The Cardiovascular Effects of Naloxone Administration after Fentanyl Anesthesia in Hypercapnic Patients

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Hemodynamic changes and plasma catecholamine levels after naloxone administration were studied in seventeen postoperative patients who received nitrous oxide, oxygen, and fentanyl anesthesia combined with epidural block. Group I consisted of ten postoperative hypercapnic (Pa_{CO_2} = 55.2 ± 2.4 torr) and group II seven postoperative normocapnic patients (Pa_{CO_2} = 38.4 ± 2.1 torr), respectively. In group I, naloxone reversal resulted in significant increases in heart rate (13.5%), mean arterial pressure (46.6%), systemic vascular resistance (32.1%), and rate pressure product (68.8%), whereas mean pulmonary artery pressure and pulmonary vascular resistance were significantly decreased. No significant hemodynamic changes after naloxone administration were observed in group II. There were no significant differences in arterial norepinephrine and epinephrine levels either before or after naloxone administration in the both groups. This study indicates that the postoperative hypercapnia elicits the cardiovascular stimulation after fentanyl reversal by naloxone. (Key words: naloxone, fentanyl, cardiovascular effects, hypercapnia)

(Kishikawa K, Namiki A, Iwasaki H: The cardiovascular effects of naloxone administration after fentanyl anesthesia in hypercapnic patients. J Anesth 3: 48–53, 1989)

When naloxone is used to reverse the effects of narcotics, the most serious problem is the appearance of unpredictable cardiovascular responses. Increases in blood pressure[1–8], rupture of cerebral aneurysm[9], pulmonary edema[10], ventricular irritability[11], and cardiac arrest[12] are reported after naloxone administration. Cardiovascular effects of naloxone have been explained by the increased release of catecholamines from the adrenal medulla[13], or the heightened sympathetic nervous activity[14]. On the contrary, Desmonts et al suggested that the cardiovascular stimulation caused by naloxone administration is related to anxiety and pain induced by the recovery from anesthesia rather than to a specific interaction between narcotics and naloxone, or a direct effect of naloxone by itself[5].

Besides pain and anxiety, carbon dioxide retention is known to stimulate the cardiovascular system in man via increasing sympathetic activity[15]. To date, however, there is no report about the influence of carbon dioxide retention on the cardiovascular response to the narcotic reversal by naloxone. Therefore, we examined the hemodynamic changes following naloxone administration after fentanyl anesthesia, where the sympathetic stimulation due to pain was excluded by epidural anesthesia.

Methods

Seventeen A.S.A. physical status I to II

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patients without cardiac, hypertensive, or respiratory disease, scheduled for total or subtotal gastrectomy, were studied. The protocol was reviewed and approved by the committee of Sapporo Medical College and Hospital on medical ethics, and informed consent was obtained from each patient prior to anesthesia. All patients were premedicated with hydroxyzine chloride 2 mg/kg, and atropine sulfate 0.01 mg/kg intramuscularly 60 min before induction of anesthesia. After placement of an epidural catheter at Th 9/10 or Th 10/11 intervertebral space, all patients received 10–12 ml of 2% lidocaine containing epinephrine 1:200,000. After the establishment of epidural anesthesia, general anesthesia was induced intravenously with 5 mg/kg of thiamylal followed by 1 mg/kg of succinylcholine chloride to facilitate endotracheal intubation. Anesthesia was maintained with 60% nitrous oxide and 40% oxygen. Fentanyl, 0.4–0.7 mg, was then administered incrementaly to obtain the adequate depth of anesthesia without precipitating hypotension or bradycardia until the beginning of skin incision. Thereafter, 0.05–0.1 mg of fentanyl was given every 60 min, or at shorter intervals when the increase of blood pressure or heart rate was observed, but preferably not within the last 30 min of the operation. At 60 min intervals during anesthesia, 8–10 ml of 1.5% lidocaine with epinephrine 1:200,000 was injected into epidural space.

