Reversal of hypotension with naloxone

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Naloxone (Narcan) is an opiate antagonist widely used for reversal of narcotic overdose. Its mode of action appears to be displacement of opiates from receptor sites in the central nervous system and gut.[1] Recent evidence suggests that the body produces endogenous opiatelike substances in response to stress and that these substances produce opioid effects, including hypotension;[2] this hypotension can be blocked or reversed by administration of naloxone.[3, 4] Scattered case reports suggest naloxone might have clinical utility in reversing septic or hypovolemic shock.[5, 6] Naloxone was administered to three patients with septic or cardiogenic shock, and a blood pressure response was observed in all three on six of nine separate occasions. The purpose of our report is to confirm previous observations of the antihypotensive effect of intravenous naloxone in septic shock and to report on a previously unreported temporary antihypotensive effect in cardiogenic shock.

Case reports

Case 1. A 70-year-old woman had been successfully treated with radiation therapy for a catecholamine-secreting chromaffin paraganglioma. She had remained in the hospital for total parenteral nutrition and on the 63rd hospital day had an

anterolateral myocardial infarction and respiratory failure. Morphine sulfate, 2 mg, was given during intubation, and subsequently the patient became normotensive. Four hours later, the blood pressure fell abruptly from 116/90 to 84/60 mm Hg. Dobutamine, 4.5 μg/kg/min, for presumed pump failure had no effect. Naloxone, 0.4 mg, was given and a rise in blood pressure to 134/102 mm Hg was noted. The dobutamine was discontinued and dopamine instituted when the blood pressure fell to 70/62 one hour later. Despite increasing doses from 3 to 10 μg/kg/min, no effect was observed. Although no morphine was administered for 5 hours, administration of naloxone, 0.4 mg, raised the pressure to 84/66 mm Hg and an additional 0.8 mg produced a rise to 108/72 mm Hg. Cardiac output rose from 1.52 to 3.57 L/min. The central venous pressure and central venous wedge pressure remained constant. Despite increasing doses of dopamine to 23 μg/kg, the blood pressure again fell to 78/56 mm Hg after 30 minutes. Levarterenol, 20 μg/kg/min, was added and the patient's blood pressure was successfully maintained. No further naloxone was administered. The levarterenol and dopamine were later tapered and discontinued.

Case 2. A 35-year-old man with rectal carcinoma metastatic to the liver was admitted for intrahepatic artery chemotherapy with 5-fluorouracil and mitomycin-C. On the seventh hospital day progressive shortness of breath developed. A chest roentgenogram disclosed a left lower lobe infiltrate for which antibiotics were started. Within the next few hours, the blood pressure fell to 60/50 mm Hg. Methylprednisolone (SoluMedrol) was administered intravenously for presumed septic shock. Respiratory failure developed and morphine sulfate, 7.5 mg, was given for intubation. The blood pressure remained at 75/52 mm Hg, despite fluid challenge and dopamine, 19 μg/kg/min, and levarterenol, 90 μg/kg/min. Naloxone, 0.8 mg, was administered with no significant response. A second dose of 0.8 mg was given 4 hours later; blood pressure rose from 60/0 to 78/57 mm Hg and fell to 67/57 mm Hg after 30 minutes. A third dose was given 40 minutes after the second, and the blood pressure rose to 76/59 mm Hg. Dopamine, 30 μg/kg/min, was also administered during this time. Two hours later ventricular fibrillation developed refractory to lidocaine therapy and the patient died.

Case 3. A 51-year-old woman with systemic lupus erythematosus involving the central nervous system, liver, and kidneys was receiving cyclophosphamide (Cytoxan), 150 mg/dl and methylprednisolone, 20 mg intravenously, every 6 hours. Hypotension, tachypnea, and tachycardia developed. Blood cultures drawn a day earlier revealed gram-positive cocci. Naloxone, 0.8 mg, produced a change in blood pressure from 93/64 to 149/96 mm Hg. Three hours later, the pressure fell to 75/44 mm Hg following diagnostic thoracentesis. Dopamine, 5.5 μg/kg, and naloxone, 0.8 mg, were administered simultaneously and pressure rose to 101/57 mm Hg. Methylprednisolone, 1.0 g intravenously, every 8 hours for three doses was administered for septic shock. The patient's pressure remained normal and the dopamine was tapered and discontinued over 10 hours. Thirty hours from the initial hypotension, the pressure again fell to 74/64 mm Hg. Dopamine was started, 10 μg/kg/min, and progressively increased to 50 μg/kg/min without response. Naloxone, 0.8 mg, produced no change. Levarterenol, 10 through 100 μg/kg/min, was ineffective,

