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Comparison of circulatory and respiratory responses between supplementary epidural buprenorphine and eptazocine administration during and immediately after total intravenous anesthesia

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Abstract: Opioid supplements are often required in total intravenous anesthesia (TIVA). Most κ-opiate receptors are found in the spinal cord, whereas μ-opiate receptors are widespread throughout the brain and spinal cord. Buprenorphine has a strong μ-action with a minute κ-action, while eptazocine stimulates κ-receptors only. From these, epidural eptazocine is expected to exert strong spinal analgesia by κ-stimulation without μ-action, which produces circulatory and respiratory depression. Therefore, the clinical effects of epidural opioids on circulation, respiration, and analgesia were compared. Continuous epidural administration of eptazocine or buprenorphine was combined with TIVA in patients scheduled for elective abdominal surgery. Epidural opioid administration was continued throughout and for 72 h after anesthesia. A significant analgesic effect ($P < 0.01$) of epidural eptazocine without circulatory and respiratory depression was observed. With epidural buprenorphine, circulatory and respiratory depression during and immediately after anesthesia were significant ($P < 0.05$). These results suggest that medullary μ-stimulation by an epidural opioid induces circulatory (hypervagotonicity and hypervagosensitivity) and respiratory depression, while κ-stimulation produces only minimal effects on circulatory and respiratory systems.

Key words: κ-Action, μ-Action, Buprenorphine, Eptazocine, Epidural opioid

Introduction

Recently, total intravenous anesthesia (TIVA) has come into widespread use [1,2], although some drawbacks of this technique have been noted, such as intraoperative awareness and hypertension [1,3]. Therefore, opioid supplements may often be required in TIVA [4]. Systemic administration of opioids, such as morphine, fentanyl, and buprenorphine, however, induces respiratory depression and bradycardia [4,5].

While most κ-opiate receptors are found in the spinal cord, μ-opiate receptors are widespread throughout the central nervous system (CNS). These two receptor subtypes have been demonstrated to be important for analgesia in the CNS [5,6], whereas circulatory and respiratory depression was demonstrated to be attributable to medullary μ-stimulation [7–9]. To stimulate spinal opiate receptors only, opioids have been administered into the epidural space [10,11]. Nevertheless, respiratory depression still occurs even following epidural administration of μ-opioids [12–15].

Analgesia without respiratory depression has been demonstrated following selective κ-stimulation by systemic and spinal opioids [16–18]. For opioid supplement in TIVA, epidural administration of a selective κ-agonist is considered beneficial because stimulation to brain opiate receptors is minimal and the μ-effect is absent. Therefore, an epidural κ-opioid is expected to exert strong spinal analgesia with minimal adverse effects, compared with epidural μ-opioids. However, the precise mechanism of circulatory and respiratory effects of epidural κ-opioids is still unclear.

Eptazocine (sodium index, 3.89; heptane/phosphate-buffer partition coefficient (pK) at pH = 7.4, 2.60) has been demonstrated to be a κ-receptor agonist without μ-action on CNS opiate receptors [19], while buprenorphine (1.07 and 1.78, respectively) was shown to have μ- and minute κ-actions [5,11–14,20,21]. In the present study, we therefore administered supplementary eptazocine or buprenorphine into the epidural space during TIVA, and studied the difference between the opioids. The significant analgesic effect of selective κ-stimulation by epidural eptazocine was not accompanied by either circulatory or respiratory depression, and was beneficial as a supplement to TIVA. In contrast,

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analgesia by buprenorphine mainly involved μ-action, and was accompanied by circulatory and respiratory depression.

Patients and methods

The study as carried out after obtaining approval from the Institutional Committee for Human Investigation of our hospital. Informed consent was obtained from 84 patients scheduled for elective abdominal surgery (total and subtotal gastrectomy, cholecystectomy, hemicolectomy, sigmoidectomy, and partial gastrectomy) under TIVA. These patients were assigned to three groups, the eptazocine group (n = 27), the buprenorphine group (n = 30), and the control TIVA group (n = 27). The groups were matched statistically for age, gender, body weight, ASA physical status, and duration of anesthesia and surgery (Table 1). One hour before the induction of anesthesia, all patients were premedicated intramuscularly with atropine sulfate, 0.01 mg·kg^{-1}, and hydroxyzine, 1 mg·kg^{-1}.

