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COMPARISON OF HEMODYNAMIC EFFECTS OF MORPHINE, BUTORPHANOL, BUPRENORPHINE AND PENTAZOCINE ON ICU PATIENTS

BY

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ABSTRACT

Morphine and narcotic agonist-antagonists have been used to assist ICU patients in adapting to mechanical ventilation. In this study, 10 mg of morphine and the equipotent doses of synthetic analgesics, 2 mg of butorphanol, 0.6 mg of buprenorphine or 30 mg of pentazocine were administered intravenously to 29 patients requiring a ventilator. Hemodynamic effects on the heart rate, mean arterial pressure (MAP), cardiac index, stroke index, left ventricular stroke work index, mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and systemic and pulmonary vascular resistance (PVR) were measured. The hemodynamic effects of the four drugs were mild and not statistically significant except for the reduction in PCWP and the increase in PVR after morphine and the increase in MAP and MPAP after pentazocine administration. These doses of the four drugs could be given safely even in critically ill patients. The hemodynamic effects of these analgesics showed a similarity between the administration of butorphanol and morphine, and between buprenorphine and pentazocine. This study demonstrates that morphine and butorphanol are preferred to the cases with hypertension, increased pulmonary arterial pressure or wedge pressure and that pentazocine and buprenorphine are more suitable for the cases with hypotension or hypovolemia.

Key words: ANALGESICS: buprenorphine, butorphanol, morphine, pentazocine;
HEMODYNAMICS, SEDATION

INTRODUCTION

In an intensive care unit (ICU), many critical patients require mechanical ventilation. The pain and stress associated with mechanical ventilation as well as the fear of illness tend to provoke a prominent anxiety state. Usually, morphine has been used in these patients because of its sedative and depressant effect on the patients to adapt to mechanical ventilation when their breathing is difficult to control. However, morphine has the disadvantages in some aspects, such as addiction and hypotension (Rouby *et al.* [1], Samuel *et al.* [2, 3]). In this meaning, the sedative drugs with less addictive and cardiovascular effect would be advantageous in the ICU.

Recently, a number of synthetic narcotic agonist-antagonist analgesics have been introduced, e.g., pentazocine, buprenorphine and butorphanol, and these drugs also have sedative effects. So these synthetic analgesics are used to allay anxiety during adaptation to mechanical ventilation. Although the hemodynamic

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effects of these analgesics have been studied in the anesthetized patients (Sederberg *et al.* [4], Aldrete *et al.* [5], Stanley *et al.* [6]), there have been only a few reports describing the hemodynamic effects of these analgesics in the critically ill patients requiring artificial ventilation (Samuel *et al.* [2], Rosenfeldt *et al.* [7]). The purposes of the present study are to examine if 10 mg of morphine, equipotent doses of butorphanol, buprenorphine or pentazocine i.v. can be given safely in the artificially ventilated critically ill patients and to compare the hemodynamic effects of morphine with those of these three synthetic analgesics.

Material and Method

Twenty-nine adult patients, 35 to 81 years (mean 59.9±11.0) in age and 40 to 65 kg (mean 49.8±7.3) in weight, were subjected to this study. Informed consent and institutional approval for the study were obtained. Twenty-three were postoperative and six were respiratory failure. The former had underwent major thoraco-abdominal surgery (13 esophageal cancer, 3 aneurysm, 3 hepatoma and 4 others) and were randomly divided into four groups. The first group (n=10) was given 10 mg of morphine, the second (n=8) 2 mg of butorphanol, the third (n=6) 0.6 mg of buprenorphine and the fourth (n=5) 30 mg of pentazocine. The four groups were similar in age, sex, weight and disease. All of the patients had a sinus rhythm with a normal arterial pressure. None had received drugs that affect the cardiovascular system within six hours preceding the study.

