The use of Naloxone in Critically-ill Patients*

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Summary

Ten critically-ill patients with prolonged hypotension or unrecordable systolic blood-pressure, impaired mental status and respiratory depression in this study. Naloxone, 0.8 - 1.2 mg was injected intravenously in all patients. in six hypotensive patients, systolic blood-pressure rose in range of 26-35%, within 5-15 minutes following the naloxone injection. In four patients systolic blood-pressure was unrecordable and after naloxone injection rose to a value of 100-120 mm Hg. Naloxone was effective in three patients in which dopamine could not maintain the systolic blood-pressure at optimal renal perfusion level. It seems that naloxone had a lesser effect in three patients treated with high doses of corticosteroids. The therapeutic effect of naloxone is suggested on the assumption that endorphins are mainly responsible for the hypotension and respiratory depression in critically-ill patients.

Key words

Opioid antagonist; naloxone.
Intensive care; critically-ill patients.

Recent discovery of the endogenous opioids, their possible role as neuromodulators and the diverse localisation of specific receptors for endogenous ligands in the body[1] initiated the current widespread interest to explore various clinical implications. It is suggested that the endogenous opioids, particularly (ß-endorphin) a sequence of pituitary ß-lipotropin contribute to the hypotension in septic shock[2] and we presume they may have the same effect in all critically-ill patients.

It was demonstrated that the hypotension resulting from intravenous[3] or intracisternal injection[4] of ß-endorphin in animals can be readily reversed by the specific opiate antagonist, naloxone.[5]

Peters et al.[2] in a clinical trial, observed an increase in systolic blood-pressure within minutes following injection of 0.4–1.2 mg naloxone in septic shock patients with prolonged hypotension.

Burnie[6], claims that specific opiate receptors exist in cardiac muscle in the rat, so the situation is more complex than appears.

If endorphins are mainly responsible for the hypotension and respiratory depression then naloxone would be expected to be of significant therapeutic value in the treatment of critically-ill patients.

Patients and Methods

All patients included in the study had prolonged hypotension or unrecordable systolic blood-pressure, impaired mental status and respiration and were being nursed in the I.T.U.

Observations were made before giving the naloxone injection and in the period after receiving naloxone.

In three patients, dopamine, which was infused at a rate of 7-20 µg/kg/min over a period of 7-12 h, was stopped just before naloxone administration.

Seven patients were on controlled or assisted ventilation. All patients were receiving intravenuous fluids and other supportive measures.

Arterial blood-pressure was measured with mercury manometer, with the cuff on the upper arm, every 1-5 min by auscultatory method. Central venous pressure, hourly urine output and blood-gases were monitored in all patients. (Table 1) Naloxone hydrochloride ("Narcan", Winthrop) was injected intravenously at a dose of 0.4 mg initially. If in 5–10 min the systolic blood-pressure did not rise to 100 mm

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Hg, naloxone was repeated.

Special emphasis was put on the naloxone effect upon systolic blood-pressure, respiration and changes in the mental status. Hourly urine output and blood-gases were also measured.

Results

Eight patients out of ten survived and were then transferred to the respective general ward and later discharged. Two patients died, one (seven days after naloxone injection) in the operating theatre on induction of anaesthesia for planned tracheostomy, and the other one (two days after naloxone administration) from liver failure. Seven patients, were on artificial respiration at the moment of naloxone injection. Five of them were put off the ventilator either the same day or in the next 48 h following the naloxone administration. Two patients died whilst still on the ventilator after 2 and 7 days respectively as mentioned above. Patients 1, 2 and 3 had received high doses of corticosteroids (1.5–2.0 gr of Solu-Cortef) and following naloxone injection, the initial rise in blood-pressure was in range of 11-25%, significantly less than in the patients who were not given exogenous corticosteroids.

The following is a more detailed presentation of four most demonstrative patients:

Patient 1 (Fig. 1) with septic shock, had sustained hypotension for 12 h before dopamine was stopped and naloxone 0.4 mg was injected intravenously. Blood-pressure rose from 80/60 to 100/70 mm Hg in ten minutes time. Hourly diuresis was 16 ml/h and in the moment of naloxone administration Lasix 40 mg was given i.v. which improved significantly hourly diuresis in the next 8 h., but the blood-pressure did not alter.

Pulse rate from 145/min decreased to 100/min in the next few hours following the naloxone injection.

