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Total intravenous anesthesia combined with epidural eptazocine

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Abstract: To reduce the doses of intravenous anesthetics (ketamine, diazepam, droperidol, and vecuronium) used in total intravenous anesthesia (TIVA), epidural administration of a κ-stimulating opioid, eptazocine, was combined with TIVA in 115 patients. Surgical procedures were uneventful under TIVA plus epidural eptazocine; significant depression of EEG and somatosensory-evoked potentials during anesthesia were observed without delay in recovery. The circulatory response and blood glucose level during and after anesthesia and surgery were stable, and there was no postanesthetic respiratory depression. On the other hand, in 46 patients given TIVA only, hypertension, tachycardia, and elevated blood glucose during and after anesthesia were observed: in 25 (54.3%) patients, a vasodepressor was required, and in 18 (39.1%) patients, nitrous oxide was needed. Therefore, epidural eptazocine may make it possible to use lower doses of anesthesia in TIVA, thus reducing the adverse effects associated with TIVA such as hypertension during surgery, intraoperative awareness, postanesthetic respiratory depression, delayed recovery from anesthesia, and neurological signs after anesthesia. This may be due to the κ-stimulating action of epidural eptazocine on the spinal cord and its σ-blocking action, as well as its lack of μ-action on the brain.

Key words: Eptazocine, Ketamine, TIVA, Epidural administration, κ Action, μ Action

Introduction

General anesthesia using a combination of intravenous anesthetics, so-called total intravenous anesthesia (TIVA), may have certain advantages over inhalation anesthesia in terms of disturbances of cardiovascular, respiratory, endocrine, metabolic and immune function [1,2]. TIVA using ketamine, fentanyl, and diazepam appears to be in widespread use [1]. However, TIVA has several drawbacks, such as hypertension during anesthesia, intraoperative awareness, delayed recovery from anesthesia, postanesthetic respiratory depression, dreaming, and extrapyramidal signs [1,2]. Large doses of opiates may also have an immunodepressant effect [3,4], and intravenous opiates including fentanyl have long-lasting effects [5].

Eliminating the need for an opiate and reducing the dose of opioids may minimize these adverse effects. A specific opioid, eptazocine, provides κ-stimulating and σ-blocking action without a μ effect [6]. Therefore, epidural administration of eptazocine was combined with TIVA, since a powerful analgesic effect of the epidural opioid, mediated by κ-stimulation in the spinal cord without μ and σ stimulation was expected [5].

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Patients and methods

The study was carried out after approval by the Institutional Committee for Human Investigation of this hospital. Informed consent was obtained from all 161 patients undergoing elective surgery. One hundred and fifteen patients were given TIVA plus epidural eptazocine (gastrectomy, 42; cholecystectomy, 31; mastectomy, 10; partial hepatectomy, 4; nephrectomy, 5; hemicolectomy, 18; other abdominal surgery, 5). Forty-six patients were given TIVA only (gastrectomy, 18; cholecystectomy, 13; mastectomy, 5; partial hepatectomy, 1; nephrectomy, 2; hemicolectomy, 4; other abdominal surgery, 3). The groups were matched statistically for surgery, age, sex, body weight (BW), ASA grade, and the duration of anesthesia and surgery (Table 1).

Induction and maintenance of anesthesia

One hour before induction of anesthesia, patients were premedicated intramuscularly with atropine sulfate 0.01 $mg \cdot kg^{-1}$ and hydroxyzine 1 $mg \cdot kg^{-1}$. Anesthesia was started after setting up one or two intravenous infusion routes with lactated Ringer's solution.

Table 1. Patients, anesthesia and surgery duration, infusion, urine output, blood loss, and transfusion

Group	Age (years)	Sex (m/f)	BW (kg)	ASA grade [range]	Duration of Anesthesia (min)	Duration of Surgery (min)	Infusion rate ($ml \cdot kg^{-1} \cdot h^{-1}$)	Urine output[1] ($ml \cdot kg^{-1} \cdot h^{-1}$)	Blood loss ($ml \cdot kg^{-1}$)	Blood transfusion[2] ($ml \cdot kg^{-1}$)
TIVA plus epidural eptazocine	62.7 ± 12.5	37/78	55.6 ± 9.9	1.4 [1–3]	233 ± 113	184 ± 112	4.4 ± 2.2	1.5 ± 2.1	8.6 ± 14.9	7.1 ± 18.9
TIVA only	57.3 ± 14.7	16/30	57.2 ± 7.1	1.3 [1–3]	257 ± 150	190 ± 138	4.2 ± 1.8	1.4 ± 1.4	9.7 ± 10.5	6.2 ± 15.8

Blood transfusion was required in 22 (19.1%) (TIVA plus epidural eptazocine) and 10 (29.0%) (TIVA only) patients of large blood loss (>15 $ml \cdot kg^{-1}$). Values are means ± SD. There are no significance differences between the groups.
BW, body weight; TIVA, total intravenous anesthesia.