In the eptazocine and buprenorphine groups, the patients were cannulated epidurally at the level of T7–T8 (upper abdominal surgery) or T11–T12 (lower abdominal surgery). Following an induction dose (diluted in 2 ml) of the epidural opioid, eptazocine hydrobromide (0.3 mg·kg^{-1}, Nihon Iyaduhin Kogyo, Tokyo, Japan) or buprenorphine hydrochloride (0.002 mg·kg^{-1}, Reckitt and Colman Pharmaceuticals, Hull, UK), a maintenance dose of the epidural opioid (0.6 and 0.004 mg·kg·day^{-1}, respectively) was continuously infused by balloon pump (SFA-0503D, Nipro, Tokyo, Japan).

Relative to morphine (value of 1), the analgesic effects of eptazocine and buprenorphine are approximately 0.3 [19] and 33 [5], respectively. These values were referred to for both induction and maintenance doses of the opioids. Epidural opioid administration was continued throughout and for 72 h after anesthesia for surgical and postoperative pain management.

The patients in all three groups received TIVA with diazepam (induction dose, 0.2 mg·kg^{-1}, and maintenance dose, 0.1 mg·kg^{-1}, given every 3 h), droperidol (0.05 mg·kg^{-1} and 0.025 mg·kg^{-1} every 6 h, respectively), ketamine (1 mg·kg^{-1}, and 1.5 mg·kg^{-1}·h^{-1} continuously by electrically driven pump, respectively), and vecuronium (0.16 mg·kg^{-1}, and 0.08 mg·kg^{-1}·h^{-1} continuously, respectively), as described previously [17]. The patients were intubated and artificially ventilated (Servo Ventilator 900C, Siemens-Elema, Solna, Sweden) with an oxygen-air mixture (30% oxygen) at 4.5%–5.0% end-tidal CO_2 concentration (CO_2 analyzer 930, Siemens-Elema). When the depth of surgical anesthesia with TIVA alone was judged to be insufficient based on the observation of tachycardia, hypertension, sweating, flush, lacrimation, and/or motion, an oxygen-nitrous oxide mixture (30% and 70%, respectively) was given by inhalation [22].

Table 1. Characteristics of buprenorphine, eptazocine, and control TIVA groups

	Group		
	Eptazocine (n = 27)	Buprenorphine (n = 30)	Control TIVA (n = 27)
Age (years)	64 ± 12	62 ± 16	57 ± 15
Gender (male/female)	21/9	18/12	15/12
Body weight (kg)	56 ± 9	52 ± 9	58 ± 7
ASA physical status	1.0 [I–III]	1.0 [I–III]	1.0 [I–III]
Duration of anesthesia (min)	275 ± 163	230 ± 79	264 ± 153
Duration of surgery (min)	227 ± 168	165 ± 66	196 ± 142
Infusion rate[a] (ml·kg^{-1}·h^{-1})	4.3 ± 1.3	4.7 ± 1.3	3.9 ± 1.7
Urine output (ml·kg^{-1}h^{-1})	1.1 ± 0.9	0.9 ± 0.7	1.4 ± 1.4
Blood loss (ml·kg^{-1})	10.2 ± 10.5	7.1 ± 7.4	10.4 ± 10.7
Blood transfusion[b] (units)	0.0 [0–25]	0.0 [0–10]	0.0 [0–11]
Droperidol[c] (mg·kg^{-1})	0.062 ± 0.017	0.059 ± 0.014	0.061 ± 0.018
Diazepam[c] (mg·kg^{-1})	0.33 ± 0.12	0.31 ± 0.08	0.31 ± 0.13
Ketamine[c] (mg·kg^{-1})	7.7 ± 3.7	7.1 ± 2.2	7.5 ± 4.1
Vecuronium[c] (mg·kg^{-1})	0.522 ± 0.278	0.467 ± 0.125	0.483 ± 0.201
Buprenorphine[c] (mg·kg^{-1})	—	0.026 ± 0.006	—
Eptazocine[c] (mg·kg^{-1})	0.41 ± 0.07	—	—

TIVA, total intravenous anesthesia.
[a] Lactated Ringer's solution was infused throughout and after anesthesia.
[b] Concentrated red cells, one unit of which was obtained from 200 ml of blood, were used.
[c] Total amount of anesthetics used for anesthesia. There were no significant differences among the three groups in any of the above parameters. Data are given as means ± SD, median and range (for ASA and blood transfusion), or patient numbers (for gender).