Table 1 CLINICAL CHARACTERISTICS

AT TIME OF NALOXONAL ADMINISTRATION

patients	N history	sex	age	DIAGNOSIS	BP before NALOXONE	BP after adm. N	BP stability	on ventilator	DOPAMIN	Transfer to the ward
1	103367	F	67	SEPTIC – SHOCK	80/60	90/65	110/70	ON	stop	yes
2	134897	M	40	HAEPATIC COMA	80/60	100/70	100/70	ON	stop	DEAD
3	132781	F	40	ANAFILACTIC SHOCK CARDIAC AREST	90/60	100/70	120/90	ON	stop	yes
4	119765	F	61	RESPIRATORY FAILURE CARDIAC AREST	0	120/70	120/80	ON	start	DEAD
5	066849	F	79	ACUTE PANCREATITIS	0	90/50	120/80	ON	no	yes
6	137038	M	60	POST-OPERATIVE SHOCK	0	120/100	160/100	ON	no	yes
7	133952	F	48	SUBTOTAL COLECTOMY	0	100/70	110/80	no	no	yes
8	005924	F	77	SEPTIC SHOCK	95/65	100/80	110/80	no	no	yes
9	018630	M	50	POST-OPERATIVE SHOCK	90/60	130/75	120/70	no	no	yes
10	000106	M	72	RESPIRATORY FAILURE MYOCARDIAL INFARCTION	70/40	130/80	120/80	ON	no	yes

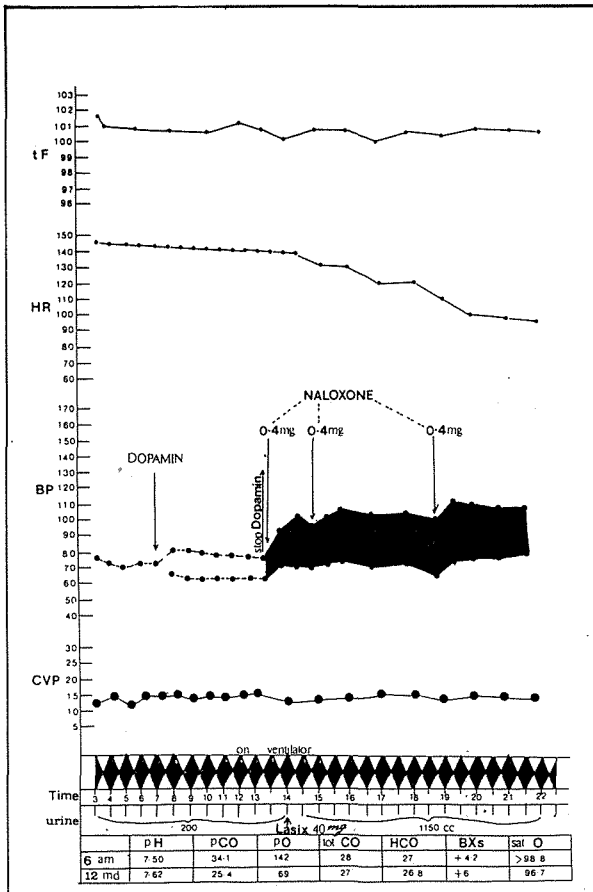
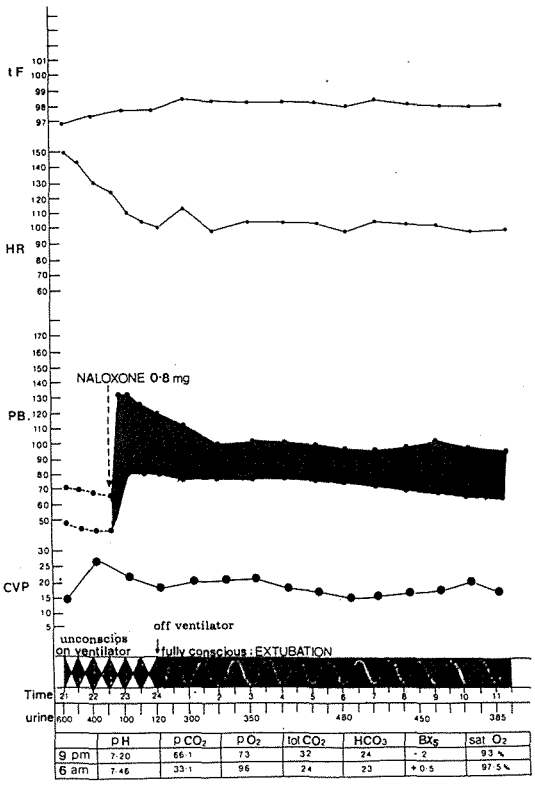


Fig. 1 G.A. No. 103367 female 67 yrs. SEPTIC SHOCK

Controlled ventilation was maintained for five days. Blood-gases improved the next day after admission to ITU. After ten days patient was transferred to the ward in stable general condition.