Table. Summary of patient responses to naloxone

(Case no.) history	Naloxone mg	Mean arterial pressure			Pulse			Time since previous opiates hr	Dose and time since methylprednisolone	Response to dopamine μg/kg/min	Response to levar terenol μg/kg/min
		Before mm Hg	After mm Hg	Change %	Before beats/min	After beats/min	Change %				
(1) Acute myocardial infarction, congestive heart failure	0.4	68	113	+66	124	130	+5	4	...	NR (10)	NA
	0.4	65	72	+11	134	134	0	5	...	NR (23)	+ (20)
	0.8	72	117	+62	136	138	+1	5	...	NA	+ (20)
(2) Septic shock	0.8	60	58	−3	131	129	−2	1 1/2	3 hr (1 g)	NR (19)	NR (90)
	0.8	53	64	+21	124	124	0	5 1/2	7 hr (1 g)	NR (26)	NA
	0.8	60	65	+8.3	126	124	−2	6 1/4	7 3/4 hr (1 g)	NR (30)	NA
(3) Septic shock	0.8	74	114	+54	117	117	0	None	6 hr (20 mg)	NA	NA
	0.8	54	72	+52	132	124	−6	None	9 hr (20 mg)	+ (5.5)	NA
	0.8	26	26	0	151	151	0	None	3 hr (1 g)	NR (50)	NR (100)

NR = no response, NA = not administered.

and the patient died. Postmortem examination revealed *Staphylococcus aureus* bronchopneumonia of the entire right lung.

Results

Naloxone was administered to three patients on nine occasions, and produced a greater than 10% change in mean arterial pressure (MAP) on six of nine trials. The *Table* summarizes the changes in MAP and the relation of the naloxone response to administration of opiates, corticosteroids, and pressor agents.

In patient 1, 0.4 mg naloxone produced a 66% rise in MAP on the first occasion approximately 4 hours after the administration of 2 mg of morphine sulfate. Prior to this the patient was normotensive. One hour later (5 hours after the administration of morphine, the patient again became hypotensive. Although dopamine, 23 μg/kg/min; and dobutamine, 4.7 μg/kg/min, were being administered, the patient remained hypotensive until 0.4 + 0.8 mg of naloxone was administered. On each occasion, the onset of naloxone's action was apparent at 30 to 60 seconds, reaching a maximum at 2 minutes and then gradually decreasing over 20 to 60 minutes. Levarterenol was administered following naloxone therapy and was effective in maintaining the blood pressure thereafter.

Before the administration of 0.8 mg of naloxone, patient 2 was receiving dopamine, 19 μg/kg/min, and levarterenol, 90 μg/kg/min, which maintained blood pressure at 75/52 mm Hg. In addition, methylprednisolone (Solu-Medrol), 1.0 g, had been administered 3 hours previously. The first dose of naloxone, 0.8 mg, produced no response and a second dose 4 hours later (7 hours after 1.0 g methylprednisolone) produced only a 21% increase in MAP. A final dose of naloxone, 0.8 mg, produced only 8.3% increase in MAP.

Patient 3 initially responded to 0.8 mg of naloxone despite a regularly administered dose of 20 mg of methylprednisolone. After the initial dosage of naloxone, 0.8 mg, a 54% rise in MAP occurred within 2 minutes and fell gradually over the next 3 hours. A subsequent dose of 0.8 mg of naloxone produced a comparable 52% rise, which was maintained with dopamine therapy. Hypotension again developed and was refractory to treatment with 50 μg/kg/min dopamine, 100 μg/kg levarterenol, or naloxone.