A vasopressor (adrenergic agent; etilefrine, 5 mg) and a vasodepressor (calcium blocker; diltiazem, 5 mg) were given when the systolic blood pressure, measured noninvasively (BP-308ET; Nippon Colin, Tokyo, Japan), was <80 mmHg for 5 min and >170 mmHg for 10 min. At the end of surgery, muscle relaxation was reversed with atropine (0.5 mg) and neostigmine (1.5–2.0 mg). The patients were extubated when spontaneous respiration with a ventilation volume of $>0.09\,ml \cdot kg^{-1} \cdot min^{-1}$ had been established. Arterial blood gases were measured at the beginning of surgery and 30 min after the termination of anesthesia.

Postoperative pain was observed for 72 h after anesthesia, and the pain intensity was scored according to the patients' reports as one of three grades: unbearable (analgesic was demanded), bearable (no analgesic was demanded) and nil (minimal or no pain). Patients who had unbearable postoperative pain received an additional epidural opioid (eptazocine, 7.5 mg, or buprenorphine, 0.05 mg, respectively) or intramuscular eptazocine (in the control TIVA group), 15 mg.

Data were analyzed with the chi-squared test, Fisher's exact probability test, one- or three-way analyses of variance (ANOVA), or the Kruskal-Wallis test. The Tukey test or Dunn test was employed when differences were significant on the above tests. Values are shown as means and standard deviation (SD). P values <0.05 were considered significant.

Results

In the eptazocine group, blood pressure and heart rate during surgery remained stable (systolic pressure, 115–150 mmHg; diastolic pressure, 65–95 mmHg; heart rate, 75–105), although the minimal values for blood pressure and heart rate during surgery were significantly lower than baseline values ($P < 0.01$, by three-way ANOVA and Tukey test). However, the maximum values for blood pressure and heart rate during surgery did not show significant differences from baseline levels (Fig. 1). A vasopressor was required in 1 patient with profound hemorrhage, and a vasodepressor was required in 2 patients. No nitrous oxide inhalation was required in the eptazocine group (Table 2).

In the buprenorphine group, significant hypotension and bradycardia occurred (both $P < 0.01$, by three-way ANOVA and Tukey test when the peritoneal cavity was opened and manipulated (smoothing of the parietal peritoneum and stretching of the mesentery), probably due to vagovagal reflex (Fig. 1). Hypotension (<80 mmHg systolic) and bradycardia ($<50\,min^{-1}$) were profound in 18 patients and required the administration of a vasopressor (Table 2). Both blood pressure and heart rate in the buprenorphine group were significantly lower ($P < 0.05$–0.01) throughout and after anesthesia compared to these values in the eptazocine and control TIVA groups (Fig. 1). No nitrous oxide inhalation was required in the buprenorphine group (Table 2).

In the control TIVA group, blood pressure and heart rate were frequently elevated during anesthesia and surgery (Fig. 1), and in 15 patients, a vasodepressor was required to control hypertension ($P < 0.01$, by Fisher's exact probability test). Nitrous oxide inhalation was required in 9 patients when the depth of anesthesia was judged to be insufficient ($P < 0.01$, by Fisher's exact probability test) (Tables 2).

After 30 min of anesthesia, partial pressure of arterial carbon dioxide ($Paco_2$) in the buprenorphine group was significantly higher and the respiratory rate was significantly lower (both $P < 0.01$, by one-way ANOVA and Tukey test) than those values in the eptazocine and control TIVA groups (Table 3). Postoperative respiratory depression was not seen in the eptazocine and control TIVA groups, whereas intravenous naloxone (0.6–0.8 mg) was helpful in seven of the buprenorphine group with severe respiratory depression ($P < 0.01$, by Fisher's exact probability test) (Table 2).

Continuous administration of epidural eptazocine and buprenorphine was also beneficial for postoperative pain relief: postoperative pain in the control TIVA group was significantly more intense than that in the eptazocine and buprenorphine groups, and administration of additional analgesic was required by all 27 patients in the control TIVA group ($P < 0.01$, Kruskal-Wallis test and Dunn test) (Table 4).

Intraoperative awareness was not noted in any patient, and it was later confirmed by interview that none of the intraoperative procedures remained in patients' memories.