All of the patients were intubated and under mechanical ventilation at a tidal volume of 10 ml/kg at the respiratory rate of 10–12/min and with F_{IO_2} 0.3–0.6 to maintain the P_{aCO_2} at 40±5 mmHg (Servo ventilator 900B). On admission to the ICU, a 20G cannula was inserted into the radial artery for blood pressure monitoring and to obtain the arterial blood samples. A 7F thermodilution triple-lumen catheter (Model 93A-131H, American Edwards Laboratories) was inserted by the Seldinger technique through the right internal jugular vein or the antecubital vein and directed into the pulmonary artery. The arterial blood pressure, pulmonary arterial pressure, lead II ECG and clinical status were continously monitored. After a stable hemodynamic condition was established, control studies were started. The heart rate was monitored with ECG. The arterial and mixed venous blood samples were obtained simultaneously for the measurements of oxygen and carbon dioxide tension (PH/Blood Gas Analyzer 813, Instrumentation Laboratory). The mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) were measured and recorded with a two-channel recorder at the end-expiratory period (Life Scope 11, Nihonkoden). The cardiac output measurements were made using the thermodilution technique with 5% iced dextrose in water solution (thermodilution cardiac output computer EQ-611V, amplifier AH-611V, Nihonkoden). The cardiac index (CI), stroke index (SI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), arteriovenous oxygen content difference ($a\text{-}\bar{v}D_{O_2}$), oxygen delivery (O_2 delivery) and oxygen consumption index ($\dot{V}_{O_2}$) were calculated with a programmed digital calculater (CASIO, FX-702P).

On completion of the control measurements, 10 mg of morphine or equipotent doses of 2 mg of butorphanol, 0.6 mg of

Table 1. Hemodynamic Data

		Control	0.5 hr	1 hr	2 hr
HR (beats/min)	Morphine	95.8±14.6	93.3±11.8	93.4±11.4	95.5±16.1
	Butorphanol	96.3±23.8	90.9±18.4	87.2±18.0	87.5±16.6
	Buprenorphine	120.6±24.0	110.0±20.9	108.5±21.0	108.7±24.0
	Pentazocine	101.2±18.3	100.0±16.3	97.0±18.6	98.6±17.7
MAP (mmHg)	Morphine	96.5±12.5	89.2±14.6	88.3±12.4	88.5±14.5
	Butorphanol	88.1±11.3	84.1± 9.0	82.6±14.4	84.1±16.0
	Buprenorphine	98.1±12.3	96.5±16.2	99.6±13.0	95.8±11.3
	Pentazocine	97.4± 5.0	108.2± 8.8*†††	101.6± 7.4†	103.4± 4.3†
MPAP (mmHg)	Morphine	12.9± 2.8	11.9± 2.6	12.5± 3.6	13.0± 2.4
	Butorphanol	13.2± 3.3	13.0± 3.5	13.3± 3.1	13.1± 4.2
	Buprenorphine	13.6± 3.5	15.6± 3.3†	15.1± 4.0	14.5± 4.9
	Pentazocine	11.2± 1.3	13.0± 1.0*††	13.4± 4.3	12.2± 3.0
PCWP (mmHg)	Morphine	7.0± 2.2	5.0± 1.5**	5.7± 1.5	5.7± 1.7
	Butorphanol	6.2± 2.6	5.8± 3.2	7.2± 4.8	6.7± 2.9
	Buprenorphine	8.1± 4.5	9.6± 4.5††	9.5± 4.0†	9.8± 5.0
	Pentazocine	5.2± 2.7	5.4± 2.3†	6.2± 2.9	5.4± 2.3
RAP (mmHg)	Morphine	6.2± 4.4	5.5± 3.6	4.9± 3.9	6.1± 4.8
	Butorphanol	3.5± 2.8	4.2± 3.3	3.5± 3.2	3.6± 2.8
	Buprenorphine	2.5± 1.0	3.0± 1.4	2.5± 1.0	3.0± 1.0
	Pentazocine	1.9± 1.0	3.0± 2.9	2.6± 1.9	3.0± 2.9

0.5, 1 and 2 hr refer to post-drug administration. Values are mean±SD. Abbreviations: HR=heart rate; MAP=mean arterial pressure; MPAP=mean pulmonary arterial pressure; PCWP=pulmonary capillary wedge pressure; RAP=right atrial pressure. *P<0.05, **P<0.01, significant difference from control values in the same group. †P<0.05, ††P<0.01, †††P<0.001, significant difference from morphine at similar time.

buprenorphine and 30 mg of pentazocine were slowly given intravenously and each measurement was repeated at 0.5, 1 and 2 hours after injection.

The hemodynamic data in the four groups were compared and the values are presented as mean±SD. The data were analyzed for statistical significance using the paired t-test for comparison with the control values in the same group and the unpaired t-test for comparison between morphine and other drugs at a similar time. The statistical significance was assumed when the P-value was less than 0.05.