Discussion

Results of recent work have shown that the body produces opiatelike substances known as endorphins and enkephalins. These peptides bind opioid receptors in the brain and gut and have a spectrum of action similar to that of exogenous opioids.[1] There are several types of endorphins, all of which share a common N-terminal sequence identical to the pentapeptide metenkephalin.[7] Much of the work involves study of the 31-amino acid molecule β-endorphin, which encompasses the smaller α, γ, and δ endorphin molecules.[7]

β-endorphin is released in response to stress.[2] Furthermore, the release of β-endorphin appears to be closely related to the release of adrenocorticotrophin (ACTH), the two substances sharing a common precursor called pro-opiocortin.[1,7] Faden and Holaday[8] have postulated that there are selective advantages to the release of β-endorphin in response to stress, especially severe injury. These advantages include reduction of blood pressure to aid in coagulation and relief of anxiety and pain. Administration of naloxone can prevent hypotension in

animals subjected to experimentally induced volume depletion or endotoxins.[3,4] The mechanism of blood pressure reduction by endorphins is uncertain and may involve release of serotonin or histamine or vagal mediation of cardiac contractility.[8] In contrast, there is evidence that β-endorphin acts as a central level in regulating blood pressure by interacting with α receptors.[9] We were unable to demonstrate the mechanism of action in our patients, but the rise in cardiac output noted in patient 1 and the lack of response to the centrally acting dopamine while response to peripherally acting levarterenol was maintained argues more for a peripheral vascular rather than a central nervous system mode of action. In addition, the absence of a change in pulse rate in any of the patients is against any sympathetic response.

Prior steroid administration has been reported to interfere with the action of naloxone on blood pressure.[6] This interference was observed in patient 2, but not in patient 3 who was receiving maintenance therapy (methylprednisolone, 20 mg every 6 hours). Since β-endorphin is thought to be tied to the same feedback mechanism as ACTH, it has been postulated that administration of corticosteroids suppresses the release of endorphins via negative feedback.[10] The use of corticosteroids may, therefore, exert an antihypotensive effect by preventing endorphin release. The lack of response to naloxone in steroid-treated patients may be due to extreme vasodilation no longer responsive to the antiendorphin effects of the agent, or that central receptors may be blocked with a weaker agent (steroids) preventing a more significant antihypotensive effect.

What advantages does naloxone have over conventional agents for increasing blood pressure, such as levarterenol and dopamine? Aside from our observation that naloxone may be effective when dopamine fails, there are theoretical advantages of naloxone over the other pressor agents. Dopamine and levophed raise not only blood pressure but also pulmonary capillary wedge pressure and myocardial oxygen consumption. This may be undesirable in any critically ill patient, particularly one with myocardial ischemia. Dopamine in doses above 20 μg/kg/min and levarterenol cause tachycardia, vasoconstriction of the splanchnic and renal vasculature, and often a reduction in urine output. Naloxone, which has no effects aside from narcotic antagonism, should not have these undesirable side effects.[1] The need for repeated doses of naloxone prompted us to use a continuous drip of naloxone (unpublished data); this appears to be a preferable mode of administration.

Naloxone is said to have no effects aside from narcotic antagonism and does not usually produce tachycardia, vasoconstriction, or changes in myocardial output.[1] However, hypertensive crisis, acute pulmonary edema, and myocardial irritability have been reported following naloxone reversal of anesthesia.[11-13] Sudden death following administration of naloxone to reverse anesthesia in two healthy young women has also been reported.[14] Although the author postulates the cause of death to be ventricular fibrillation precipitated by hypoxia and an abrupt increase in blood catecholamine levels secondary to naloxone, idiosyncratic reaction could not be excluded.[14] We did not observe any immediate changes in heart rate or rhythm in our patients. However, the concern about possible effects of bolus administration of naloxone and the need for repeated doses has prompted us to change the mode of administration

to a bolus of 0.0 to 0.2 mg followed by continuous intravenous drip.

Summary

Although our analysis lacks comparison with a control population, intravenous injection of 0.4 to 0.8 mg of naloxone can effect a change in blood pressure in patients who have not recently received high-dose steroids. In addition, the observed antihypotensive effects of naloxone were recorded at a time sufficiently beyond morphine administration to suggest additional benefits of the agent. An effect was noted in a patient who failed to have a response to dopamine and dobutamine, but no effect was observed if a response to levarterenol was absent. Improved survival has already been demonstrated in animals subjected to experimental endotoxic or hypovolemic shock when naloxone was administered.[3, 4] Our observations, along with these experiments, suggest that naloxone may have clinical utility in hypotensive states and that large scale studies would be appropriate.

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