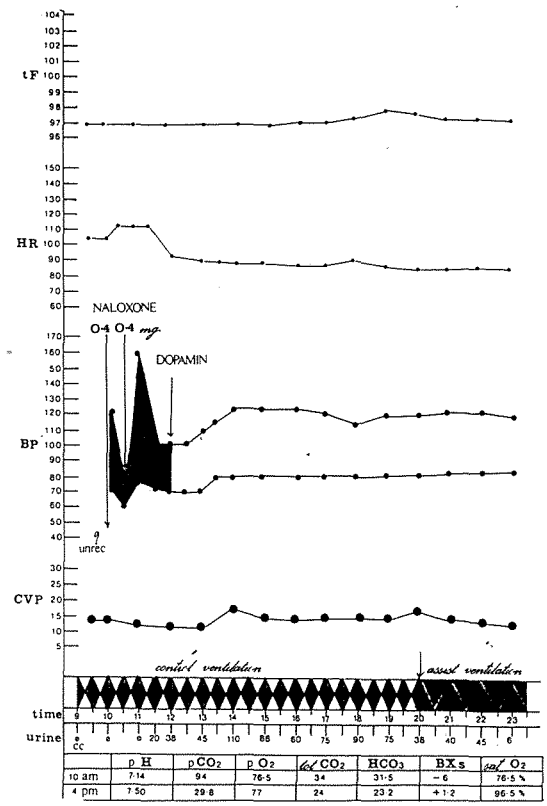
Patient 10 (Fig. 2) was admitted unconscious with a respiratory failure and myocardial infarction. Blood-pressure was 70/40, heart rate 150/min. Endotracheal intubation was carried out immediately in the Casualty Dept. He was put on controlled ventilation and subclavian vein cannulation was done simultaneously. Naloxone 0.8 mg was injected intravenously and in 5 min BP rose to 130/70 mm Hg. After 12 min. the patients became fully conscious. Shortly after that spontaneous respiration (V_t 600 ml) enabled us to extubate the patient, It was the most striking improvement in BP, mental status other clinical parameters in our study. After 48 h patient was transferred to the Coronary Care Unit for further treatment.

Patient 4 (Fig. 3), a 61 year old female, referred to Casualty dept. with cardiac arrest and respiratory failure was given naloxone 0.4 mg subsequent to



	pH	pCO₂	pO₂	tot CO₂	HCO₃	BXs	sat O₂
9 pm	7·20	66·1	73	32	24	- 2	93 %
6 am	7·46	33·1	96	24	23	+ 0·5	97·5 %

Fig. 2 F.B. no. 000106 male 72 yrs.
RESPIRATORY FAILURE: MYOCARDIAL INFARCTION

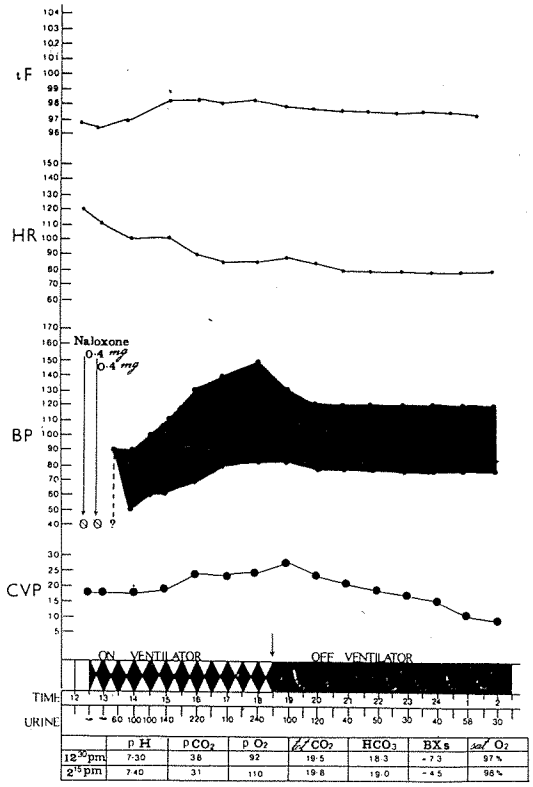


	p H	pCO₂	p O₂	tot CO₂	HCO₃	BXs	sat O₂
10 am	7·14	94	76·5	34	31·5	- 6	76·5 %
4 pm	7·50	29·8	77	24	23·2	+ 1·2	96·5 %