Ventilation was controlled throughout anesthesia to maintain arterial carbon dioxide partial pressure (Pa_{CO_2}) within a range of 35–40 torr. Systemic blood pressure was continuously measured with a Gould P23 ID transducer through a percutaneous catheter placed in the radial artery. The catheter was also used for blood sampling for measurement of arterial blood gas tensions and plasma levels of epinephrine (E) and norepinephrine (NE). A No.7 french size triple lumen Swan-Ganz flow-directed catheter was placed in the pulmonary artery through the internal jugular or femoral vein, immediately after the induction of anesthesia. Measurements of mean pulmonary arterial pressure (PAP) and mean pulmonary capillary wedge pressure (PCWP) were made using a Gould P23 ID transducer placed at the level of the right atrium, and were recorded together with lead II of the ECG and systemic blood pressure on the oscilloscope and the multichannel recorder (Polygraph system RM-6000, Nihon Kohden Co. Ltd.). Heart rate (HR) was calculated from the systemic blood pressure tracing. Cardiac output (CO) was measured by a thermodilution technique (Edwards Cardiac Computer, Model 9520A). From the recorded variables the following data were derived: systemic (SVR) and pulmonary (PVR) vascular resistances in dynes·sec·cm^{-5}.

$$SVR = 79.92 \times (MAP\text{-}RAP)/CO$$

where, MAP = mean arterial pressure

$$PVR = 79.92 \times (PAP\text{-}PCWP)/CO$$

Cardiac index (CI) was calculated by dividing CO by the estimated body surface area. The heart rate-systolic blood pressure product (RPP) was used to evaluate relative changes in myocardial oxygen consumption.

After surgery, nitrous oxide was discontinued and the patients were allowed to breathe 100% oxygen. At least three minutes were allowed to elapse after spontaneous respiration was established, and the following data were recorded: HR, MAP, PAP, PCWP, CI, SVR, PVR, Pa_{CO_2}, Pa_{O_2}, and pH values. All blood samples for NE and E measurements were collected and centrifuged.

All patients were administered 0.1 mg increments of naloxone intravenously every one minute until the patients regained consciousness and open their eyes on verbal command. Naloxone administration was performed within 30 min after the last injection of lidocaine to the epidural space in all patients. One minute after the last administration of naloxone, the measurements as indicated above were repeated. After all values were obtained, the trachea was extubated soon thereafter. The level of epidural anesthesia was examined by the pin-prick method after the extubation. The plasma was frozen and E and NE levels were measured by high

Table 1. Mean values of age, body weight, height, and dosage of drugs

	Age (yrs)	Body Weight (kg)	Height (cm)	Fentanyl (μg/kg/hr)	Naloxone (μg/kg)
Group I Hypercapnia (n=10)	56 ± 3	55 ± 2	164 ± 5	4.1 ± 0.4*	15.0 ± 1.7
Group II Normocapnia (n=7)	56 ± 3	52 ± 3	166 ± 4	3.0 ± 0.4	14.8 ± 2.9

All values are given as mean ± SEM.
* $P < 0.05$, as compared with group II.

Table 2. The blood gas analyses before and after administration of naloxone

	Pa_{CO_2} (torr)		PH	
	Before Naloxone	After Naloxone	Before Naloxone	After Naloxone
Group I Hypercapnia (n=10)	55.2 ± 2.4*	42.6 ± 1.4*,**	7.29 ± 0.01*	7.36 ± 0.02*,**
Group II Normocapnia (n=7)	38.4 ± 2.1	36.8 ± 2.4	7.39 ± 0.02	7.41 ± 0.01**

All values are given as mean ± SEM.
* $P < 0.05$, as compared with group II.
** $P < 0.05$, as compared with the value before naloxone.

Table 3. Hemodynamic and plasma catecholamine values before and after naloxone administration

	Group I		Group II	
	Before Naloxone	After Naloxone	Before Naloxone	After Naloxone
HR (beats/min)	80±4*	89±2**	67±6	68±7
MAP (torr)	78±8*	108±6***	101±6	101±5
CI (l/m^2)	4.0±0.2*	4.5±0	3.3±0.3	3.7±0.3
SVR ($dyn \cdot sec \cdot cm^{-5}$)	1004.5±151.9*	1222.4±98.9**	1640.3±284.2	1415.8±198.9
RPP	6158.3±629.6	9562.5±545.0***	6788.6±810.9	6907.3±865.2
PAP (torr)	21.1±1.9	17.9±2.0**	16.5±2.7	19.7±4.2
PVR ($dyn \cdot sec \cdot cm^{-5}$)	143.5±22.1	79.8±1.0**	100.9±30.2	106.2±30.8
PCWP (torr)	10.3±1.4	11.3±2.0	10.7±3.4	12.5±2.6
E (ng/ml)	0.15±0.04	0.19±0.03	0.12±0.02	0.10±0.04
NE (ng/ml)	0.37±0.14	0.44±0.20	0.45±0.07	0.45±0.02

All values are given as mean ± SEM. See text for the abbreviations.
* $P < 0.05$, as compared with the values before naloxone in group II.
** $P < 0.05$, as compared with the values before naloxone in group I.
*** $P < 0.01$, as compared with the values before naloxone in group I.

performance liquid chromatography[16]. Based on the results of arterial blood gas analysis before naloxone administration, the patients were assigned to one of the following two groups:
Group I (n = 10); Pa_{CO_2} > 45 torr, Group II (n = 7); Pa_{CO_2} < 45 torr.