Results

The hemodynamic measurements before and at 0.5, 1 and 2 hours after injection are shown in Tables 1–3 and Figures 1–6. The control hemodynamic measurements and control arterial blood gas tension were similar (P>0.05) in the four groups.

I. HR, MAP (Table 1, Figure 1)

The heart rate tended to decrease after the administration of buprenorphine and butorphanol. The mean arterial pressure increased from 97.4±5.0 to 108.2±8.8 mmHg (P<0.05) at 0.5 hour after the administration of pentazocine but it tended to decrease after the morphine administration. Therefore, the difference in MAP between the administration of morphine and pentazocine was statistically significant.

II. MPAP, PCWP, RAP (Table 1, Figures 2 and 3)

Mean pulmonary arterial pressure increased from 11.2±1.3 to 13.0±1.0 mmHg (P<0.05) at 0.5 hour after the administration of pentazocine and also

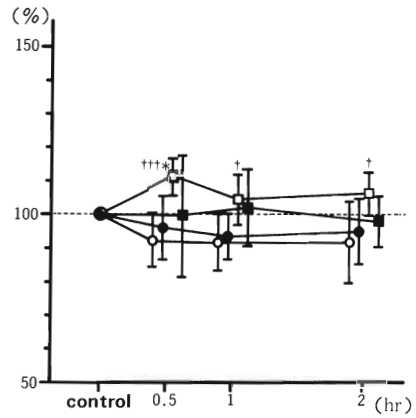

Fig. 1. Percentage Changes in Mean Arterial Pressure of Control and 0.5, 1 and 2 Hours After the Drugs. Mean±SD. ○: morphine, ●: butorphanol, □: pentazocine, ■: buprenorphine. *P<0.05, significant difference from control values in the same group. †P<0.05, ††P<0.01, †††P<0.001, significant difference from morphine at similar time.

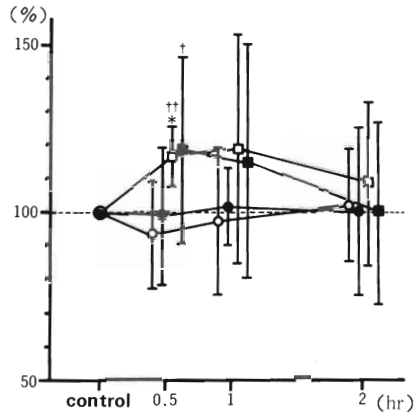

Fig. 2. Percentage Changes in Mean Pulmonary Arterial Pressure of Control and 0.5, 1 and 2 Hours After the Drugs. Mean±SD. ○: morphine, ●: butorphanol, □: pentazocine, ■: buprenorphine. *P<0.05, significnat difference from control values in the same group. †P<0.05, ††P<0.01, significant difference from morphine at similar time.

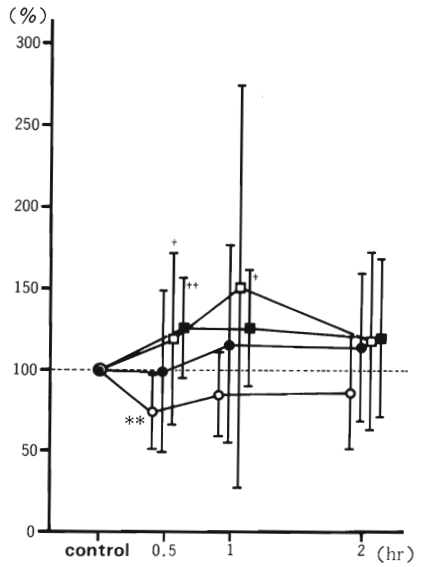

Fig. 3. Percentage Changes in Pulmonary Capillary Wedge Pressure of Control and 0.5, 1 and 2 Hours After the Drugs. Mean±SD. ○: morphine, ●: butorphanol, □: pentazocine, ■: buprenorphine. **P<0.01, significant difference from control values in the same group. †P<0.05, ††P<0.01, significant difference from morphine at similar time.

tended to increase after the administration of buprenorphine, but it tended to decrease after the morphine administration. There were significant differences in MPAP between the administration of morphine and pentazocine and between the administration of morphine and buprenorphine administration.

On the other hand, PCWP decreased from 7.0±2.2 to 5.0±1.5 mmHg ($P<0.01$) at 0.5 hour after the administration of morphine but it tended to increase after the administration of buprenorphine and pentazocine. There were significant differences in PCWP between the administration of morphine and buprenorphine and between the administration of morphine and pentazocine.