There were no significant differences in infusion rate of lactated Ringer's solution, urine output, blood loss, blood transfusion amount, or total amount of anesthetics used for anesthesia among the three groups (Table 1). No headache, nausea, or vomiting was observed, and no abnormal neurological signs, such as hallucinations or extrapyramidal signs, due to epidural opioid administration were noted.

Discussion

The present study demonstrated that epidural administration of a selective κ-opioid, eptazocine, produced evident spinal analgesia, and was not accompanied by either circulatory effects or respiratory depression. Therefore, no nitrous oxide inhalation was required, a vasodepressor was used during anesthesia in only 2 patients, and the use of additional analgesics for postoperative pain relief was infrequent. These effects are

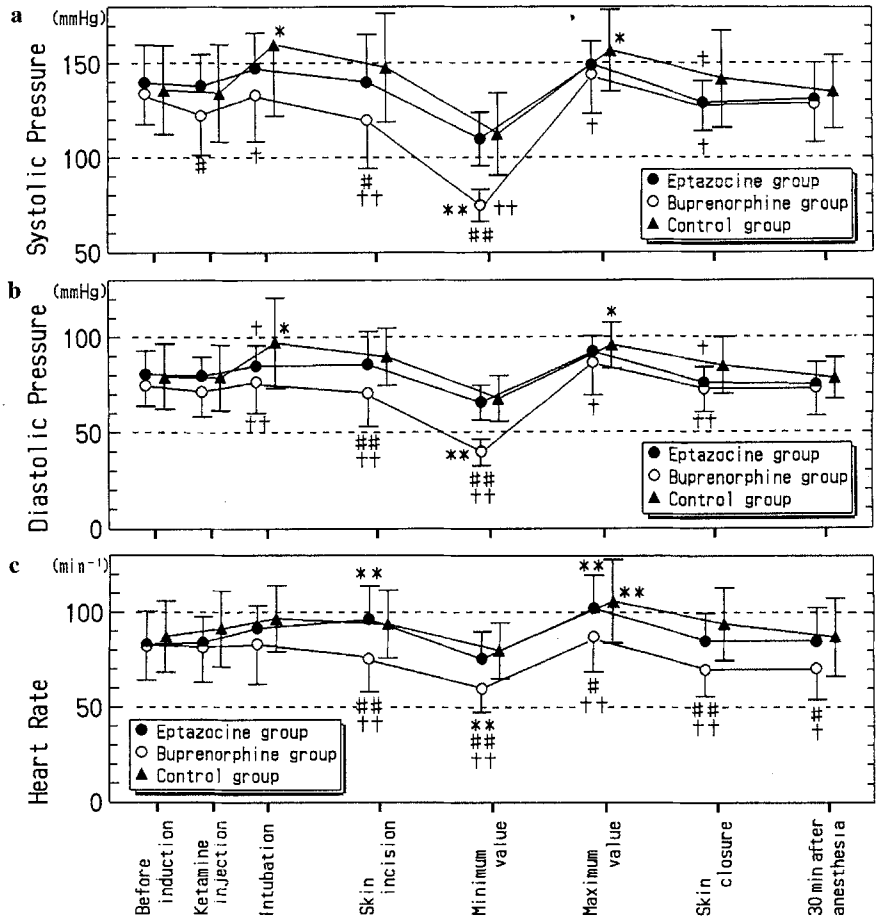

Fig. 1. Systolic pressure (**a**), diastolic pressure (**b**), and heart rate (**c**) during and after anesthesia. In the eptazocine group (*solid circles*), blood pressure and heart rate were stable. In the buprenorphine group (*open circles*), profound hypotension and bradycardia occurred during peritoneal manipulation. At this time, the minimum values of systolic and diastolic pressure as well as heart rate in the buprenorphine group (23 of 32) was recorded, while mild hypotension and bradycardia in a few of the eptazocine (3 of 32) and control (3 of 27) group were observed, respectively. Both blood pressure and heart rate in this group were significantly lower throughout and after anesthesia compared to the corresponding values in the eptazocine and control TIVA (*triangles*) groups. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with value before the induction of anesthesia. $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ for differences between the eptazocine and buprenorphine groups, and $^{\dagger}P < 0.05$ and $^{\dagger\dagger}P < 0.01$ comparison between buprenorphine and control TIVA groups. Symbols represent means ± SD

Table 2. Additional drugs used during and after anesthesia

Drug	Group		
	Eptazocine (n = 27)	Buprenorphine (n = 30)	Control TIVA (n = 27)
Vasopressor	1[a]	18*	0
Vasodepressor	2	0	15*
Nitrous oxide[b]	0	0	9*
Naloxone	0	7*	0

[a] Vasopressor was required because of profound hemorrhage.
[b] Nitrous oxide was given by inhalation when the depth of surgical anesthesia was judged to be insufficient with TIVA alone.
*$P < 0.01$ compared with the other two groups.