Fig. 3 H.E. No. 119765 female 61 yrs.
RESPIRATORY FAILURE: CARDIAC ARREST

emergency intubation. Systolic blood-pressure was unrecordable and following naloxone injection rose to 120/80 mm Hg. Forty minutes later BP fell to 80/60. Another injection of naloxone 0.4 mg increased the BP to 160/80 mm Hg. Forty minutes later BP fell to 80/60. Another injection of naloxone 0.4 mg increased the BP to 160/80 mm Hg. Later it was decided to give dopamine at a rate of 7μg/kg/min and blood-pressure was maintained at the level of 120/80 mm Hg. After 8 hours controlled ventilation was turned to assisted ventilation. Patient had only one lung due to pulmonectomy 21 yr before. Assisted ventilation was employed for seven days because of concomitant bronchopneumonia. Patient died after seven days in the operating theatre on the induction of anaesthesia for planned tracheostomy to facilitate bronchial toilet.

Patient 5 (Fig. 4) a 79 yr old female, transferred to ITU from the operating theatre after partial gastrectomy, partial pancreatic resection, cholecystojejunostomy. Systolic blood pressure was unrecordable. Naloxone 0.4 mg given intravenously did not increase the blood-pressure. In ten minutes another dose of



	p H	pCO_2	pO_2	$\not{C}CO_2$	HCO_3	BXs	$\not{S}O_2$
12^{30}pm	7·30	38	92	19·5	18·3	−7·3	97%
2^{15}pm	7·40	31	110	19·8	19·0	−4·5	98%

Fig. 4 L.M. No. 066849 female 79 yrs.

Dg. GASTRIC ULCFR; PSEUDOPANCREATIC CYST; PANCREATITIS

naloxone 0.4 mg increased the systolic blood-pressure to 90 mm Hg. Fifteen minutes later BP was 90/50 mm Hg and after one hour 110/70 mm Hg. The patient was initially unconscious and on controlled ventilation. Seven hours later she was on spontaneous respiration. Blood gases improved markedly. Hourly diuresis was 30–240 ml/h in the next 12 h following naloxone injection but CVP remained stable.

No corticosteroids or vasopressor drugs were given. After 72 h patient was transferred to the ward.

Discussion

Prolonged hypotension may lead to complex biochemical, cardiovascular and haemodynamic derangements thus making cellular perfusion inadequate for normal cellular function i.e. shock. Adequate fluid therapy plays a part in the compensation for some of these derangements. When renal function is impaired management becomes more complicated. Regaining an adequate cellular perfusion is the aim in the treatment of the shock state.

If all these derangements, including the CNS activity, are partly associated with endorphin release than it would be expected that naloxone could delay the physiologic homeostatic breakdown imminent in critically-ill patients. How exactly neurotransmitters act when the body is in an emergency state is still a medical enigma. The diverse localization of specific receptors for endogenous ligands in the body make it possible to postulate their probable role in stress and near-death situations. Naloxone has been used extensively in man and has had no adverse effects, even in high doses.[7,8]. Demonstrating that intravenous naloxone is effective in raising the systolic blood-pressure, improving the mental status, respiration (and secondary to this also diuresis and acid-base status) itsuse in critically-ill patients of different pathology may be justified.

Naloxone was effective in raising and maintaining the blood-pressure even when dopamine was stopped although Peters and others were giving naloxone concurrently with dopamin.

In three patients corticosteroids were given in high doses and naloxone did not promptly increase the systolic blood-pressure as it did in the other seven patients which were not injected with exogenous steroids. This is in agreement with the findings that exogenous steroids may supress endorphin release from the pituitary[2]. More clinical data are needed to elucidate the exact pharmacological mechanisms of naloxone in critically-ill patients and to define the criteria and exact indications for its clinical application.

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