2. DURATION OF HYPOTENSION BEFORE NALOXONE INFUSION

Patient	Hours	Naloxone Dose Associated with Increased MAP*
1	15	yes
2	24	yes
3	48	yes
4	30	yes
5	26	yes

* A 10 mmHg increase lasting at least 15 minutes.
MAP = mean arterial pressure.

ring opioid peptides.[22,23] Of these, enkephalins, dymorphins, and endorphins are most likely to have physiologic, pathologic, or pharmacologic involvement. Endogenous opiates, β-endorphins are stored with pituitary adrenocorticotrophic hormone[24,25] and stress seems to release both peptides. The cardiovascular system is extremely sensitive to the effects of both exogenous[26,27] and endogenous[28] opiates. Holaday and Fader[29] first reported that naloxone could increase blood pressure in experimental septic shock animal models. Several other reports have described the use of naloxone in patients with refractory hypotension secondary to sepsis.[30,31] Case reports have also documented the pressor effects of naloxone in septic shock.[31-35]

Despite the introduction of dopamine and dobutamine in the treatment of shock and administration of antibiotics and intensive supportive care, the mortality rate remains 40% to 70%.[36-37] The use of naloxone in humans with shock has been limited. The authors report their experience with the continuous infusion of naloxone and dopamine in treating patients with septic shock unresponsive to conventional supportive therapy.

MATERIALS AND METHODS

This study was performed in the surgical intensive care unit of the Veterans Administration hospital in Murfessboro, Tennessee, and St. Anthony's Medical Center in Columbus, Ohio, from December 1986 to December 1987. Criteria for inclusion in this study were: clinical evidence of shock (alteration in mental status, oliguria, cold extremities), systolic blood pressure less than 80 mmHg (30 minutes or longer), and pulmonary capillary wedge pressure between 10 and 15 mmHg while receiving dopamine (10-12 μg/kg/min). Patients were excluded if blood pressure was restored in 20 minutes by transfusion of appropriate fluids, pulmonary capillary wedge pressure was less than 10 mmHg, cardiogenic shock, myocardial infarction, or response in systolic blood pressure (greater than 90 mmHg) was apparent while receiving continuous infusion of dopamine or dobutamine (10-12 μg/kg/min).

Procedure

Before entry into the protocol all patients received sufficient intravascular volume expansion: wedge pressure was increased to 10 to 15 mmHg, appropriate antibiotics were administered, and metabolic acidosis and hypoxemia were corrected. Inotropic agents were immediately initiated upon arrival to the surgical intensive care unit. If hypotension persisted despite conventional therapy, patients were considered for naloxone administration. All patients had Swan-Ganz and radial artery catheters; electrocardiograms were continuously monitored. The transducers were calibrated against a

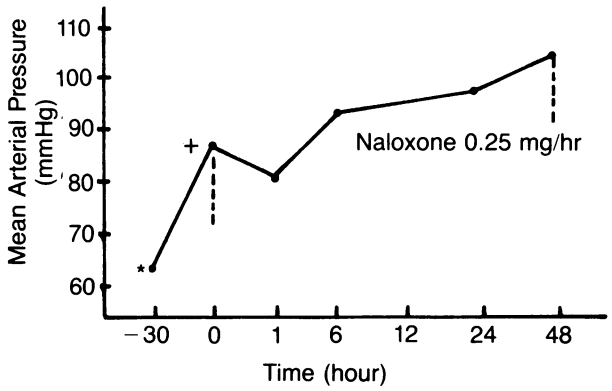

Figure 1. Mean arterial pressure (*) during control period with dopamine (10-12 μg/kg/min) in five patients. Mean value of the mean arterial pressure (+) after bolus infusion of naloxone (2 mg) in five patients.

reference to the midaxillary line. Systolic pressure in patients with a radial artery catheter was displayed from digital monitoring equipment. Right atrial pressure, pulmonary arterial pressure, and pulmonary capillary wedge pressure were monitored through a balloon-tipped Swan-Ganz catheter inserted percutaneously through a subclavian vein puncture. Cardiac output was measured in triplicate by thermodilution technique, and cardiac index was calculated from cardiac output and body surface areas. Data were obtained before the infusion of naloxone in all the patients.