Table 3. Respiratory function during and after anesthesia

		Group		
		Eptazocine (n = 27)	Buprenorphine (n = 30)	Control TIVA (n = 27)
Pao_2 (mmHg)	During[a]	126 ± 33	125 ± 29	120 ± 33
	After[d]	162 ± 87	161 ± 41	168 ± 46
$Paco_2$ (mmHg)	During[b]	39.7 ± 5.5	36.8 ± 4.3	37.1 ± 6.7
	After	42.8 ± 2.6	48.0 ± 7.1*	41.5 ± 5.3
pH	During	7.42 ± 0.05	7.43 ± 0.05	7.40 ± 0.06
	After	7.38 ± 0.05	7.37 ± 0.05	7.39 ± 0.06
Respiratory rate	During		(14.0)[c]	
($\cdot min^{-1}$)	After	15.5 ± 1.6	11.8 ± 2.4*	16.2 ± 1.6

Pao_2, partial pressure of arterial O_2; $Paco_2$, partial pressure of arterial CO_2.
During anesthesia, the patients were artificially ventilated[a] with 30% oxygen [b]at 4.5%–5% of end-tidal carbon dioxide ($ETco_2$), and [c]at a constant respiration rate (14.0 $\cdot min^{-1}$). [d]After anesthesia, oxygen (3.01 $\cdot min^{-1}$), was inhaled through a face mask under conditions of spontaneous respiration.
* $P < 0.01$ compared with the other two groups.

Table 4. Intensity of postoperative pain

	Group		
	Eptazocine (n = 27)	Buprenorphine (n = 30)	Control TIVA (n = 27)
Unbearable	1	1	27*
Bearable	7	8	0
Nil	19	21	0

Unbearable, analgesic was demanded; bearable, no analgesic was demanded; nil, minimal or no pain.
* $P < 0.01$ compared with the other two groups.

thought to have resulted from epidural administration of a κ-opioid, eptazocine [16–18], and may have minimized the direct peripheral effects as well as brain μ-stimulation [11]. Thus, the analgesic effect of eptazocine is more powerful without circulatory and respiratory depression when given epidurally. This is supported by a previous study on somatosensory evoked potentials during TIVA [17]. On the basis of these results, epidural eptazocine as a supplement to TIVA is suggested to be beneficial. In the buprenorphine group, however, hypotension, bradycardia, and respiratory depression occurred.

Although buprenorphine has been shown to have both μ- and κ-actions in the CNS, the opioid strongly stimulates μ-receptors while minutely stimulating κ-receptors. Therefore, μ-action is mainly observed in the clinical use of buprenorphine [5]. Although the opioid was administered into the epidural space only [10,11], circulatory and respiratory depression could not be avoided. Stimulation of medullary μ-receptors has been demonstrated to increase vagotonicity (induction of hypotension and bradycardia) [7,8], and depress inspiratory neurons [9]. Therefore, the circulatory and respiratory depression seen in the buprenorphine group was considered to be attributable to the medullary μ-action. This hypervagotonicity appeared to be related to profound hypotension and bradycardia (hypervagosensitivity) that occurred on peritoneal stimulation (vagovagal reflex). Furthermore, adverse vagal responses may not be blocked even by premedication with atropine [23].

Since no significant respiratory depression has been demonstrated with the respective clinical doses of intravenous anesthesia, ketamine, diazepam, or droperidol [24–26], no postanesthetic respiratory depression was noted in the eptazocine or control TIVA groups (Table 3). In the buprenorphine group, however, an opioid antagonist, naloxone, was helpful for postanesthetic respiratory depression. Therefore, the postanesthetic respiratory depression seen in the buprenorphine group was also considered to be attributable to the medullary μ-action of this agent.

In conclusion, the circulatory and respiratory responses to these two opioids appeared to differ. Spinal analgesia without the adverse circulatory and respiratory effects of specific κ-agonists was considered beneficial, whereas the effects of μ-agonists were accompanied by circulatory and respiratory depression.

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