The data for the two groups were compared using Student's t-test. Statistical significance was defined as P less than 0.05. All values are presented as mean ± SEM.

Results

There were no significant differences between group I and group II with respect to age, body weight, and total dose of naloxone. Total dose of fentanyl administered in group I was significantly larger than group II ($P<0.05$) (table 1).

The blood gas analyses before and after the administration of naloxone in the two groups are shown in table 2. Significant differences were presented between the two groups for Pa_{CO_2} and arterial pH either before or after administration of naloxone. Following the administration of naloxone, Pa_{CO_2} in Group I decreased and pH in the both groups increased significantly ($P<0.05$). Pa_{O_2} values in the both groups before and after naloxone administration were above 100 torr, and no significant differences were observed.

Hemodynamic and plasma levels of E and NE values before and after naloxone administration in the two groups are listed in table 3. Before the administration of naloxone, HR and CI in group I were significantly higher than group II. MAP and SVR in group I were significantly lower compared to those in group II. After the administration of naloxone, HR, MAP, SVR, and RPP in group I were significantly increased by 13.5%, 46.6%, 32.1%, and 68.8% respectively, compared to the values before naloxone. In group I, PAP and PVR were significantly decreased by 14.3% and 31.6% respectively after naloxone. CI increased in the both groups after naloxone administration, but not significant. With respect to mean plasma levels of E and NE, no significant differences before and after naloxone administration were observed in the both groups. No undesirable complications such as severe hypertension, anxiety, or pulmonary edema were noted in all patients after naloxone administration. The levels of epidural anesthesia after extubation were from Th 6 to L 3 in all patients. None of the patients complained of pain after naloxone administration.

Discussion

The mechanisms of cardiovascular stimulation caused by naloxone are not known clearly. Hernandes et al confirmed the release of catecholamine from adrenal medulla by naloxone[13] and Koyama et al presented an increased sympathetic activity after naloxone administration[14]. On the other hand, Freye concluded that naloxone shows little cardiovascular effect when it is administered alone[2]. Also, neither significant hemodynamic changes nor altered catecholamine release was demonstrated in the narcotic reversal by naloxone[17,18]. It was suggested that the state of sympathetic tone seems to be important when naloxne is used to reverse the effects of narcotics[5]. We consider that in this study, sympathetic activation resulted from pain was excluded by sufficient epidural anesthesia, because none of the patients complained of pain when they were extubated after the administration of naloxone. Thus, It is obvious that hypercapnia due to postoperative respiratory depression predisposed a patient to increased sympathetic activity.

Before naloxone treatment, HR and CI in group I were significantly higher than those in group II, while MAP and SVR in group I were lower than those in group II. These differences of hemodynamics between group I and group II were in agreement with cardiovascular responses to hypercapnia described by Cullen and Eger[15]. They demonstrated that heart rate, cardiac output, and mean arterial pressure increased, while the total peripheral resistance decreased in response to hypercapnia (Pa_{CO_2} = 50.2 torr). After naloxone administration, group I showed significant increase in HR, MAP, RPP, and SVR. Hemodynamic responses after naloxone

administration was affected by hypercapnic state after fentanyl anesthesia. The absence of statistically significant alteration in the catecholamine levels could be due to the effect of epidural anesthesia. Engquist et al found that epidural anesthesia leads to the suppression of epinephrine secretion in response to surgical stimulation[19].

The effects of naloxone for PAP and PVR in group II were consistent with the result of Desmonts et al[5]. They showed no significant changes in PAP and PVR after administration of naloxone. In this study, PAP and PVR in group I were significantly decreased after naloxone. These decreases can be explained by the return of arterial pH values resulting from stimulated ventilation after naloxone administration. It is well known that the decrease in arterial pH elicits the rise in pulmonary artery pressure[20]. Furthermore, Harvey et al pointed out that hyperventilation brings about the decrease of pulmonary arterial pressure[21]. In conclusion, postoperative hypercapnia after fentanyl anesthesia exaggerated the cardiovascular changes by the administration of naloxone, because of the elevated sympathetic tone as a consequence of hypercapnia. Therefore, we should be careful in the administration of naloxone for the reversal of narcotics, especially when Pa_{CO_2} is elevated.

(Received Aug. 24, 1989, accepted for publication Oct. 21, 1989)

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