III. CI, SI, LVSWI (Table 2, Figures 4–6)

The cardiac index, SI and LVSWI tended to decrease after the administration of morphine, but these parameters tended to increase after the administration of pentazocine and buprenorphine. There were significant differences in CI,

Table 2. Hemodynamic Data

		Control	0.5 hr	1 hr	2 hr
CI	Morphine	3.8± 0.6	3.6± 0.7	3.4± 0.8	3.3± 0.7
(l/min/m^2)	Butorphanol	3.5± 0.9	3.2± 0.9	3.2± 0.8	3.3± 0.7
	Buprenorphine	3.5± 1.1	3.7± 1.2†	3.7± 1.1†	3.5± 1.0†
	Pentazocine	3.9± 1.0	4.2± 0.7†	4.3± 0.7†	4.3± 0.6†
SI	Morphine	41.3± 10.4	39.5± 11.4	38.1± 11.4	36.0± 9.1
(ml/beat/m^2)	Butorphanol	37.5± 9.3	36.6± 10.3	38.0± 8.7	38.2± 5.4
	Buprenorphine	30.2± 9.8	34.4± 9.2††	34.9± 9.5†	31.0± 8.3†
	Pentazocine	38.7± 14.7	43.6± 13.1†	44.9± 12.9†	44.3± 10.4†
LVSWI	Morphine	51.1± 16.7	46.7± 19.7	44.4± 19.5	41.0± 14.7
(gm·m/m^2)	Butorphanol	41.2± 8.2	38.3± 8.8	37.9± 6.5	39.8± 7.5
	Buprenorphine	38.0± 14.3	41.4± 16.2	43.9± 16.5†	40.5± 14.5†
	Pentazocine	48.1± 19.9	58.9± 16.5††	57.9± 16.2†	59.7± 14.7††
SVR	Morphine	1314 ±240	1309 ±257	1340 ±217	1384 ±325
(dynes·sec·cm^{-5})	Butorphanol	1443 ±467	1471 ±463	1473 ±502	1441 ±528
	Buprenorphine	1509 ±345	1397 ±383	1455 ±336	1640 ±238
	Pentazocine	1386 ±294	1380 ±340	1288 ±339	1336 ±294
PVR	Morphine	85 ± 31	113 ± 39	108 ± 55	123 ± 37*
(dynes·sec·cm^{-5})	Butorphanol	116 ± 35	134 ± 56	119 ± 61	113 ± 52
	Buprenorphine	86 ± 31	86 ± 22	79 ± 25	69 ± 25
	Pentazocine	76 ± 66	88 ± 76	85 ± 50	77 ± 41

0.5, 1 and 2 hr refer to post-drug administration. Values are mean±SD. Abbreviations: CI=cardiac index; SI=stroke index; LVSWI=left ventricular stroke work index; SVR=systemic vascular resistance; PVR=pulmonary vascular resistance. *$P<0.05$, significant difference from control values in the same group, †$P<0.05$, ††$P<0.01$, significant difference from morphine at similar time.

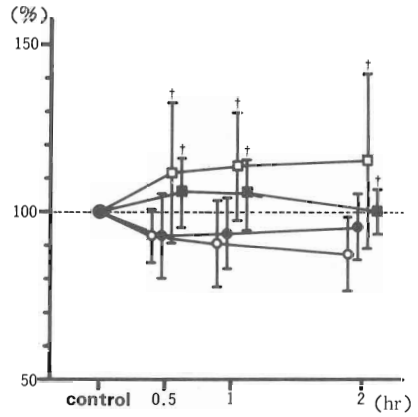

Fig. 4. Percentage Changes in Cardiac Index of Control and 0.5, 1 and 2 Hours After the Drugs. Mean±SD. ○: morphine, ●: butorphanol, □: pentazocine, ■: buprenorphine. †P<0.05, significant difference from morphine at similar time.