Protocol

Hemodynamic measurements were made during the control period before infusing naloxone. Naloxone was supplied in a 2 mg bolus solution and then 2 mg in 500 cc 5% dextrose in water. The 2 mg bolus of naloxone was given over two to three minutes and systemic arterial pressure, pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac index (CI) were measured five minutes after the bolus infusion. Continuous infusion of naloxone at 0.25 mg/hr was immediately started after obtaining hemodynamic data during the naloxone bolus infusion. Dopamine was decreased from 10 to 12 μg/kg/min to 5 to 6 μg/kg/min and remained at a constant dose. PCWP was kept above 12 mmHg. Hemodynamic calculations were obtained at 1, 6, 12, 24, and 48 hours during the study period. Naloxone was stopped after 48 hours.

RESULTS

Over the 12-month study, four males and one female were entered into the study (Table 1). The mean age was 69.6 years. Four patients underwent surgery prior to

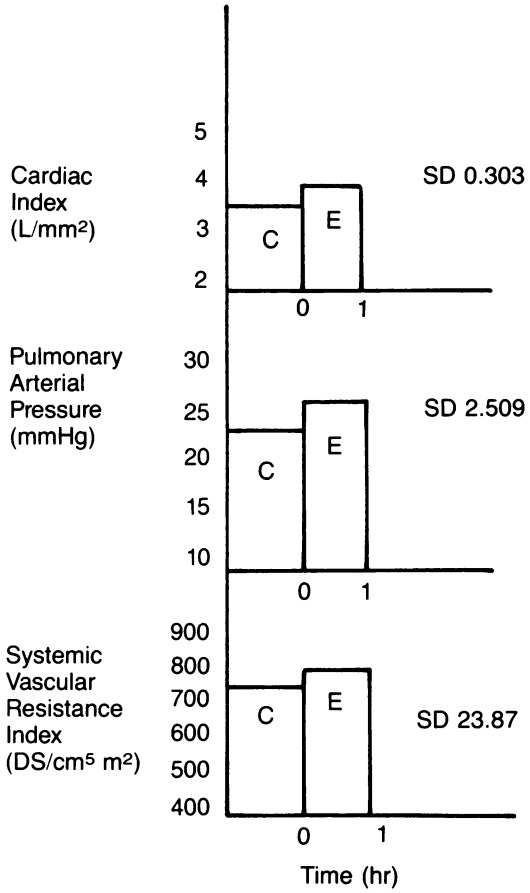

Figure 2. Mean hemodynamic values in five patients. C = control group; E = experimental group.

naloxone infusion. The control group consisted of patients who were receiving dopamine (10-12 μg/kg/min) prior to naloxone infusion. Duration of hypotension prior to naloxone infusion ranged between 15 and 48 hours (Table 2). Figure 1 demonstrates the continuous improvement of mean arterial pressure with the infusion of naloxone (0.25 mg/hr) plus dopamine (5-6 μg/kg/min) ($P < 0.0012$). There were no significant changes in systemic vascular resistance index, CI, and PAP; however, a significant difference in urinary output and PCWP was noted (Figures 2 and 3). No side effects were observed and none of the patients showed a decrease in analgesia postoperatively after the bolus or continuous infusion of naloxone. Four of the patients died but none died of septic shock. All subsequently died of underlying disease processes 10 to 20 days after cessation of naloxone infusion. Results were analyzed using the paired *t* test at a 0.05 level of significance.

