NALOXONE IN SEPTIC SHOCK: REPORT OF TWO CASES

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Two cases are reported describing the use of intravenous naloxone in surgical patients with prolonged hypotension unresponsive to conventional intensive care, including dopamine, intravenous fluids, diuretics, and steroids.

The findings were in agreement with those of previous reports suggesting that endorphins may contribute to the hypotension of sepsis and that naloxone's antagonistic effect on endorphin may have therapeutic value in the treatment of septic shock.

The endorphins, natural endogenous opiates released by stress, bind to opiate receptors and produce analgesia. Similar binding may play a role in the acute hypotension associated with sepsis. Recent animal studies and a few clinical reports indicate that both the analgesia and the hypotension can be reversed by naloxone, the opiate antagonist, without partial agonist activity. Because experience in the use of naloxone in treatment of shock in human beings has been limited, the authors report their experience with naloxone in treating two surgical patients with septic shock refractory to conventional intensive therapy.

CASE REPORTS

Case 1

A 65-year-old woman was brought to Howard University Hospital after several days of abdominal pain, distention, and vomiting. Abdominal radiological findings were suggestive of small bowel obstruction. The patient had cardiorespiratory arrest preoperatively. Cardiopulmonary resuscitation (CPR) was successful and the patient was started on dopamine infusion at a rate of 20 μg/kg/min. At this time her blood pressure (BP) was 70/0 mmHg. A Swan-Ganz catheter was inserted and therapy was initiated with intravenous (IV) fluid, antibiotics (clindamycin and gentamicin), and methylprednisolone. Surgery revealed a gangrenous loop of small bowel that was resected with subsequent anastomosis. Immediately postoperatively, the patient remained hypotensive, 79/50 mmHg, while receiving dopamine 15 μg/kg/min. She was then given 0.4 mg of naloxone intravenously and within five minutes the BP rose to 110/55 mmHg, at which level it remained for four hours (Table 1). Subsequently, the patient developed another cardiac arrest and resuscitation was unsuccessful.

Case 2

A 61-year-old man was operated upon following four days of abdominal pain, distention, and shock. Gangrene of the entire mid-gut was found. A resection from the duodenojejunal junction to distal transverse colon was performed. The patient remained hypotensive during the intraoperative period. Immediately postoperatively the findings were BP 60/40 mmHg, pulmonary wedge pressure (PWP) 21 mmHg, pulse 120 beats/min, serum creatinine level 2.7 mg/dL. In the surgical intensive care unit, the arterial line, Swan-Ganz line and respirator (Bear I type) were continued and IV

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TABLE 1. RESPONSE OF CASE 1 PATIENT TO NALOXONE THERAPY

Hospital Day	Time	Dose of Naloxone (mg)	Blood Pressure (mmHg)	Cardiac Output (L/min)	PWP* (mmHg)	Urine Output (mL)
1	1600	None	70/46	ND	ND	0
2	1000	None	50-70/30-50	1.9	19	0
3	0900	0.4	110/65	2.6	22	15
3	1500	None	80/60	ND	ND	45

*Pulmonary wedge pressure
ND = Not determined

fluids (200 to 300 mL/h), dopamine (20 μg/kg/min), and IV antibiotics (600 mg of clindamycin every six hours and 80 mg of tobramycin every 12 hours) were started. Hypotension (60/40 mmHg) persisted and on the second postoperative day, 0.4 mg of IV naloxone was administered; within minutes the blood pressure increased to 90/60 mmHg and remained so for 30 minutes. Another 0.4-mg dose of naloxone was given, resulting in a BP of 120/80 mmHg, PWP of 22 mmHg, pulse of 110 beats/min, and a cardiac output of 3.25 L/min. The patient became more responsive and psychomotor agitation was visible. During the next two days, he received nine additional 0.4-mg doses of naloxone at varying intervals and showed improvement in blood pressure and minimal increase in cardiac output with little change in heart rate or PWP (Table 2). The patient recovered from shock and did not require additional naloxone. Dopamine was continued at the dose of 3 to 5 μg/kg/min throughout the naloxone therapy and the patient received dopamine for five weeks postoperatively. Bacterial cultures remained negative.

DISCUSSION

It has been more than 20 years since Lowenstein and Fishman first synthesized naloxone, one of the most potent opiate antagonists.[1] Unlike its predecessors, naloxone has no agonist activity and, thus, does not produce dependence or withdrawal symptoms.[1,2] The discovery of the endogenous ligands, the endorphins, which bind to opiate receptors, led to the observation that endogenous opioid peptides were released by stress.[3] It is believed that the endogenous opiate, beta-endorphin, is formed by cleavage of beta-lipotropin, a polypeptide derived from the pituitary protein proopiocortin, which also contains adrenal corticotropic hormone (ACTH).[4,5] In laboratory animals the release of both ACTH and beta-endorphin can be stimulated by acute stress, adrenalectomy, or the administration of corticotropin-releasing factor, and can be inhibited by administration of corticosteroids.