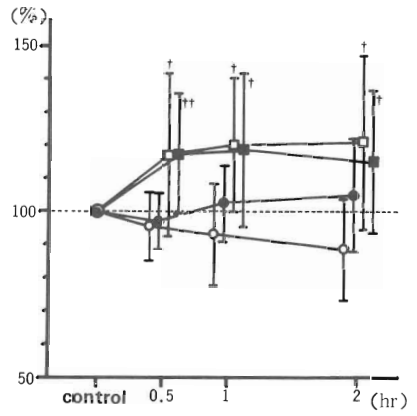

Fig. 5. Percentage Changes in Stroke Index of Control and 0.5, 1 and 2 Hours After the Drugs. Mean±SD. ○: morphine, ●: butorphanol, □: pentazocine, ■: buprenorphine. †P<0.05, ††P<0.01, significant difference from morphine at similar time.

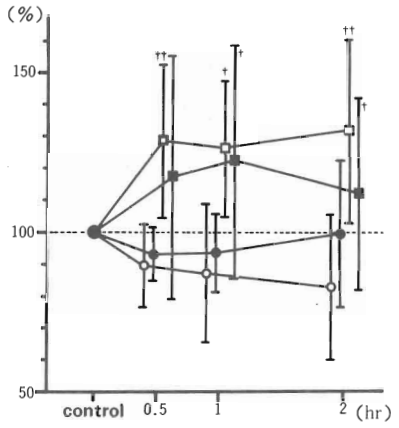

Fig. 6. Percentage Changes in Left Ventricular Stroke Work Index of Control and 0.5, 1 and 2 Hours After the Drugs. Mean±SD. ○: morphine, ●: butorphanol, □: pentazocine, ■: buprenorphine. †P<0.05, ††P<0.01, significant difference from morphine at similar time.

SI and LVSWI between the administration of morphine and pentazocine and between the administration of morphine and buprenorphine.

IV. SVR, PVR (Table 2)

There were no significant changes in SVR from the control values in any group. On the other hand, PVR increased from 85±31 to 123±37 dynes·sec·cm^{-5} (P<0.05) at 2 hours after the administration of morphine. However, no significant difference in PVR was noted between the administration of morphine and other drugs.

V. Pa_{O_2}, $a\text{-}\bar{v}D_{O_2}$, O_2 delivery, $\dot{V}_{O_2}$ (Table 3)

There were no significant differences in Pa_{O_2}, $a\text{-}\bar{v}D_{O_2}$ and O_2 delivery from the control values in any group. The oxygen consumption tended to decrease after the administration of morphine and butorphanol but not after buprenorphine.

Discussion

In the present study, morphine and narcotic agonist-antagonists are used to help patients by allaying their anxiety during the adaptation to mechanical ventilation. Since morphine is the standard drug used for comparison with other analgesics, we also compared the hemodynamic effect of morphine and the equipotent doses of synthetic analgesics (Dobkin *et al.* [9, 10], Nagashima *et al.* [11]).

The present study demonstrated that morphine decreased PCWP significantly

Table 3. Arterial Blood Oxygen Pressure, Arteriovenous Oxygen Content Difference, Oxygen Delivery and Oxygen Consumption

		Control	0.5 hr	1 hr	2 hr
Pa_{O_2} (mmHg)	Morphine	135.6± 15.8	134.4± 25.1	131.0± 26.1	130.0± 19.1
	Butorphanol	130.6± 25.9	125.3± 20.0	128.0± 25.8	126.4± 32.5
	Buprenorphine	108.1± 48.9	131.4± 74.3	131.4± 82.0	124.1± 47.5
	Pentazocine	111.2± 19.8	127.8± 39.6	119.9± 53.0	131.4± 43.2
a-$\bar{v}D_{O_2}$ (ml/dl)	Morphine	5.3± 1.3	4.9± 1.2	4.9± 1.2	5.3± 1.0
	Butorphanol	5.4± 1.6	4.9± 1.5	5.3± 1.1	5.0± 1.1
	Buprenorphine	5.2± 0.9	4.9± 0.0	5.0± 0.2	5.6± 0.2
	Pentazocine	4.7± 1.1	4.3± 1.5	3.8± 1.2	4.4± 1.5
O_2 delivery (ml/min/m²)	Morphine	754 ±146	716 ±175	685 ±182	643 ±209
	Butorphanol	677 ±249	627 ±262	630 ±227	628 ±209
	Buprenorphine	476 ±148	506 ± 88	543 ±125	482 ± 91
	Pentazocine	648 ±211	689 ±189	714 ±202	717 ±238
$\dot{V}_{O_2}$ (ml/min/m²)	Morphine	199 ± 38	178 ± 43	168 ± 41	173 ± 28
	Butorphanol	185 ± 62	158 ± 60	171 ± 49	167 ± 56
	Buprenorphine	154 ± 54	155 ± 6	166 ± 23	168 ± 10
	Pentazocine	180 ± 53	174 ± 61	160 ± 36	183 ± 54