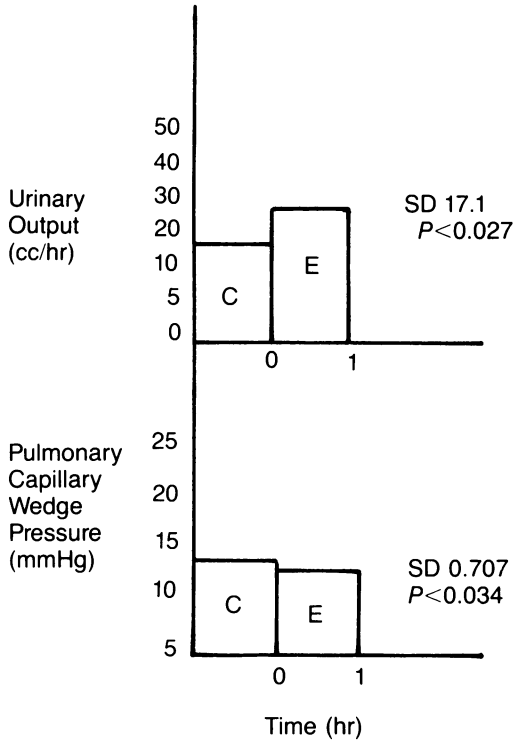

Figure 3. Mean hemodynamic values in five patients. C = control group; E = experimental group.

DISCUSSION

After Holaday and Fader reported the reversal of endotoxin hypotension by naloxone in rats,[29] other authors subsequently reported this reversal effect in other animal models.[38-41] In an uncontrolled study, Peters et al[21] described the use of intravenous naloxone in 13 patients with prolonged hypotension. Total dosage was between 0.4 and 1.2 mg/kg, with a clinical response in nine patients who did not receive corticosteroids. In another uncontrolled study, Groeger et al[35] observed ten patients in septic shock treated with naloxone (0.3 mg/kg as a single bolus). Results showed patients who responded to naloxone had been hypotensive fewer than eight hours compared with nonresponders who had been hypotensive for more than 24 hours. Peters[21] proposed that the role of concomitant steroid use to suppress endorphins during shock might prevent a blood pressure response to naloxone. Subsequently, Hughes[42] and Groeger[35] found that blood pressure increased in patients who received naloxone and corticosteroids. In our series, one patient received corticosteroids after the infusion of naloxone had no effect on blood pressure.

Higgins and Sivak[43-44] advocated the continuous infusion of naloxone in shock patients. They reported the administration of naloxone in three patients with septic or cardiogenic shock. Blood pressure increase was observed in all three patients. Furnum et al[45] reported the use of naloxone in two neonates with overwhelming sepsis. The bolus infusion of naloxone caused a transient increase in blood pressure, which subsequently required continuous naloxone infusion to maintain. In addition, Tiengo[46] reported an 8-year-old child with meningococcemia whose blood pressure was unresponsive to conventional therapy. The child received naloxone 0.01 mg/kg initially and then two doses of 0.2 mg subcutaneously, with immediate and continuous elevation in blood pressure.

Several factors modify the efficacy of naloxone in hypotension. Kaufman[47] reported that acidosis severely reduces the effectiveness of naloxone in animal studies. Furthermore, Jansen[48] showed that the pressor response to naloxone in endotoxin hypotension was also affected by hypothermia.

The experience of naloxone in critically ill patients is limited to a few clinical studies. Naloxone has a short half-life of 60 minutes,[49] but the clinical effects may diminish more quickly and continuous infusion or repetitive doses may be required. Naloxone has been given in dosages ranging from 0.1 to 0.3 mg/kg without adverse effects. Dosages as high as 4 mg/kg have been given intravenously without side effects[50]; however, pulmonary edema and congestive heart failure have been reported after naloxone-induced anesthesia reversal in patients who have undergone cardiac surgery.[51-53] No patient in our series had any adverse side effects or loss of analgesia postoperatively.

Our data demonstrated that naloxone improves blood pressure in patients with septic shock who were unresponsive to conventional therapy. Because the pharmokinetics are unknown in patients with shock, we advocate the continuous naloxone infusion. We have found that the continuous infusion of naloxone at 0.25 mg/hr with dopamine at 5 to 6 μg/kg/min reverses endotoxin hypotension.

Literature Cited

1. Tuttle RR, Mills J: Dobutamine: Development of a new catecholamine to selectively increase cardiac contractility. *Circ Res* 1975; 36:185-196.

2. Goldberg LI: Dopamine clinical use of an endogenous catecholamine. *N Engl J Med* 1974; 291:707-710.

3. Brooks HL, Stern PD, Matson JL, et al: Dopamine-induced alterations in coronary hemodynamics in dogs. *Circ Res* 1969; 24:699-704.