In stress, the opioid peptides are believed to be released from sources containing catecholamines and endorphins in the same chromaffin cells, such as the pituitary gland, sympathetic ganglia, sympathetic nerves, or adrenal medulla.[6] It has been shown that blood pressure can be affected not only by exogenous opiates, such as morphine sulfate, but also by beta-endorphin. For example, animals become hypotensive within minutes of an IV injection of morphine or following either IV or intracisternal injection of beta-endorphin. This hypotensive response can be either reversed or prevented by naloxone.[7-9] A poor response in septic shock in the presence of adrenal deficiency has been noted in some studies and may be due to the secretion of endorphins from the adrenal medulla. Studies have shown that naloxone reverses hypotension not only when associated with endotoxin, but also in cases of experimental spinal and hemorrhagic shock.[10-13]

In several series of patients with septic shock, 40 to 70 percent died despite administration of antibiotics and intensive supportive care.[14,15]

TABLE 2. RESPONSE OF CASE 2 PATIENT TO NALOXONE THERAPY

Hospital Day	Time	Dose of Naloxone (mg)	Blood Pressure (mmHg, B*→A**)	Cardiac Output (L/min)	PWP† (mmHg)	PAP†† (mmHg)
3	1430	0.4	60/40→90/60	3.25	21	34/19
	1500	0.4	60/50→130/80	3.25	22	40/16
	1545	0.4	83/50→120/65	3.60	22	45/25
	1700	0.4	80/55→120/72	ND	ND	49/20
4	0900	0.4	85/60→92/62	3.64	21	42/21
	1620	0.4	85/58→120/90	3.66	24	38/25
5	1830	0.4	71/53→127/90	ND	ND	35/20
6	0500	0.4	84/62→110/78	3.42	22	35/17
	0900	0.4	80/62→120/80	ND	ND	ND
	1500	0.4	80/50→120/65	4.64	20	36/20
	2300	0.4	85/60→110/80	ND	16	40/22
10	1000	None	105/85	6.8	ND	ND
30	1000	None	100/85	3.5	20	38/22

*B is observation before naloxone administration
**A is observation after naloxone administration
†PWP is pulmonary wedge pressure
††PAP is pulmonary artery pressure
ND = Not determined

Wright[11] suggested that the vasodilation following lysis of bacteria in septicemia, or the administration of endotoxin, causes reflex sympathetic activity and catecholamine release from the adrenal medulla. Renin is released via beta-adrenergic stimulation as a result and, in turn, stimulates the release of angiotensin II, raising the blood pressure. Beta-adrenergic stimulation releases opioid peptides, and the release of these endorphins inhibits the action of both catecholamines and renin and could, therefore, cause severe hypotension. This may account for the inadequacy of intense sympathetic activity in maintaining arterial blood pressure in the terminal stage of shock. Naloxone reverses these endorphin effects; thus, its ability to stabilize blood pressure can be explained as a consequence of its antagonism on the effect of endogenous opioid secretion.[6]

CLINICAL STUDIES

During the past three years a few reports have appeared describing the use of naloxone in human beings as treatment for refractory shock.[16-19] Encouraged by results in animal studies,[3,7-9] Tiengo[16] successfully treated an 8-year-old child with irreversible septic shock secondary to meningococcemia with 0.01 mg/kg of IV naloxone followed by two additional 0.2-mg doses subcutaneously. The arterial blood pressure was brought to 110/65 mmHg and the heart rate to 110 beats/min within 25 minutes. Based on the result of Tiengo's report, Wright et al[18] administered 0.1 mg/kg of naloxone (0.01 mg/kg was ineffective) to a 33-year-old woman with terminal carcinoma complicated by Pseudomonas septicemia, acute hypotension, and oliguria. Dopamine (dose not stated) was ineffective. However, after administration of naloxone, the systolic blood pressure increased from 50 mmHg to 130 mmHg and diuresis ensued.

A 62-year-old woman with cardiogenic shock secondary to myocardial infarction was also treated with naloxone.[17] Her blood pressure temporarily stabilized at 106/74 mmHg after receiving dopamine and dobutamine infusions, an intra-aortic balloon pump, a pacemaker, furosemide, sodium bicarbonate, and oxygen. However, her blood pressure gradually decreased to 50/30

mmHg over two hours despite an increase in the dobutamine infusion rate to 30 μg/kg/min. She was then given 5 mg of IV naloxone in divided doses and the blood pressure rose to 100/40 mmHg. Urinary production also began, reaching 25 mL/h. The patient remained stable for 11 hours. In another case reported by the same author, a 68-year-old man developed Klebsiella pneumonia six days after mitral valvuloplasty and a coronary artery bypass. His circulation deteriorated and he rapidly went into septicemic shock with severe hypotension that did not respond to fluid infusion or dopamine dosages of up to 300 mg/h. After receiving 5 mg of IV naloxone in divided doses, his blood pressure rose from 20/0 mmHg to 90/40 mmHg. Methylprednisolone was added, and his circulation remained stable for two days. The authors concluded that naloxone may be an effective means of initiating an improvement in circulation in refractory shock in order to provide time for conventional treatment to take effect.[17]

Peters et al[19] performed a more elaborate study in 13 patients in shock with sustained hypotension of systolic BP $\leq$ 90 mmHg, oliguria $\leq$ 15 mL/h, and impaired mental status, despite treatment with pressor agents, IV fluids, dopamine (3 to 25 μg/kg/min), and hydrocortisone. Naloxone (0.4 mg IV) was added, with increasing increments every five minutes until the systolic BP reached 100 mmHg, and the total naloxone dose reached 8 mg. Eight of nine patients not receiving corticosteroids showed "an immediate and marked increase in blood pressure after naloxone (BP increased 30.4 ± 5.1 mmHg, $P < .005$)."[19] No response was seen in the patients receiving corticosteroids nor in one patient with hypoadrenocorticotropism. The results in these nonresponders may have been due to the fact that endorphin release either was not involved or was suppressed in each case. The authors contended that naloxone may reverse the effect of endorphins released in response to stress, that endorphins can lower blood pressure, and that exogenous steroids, or hypoadrenocorticotropism, may suppress endorphin release from the pituitary.

Naloxone has been given in doses of up to 10 mg IV without adverse effects in patients without physical disease.[19] However, naloxone can convert analgesia to hyperalgesia.[6] Whether this will cause a problem needs further evaluation. Naloxone has a short half-life of about 60 minutes and, as observed in the cases presented, may require frequent repetitive doses to maintain its effects.

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