0.5, 1 and 2 hr refer to post-drug administration. Values are mean±SD. Abbreviations; Pa_{O_2}=arterial blood oxygen pressure; a-$\bar{v}D_{O_2}$=arteriovenous oxygen content difference; $\dot{V}_{O_2}$ =oxygen consumption.

in association with the decreasing tendency of MAP, CI, SI and LVSWI. This result coincides with that in the previous reports that morphine increases the peripheral venous capacitance and at the same time decreases the venous return (Alderman *et al.* [8], Downig *et al.* [12], Kay *et al.* [13]). Morphine has been widely used due to its potent analgesic activity and sedative effect, as well as the beneficial effects on pulmonary congestion (Alderman *et al.* [8]). However, morphine may produce hypotension (Rouby *et al.* [1], Samuel *et al.* [2, 3]), therefore, morphine should be given carefully in the presence of reduced cardiac reserve or hypovolemia.

On the other hand, our study revealed a significant increase of PVR at 2 hours after the injection of morphine. Because MPAP did not change during the study, the decline of PCWP and CI may explain the increase in PVR. Grendahl *et al.* [16] also observed an increase of PVR after the i.v. injection of 10 mg of morphine in the patients with pulmonary hypertension. They suggested that an increase in PVR will protect the alveoli against transudation due to congestive heart failure and pulmonary edema. In addition, they reported that morphine diminished $\dot{V}_{O_2}$ by the sedative action. Our study also demonstrated a tendency for $\dot{V}_{O_2}$ to decrease after the morphine injection.

Pentazocine

Thirty mg of pentazocine intravenously resulted in a significant increase of MAP and MPAP with a resultant increase of the ventricular afterload stress. These results coincide with the previous reports (Alderman *et al.* [8], Downig *et al.* [12], Zellis *et al.* [15]). Further, pentazocine-induced augmentation of the left ventricular preload and afterload increased the myocardial oxygen demand (Grendahl *et al.* [16]). Therefore, pentazocine may be unsuitable in the cases with myocardial infarction and congestive heart failure. On the contrary, pentazocine may be useful in the cases with hypotension or

hypovolemia, because in increases MAP.

Buprenorphine

After the administration of buprenorphine, MPAP, PCWP, CI, SI and LVSWI tended to increase and HR tended to decrease, but the changes were not statistically significant compared to the control values. These findings was almost the same as the results of Rosenfeldt *et al.* [7].

On the other hand, there were significant differences in MPAP, PCWP, CI, SI and LVSWI between the administration of morphine and buprenorphine. These changes after the buprenorphine injection were similar to those caused by pentazocine. In addition, caution should be taken into consideration to administer buprenorphine to the patients with a high pulmonary arterial pressure or wedge pressure, because of its tendency to increase MPAP and PCWP.

In the present study, 0.6 mg of buprenorphine was administered intravenously. Although this dose may be a little stronger than 10 mg of morphine, 0.3 mg of buprenorphine was inadequate to adapt the patients to mechanical ventilation and had no influence on $\dot{V}_{O_2}$. Therefore, the sedative effect of buprenorphine may be less than that of morphine.

Butorphanol

Butorphanol produced no statistically significant hemodynamic change from the control values. However, Popio *et al.* [19] reported that CI and MPAP increased significantly. As their patients were breathing spontaneously, the situation of their ventilation was different from those of our patients. In our study, $\dot{V}_{O_2}$ tended to decrease after butorphanol injection. This fact may be due to the sedative effect of butorphanol. In addition, we found no adverse effect of butorphanol on the cardiovascular system. Butorphanol appears to be a safe analgesic for the critically ill patients.

In conclusion, the hemodynamic effects of the four drugs were mild and could be given safely even on the critically ill patients. The hemodynamic effects of these analgesics showed a similarity between butorphanol and morphine and between buprenorphine and pentazocine. This study demonstrates that morphine and butorphanol are preferred to the cases with hypertension, increased pulmonary arterial pressure or wedge pressure and that pentazocine and buprenorphine are more suitable for the cases with hypotension or hypovolemia.

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