4. Goldberg LI: Cardiovascular and renal actions of dopa-

mine: potential clinical applications. *Pharmacol Rev* 1972; 24:1-29.

5. Leier CV, Webal J, Bush CA, et al: The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure. *Circulation* 1977; 56:468-472.

6. Ganz W, Swann HJC: Measurement of blood flow by thermodilution technique. *Am J Cardiol* 1972; 29:241-246.

7. Guiha NH, Cohn JN, Mikulic E, et al: Treatment of refraction heart failure with infusion of nitroprusside. *N Engl J Med* 1974; 291:587-592.

8. Wilson RF, Sibbald WS, Jaanimagi JL: Hemodynamic effects of dopamine in critically ill septic patients. *J Surg Res* 1976; 20:163-172.

9. Loeb HS, Sirno MZ, Saudize AI, et al: Electrophysiologic properties of dobutamine. *Circ Shock* 1974; 1:217-220.

10. Jewitt D, Birkhead H, Mitchell A, et al: Clinical cardiovascular pharmacology of dobutamine, a selective inotropic catecholamine. *Lancet* 1974; 2:363-367.

11. Mikulic E, Cohn JN, Franciosa JA: Comparative hemodynamic effects of inotropic and vasodilator drugs in severe heart failure. *Circulation* 1977; 56:528-533.

12. Perlroth M, Harrison D: Cardiogenic shock: A review. *Clinical Pharmacology and Therapeutics* 1969; 10:449-467.

13. Vatner SF, McRitchie RJ, Braunwald E: Effects of dobutamine on left ventricular performance, coronary dynamics and distribution of cardiac output in conscious dogs. *J Clin Invest* 1974; 53:1265-1273.

14. Leier CV, Huss P, Heban PT, et al: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation* 1978; 53:466-475.

15. Loeb HS, Bredakis J, Gunner RM: Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation* 1977; 55:375-378.

16. Stoner JD, Bolen JC, Harrison DC: Comparison of dobutamine and dopamine in treatment of severe heart failure. *Br Heart J* 1977; 39:536-539.

17. Meretoja AO: Hemodynamic effects of combined nitroglycerin and dobutamine infusions after coronary bypass surgery with one nitroglycerin-related complication. *Acta Anaesthesiol Scand* 1980; 24:115-211.

18. Oyama T, Yao M, Ishhara H, et al: Effects of hemorrhagic shock and endotoxin shock on plasma levels of β-endorphin & β-lipotropin. *Prog Clin Biol Res* 1983; 111:185-196.

19. Gurll NJ, Reynolds DG, Vargish T, et al: Body temperature and acid base balance determine cardiovascular response to naloxone in primate hemorrhagic shock. *Fed Proc* 1982; 41:1135-1138.

20. Faden AI, Jacobs TP, Mougey EH, et al: Endorphins in spinal injury. Therapeutic effect of naloxone. *Ann Neurol* 1981; 10:326-332.

21. Peters WP, Johnson MW, Friedman PA, et al: Pressor effect of naloxone in septic shock. *Lancet* 1981; 1:529-532.

22. Hughes J, Kosterlitzs HW: Opioid peptides: Introduction. *Br Med Bull* 1983; 39:1-3.

23. Morley JS: Chemistry of opioid peptides. *Br Med Bull* 1983; 39:5-10.

24. Rosier J, French ED, Rivier C, et al: *Nature* 1978; 270:618-620.

25. Guillemin R, Vargo T, Rossier J: β-endorphin & adrenocorticotropin are secreted concomitantly by the pituitary gland. *Science* 1977; 197:1367-1369.

26. Evans GJ, Naismyth PA, Steward HC: The fall of blood pressure caused by intravenous morphine in the rat and cat. *Br J Pharmacol* 1952; 7:542-552.

27. Gokhale SD, Gulati OD, Joshi NY: Effects of some blocking drugs on the pressor response to physostigmine in the rat. *Br J Pharmacol* 1963; 21:273-284.

28. Florey J, Mdeiavilla A: Respiratory and cardiovascular effects of met-enkephalin applied to the ventral surface of the brain stem. *Brain Res* 1977; 138:585-590.

29. Holaday JW, Faden AI: Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. *Nature* 1978; 275:450-451.

30. Wright DJM, Phillips M, Weller, et al: Naloxone in shock. *Lancet* 1980; 2:1360.

31. Pourriat JL, Lapandry C, Gabry AL, et al: Naloxone in septic shock. Abstr. Sixth European Congress of Anesthesiology. London, Academic Press, 1982, p 87.

32. Dirsken R, Otten MH, Wood GJ, et al: Naloxone in shock. *Lancet* 1980; 2:1360-1361.

33. Boskouski N, Lewinski A, Costic M, et al: The use of naloxone in critically ill patients. Abstr. Sixth European Congress of Anesthesiology. London Academic Press, 1982, p 174.

34. Swinburn WR, Phelan P: Response to naloxone in septic shock. *Lancet* 1982; 1:167.

35. Groegers JS, Carlon GC, Howland WS: Naloxone in septic shock. *Crit Care Med* 1983; 2:650-654.

36. McGowan JE, Burnes HW, Finland M: Bacteremia at Boston City Hospital: Occurrence and mortality during 12 selected years (1935-1972) with special reference to hospital acquired cases. *J Infect Dis* 1975; 132:316-335.

37. Ledingham I: Septic shock. *Br J Surg* 1975; 62:77-80.

38. Vargish T, Reynolds DG, Gurll NJ, et al: Naloxone reversal of hypovolemic shock in dogs. *Circ Shock* 1980; 7:31-38.

39. Reynolds DG, Gurll NJ, Vargish T, et al: Blockage of opiate receptors with naloxone improves survival and cardiac performance in canine endotoxic shock. *Circ Shock* 1980; 7:39-48.

40. Faden AI, Holaday JW: Naloxone treatment of endotoxin shock: Stero-specificity of physiologic and pharmacologic effects in the rat. *J Pharmacol Exp Ther* 1980; 212:441-447.

41. Faden AI, Holaday JW: Opiate antagonist a role in the treatment of hypovolemic shock. *Science* 1979; 205:317-318.

42. Hughes GH, Porter RS, Marx R, et al: Naloxone therapy in septic shock. *Abstracts of Clinical Research* 1983; 31:258A.

43. Higgins TL, Sivak ED: Reversal of hypotension with naloxone. *Cleveland Clinic Quarterly* 1981; 48:283-288.

44. Higgins TL, Sivak ED, O'Neil DM, et al: Reversal of hypotension by continuous naloxone infusion in a ventilator-dependent patient. *Ann Intern Med* 1983; 98:47-48.

45. Furnum WL, Menke JA, Bursin WJ, et al: Continuous naloxone infusion in two neonates with septic shock. *J Pediatr* 1984; 105:649-650.

46. Tiengo M: Naloxone in irreversible shock. *Lancet* 1980; 2:690.

47. Kaufman JJ: Acidosis decreases in vivo potency of narcotics and narcotic antagonists and can even abolish narcotic antagonist activity. *Lancet* 1982; 1:559-560.

48. Jansen HF, Pugh JL, Luther LO: Reduced ambient temperature blocks the ability of naloxone to prevent endotoxin induced hypotension. *Adv Shock Res* 1982; 7:117-124.

49. Ngai SH, Berkowitz BA, Yang JC, et al: Pharmokinetics of naloxone in rats and in man: Bases for its potency and short duration of action. *Anesthesiology* 1976; 44:398-401.

50. Cohen MR, Cohen RM, Picar D: Behavioral effects after high dose naloxone administration to normal volunteers. *Lancet* 1981; 2:110.

51. Michaelis LI, Hickey PR, Clark TA, et al: Ventricular irritability associated with the use of naloxone hydrochloride. *Ann Thorac Surg* 1974; 18:608.

52. Tanaka GY: Hypertensive reaction to naloxone. *JAMA* 1974; 25:228.

53. Flacke JW, Flacke WE, Williams GD: Acute pulmonary edema following naloxone reversal of high dose morphine anesthesia. *Anesthesiology* 1977; 47:376-378.