Table 2. Regime of induction and maintenance doses of drugs

	Induction	Maintenance
Epidural Administration (in TIVA plus epidural eptazocine group)		
Eptazocine	7.5 mg	1.2 $mg \cdot h^{-1}$
Intravenous Administration		
Diazepam	0.2 $mg \cdot kg^{-1}$	0.1 $mg \cdot kg^{-1}$
Droperidol	0.05 $mg \cdot kg^{-1}$	0.025 $mg \cdot kg^{-1}$
Vecuronium	0.16 $mg \cdot kg^{-1}$	0.08 $mg \cdot kg^{-1} \cdot h^{-1}$
Ketamine	1.0 $mg \cdot kg^{-1}$	1.5 $mg \cdot kg^{-1} \cdot h^{-1}$

Before TIVA plus epidural eptazocine, patients were cannulated epidurally at the following levels: T3–4 (mastectomy), T7–8 (upper abdominal and retroperitoneal surgery), or T11–12 (lower abdominal surgery). After an induction dose of epidural eptazocine hydrobromide 7.5 mg (Nihon Iyakuhin Kogyo, Toyama, Japan) diluted in 2 ml, a maintenance dose of epidural eptazocine (1.2 $mg \cdot h^{-1}$) was infused continuously by a balloon pump (SFA-0503D, Nipro, Tokyo, Japan). Epidural eptazocine administration was continued throughout anesthesia and for 72 h thereafter for postoperative pain management. Patients given TIVA only were not canulated epidurally.

TIVA in both groups was induced and maintained as follows. Induction doses of 0.2 $mg \cdot kg^{-1}$ diazepam (Yamanouchi Pharmaceutical, Osaka, Japan), and 0.05 $mg \cdot kg^{-1}$ droperidol (Sankyo, Tokyo, Japan), were given intravenously. Thereafter, 0.16 $mg \cdot kg^{-1}$ vecuronium bromide (Organon Tekniks, Amsterdam, Netherlands) was administered according to the time-principle method [7], and an induction dose of ketamine hydrochloride 1.0 $mg \cdot kg^{-1}$ (Sankyo) was given intravenously. When muscle relaxation was achieved, patients were intubated and artificially ventilated with an oxygen-air mixture (30% oxygen) at 4.5%–5% of endtidal CO_2 concentration. For maintenance of anesthesia, a mixed solution of ketamine (1.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and vecuronium (0.08 $mg \cdot kg^{-1} \cdot h^{-1}$) was infused intravenously using an electrically driven syringe pump (SP-60, Nipro, Japan). Additional diazepam and droperidol were administered intermittently every 3 and 6 h in doses of 0.1 $mg \cdot kg^{-1}$ and 0.025 $mg \cdot kg^{-1}$, respectively. Doses of the drugs used are summarized in Table 2. When the depth of surgical anesthesia with TIVA alone was judged to be insufficient, an oxygen-nitrous oxide mixture (30% and 70%, respectively) was inhalated [8].

A vasopressor (α-adrenergic agent; etilefrine, 5 mg) and a vasodepressor (calcium antagonist; diltiazem, 5 mg) were given intravenously when the systolic blood pressure was less than 80 mmHg for 5 min and greater than 180 mmHg for 15 min, respectively. Approximately 5 min before the start of skin closure, intravenous infusion of the ketamine-vecuronium mixture was terminated. At the end of surgery, muscle relaxation was reversed with 0.5 mg atropine and 1.5–2.0 mg neostigmine. Patients were extubated when spontaneous respiration with endtidal CO_2 concentration of <6% had been established. Patients who had unbearable postoperative pain were given additional epidural eptazocine (3.8 mg) or intramuscular eptazocine (15 mg).

Monitoring and laboratory measurements

Throughout anesthesia, the electrocardiogram, heart rate, noninvasive blood pressure (BP-308ET, Nippon Colin, Komaki, Japan), oxygen saturation, inspired oxygen concentration, endtidal CO_2 concentration, minute ventilation volume and urine output were monitored. Arterial blood gases were measured at the start of surgery and 30 min after the termination of anesthesia. Serum electrolytes (Na, K, and Cl), blood urea nitrogen (BUN), serum creatinine, glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) were checked on the day before surgery and on the 3rd postoperative day. Blood glucose was measured before induction, at the start of surgery (skin incision), at 30 and 60 min after the skin incision, at the end of surgery, and 30 min after the termination of anesthesia.

In five of the patients given TIVA plus epidural eptazocine, the electroencephalogram (EEG) and somatosensory-evoked potentials (SEPs) were monitored (Neuropack Four Mini, Nihon Kohden, Tokyo, Japan) with a recording and two reference electrodes (Ag-

AgCl) placed at C4′ and both earlobes, respectively. Electrical stimulation with a square pulse (20 mA, 2 ms) through a pair of Ag-AgCl electrodes (20 mm apart) was given to the left (contralateral) median nerve at the wrist.

Statistical analysis

Data were analyzed using the chi-square test or by two- or three-way analyses of variance (ANOVA), and by Dunnett's multiple comparison test or Student's *t*-test when significant by the above tests. Values are shown as the mean and standard deviation (SD). $P < 0.05$ was considered significant.

Results

During TIVA plus epidural eptazocine, blood pressure fell slightly but significantly ($P < 0.05$), while the heart rate did not change significantly (Fig. 1). None of the patients became hypertensive (systolic pressure >180 mmHg for more than 15 min) in the group undergoing TIVA plus epidural eptazocine. Hypotension due to hemorrhage occurred in 5 cases. Pre-existing arrhythmias (34 cases) did not become more frequent in any of the cases; and arrhythmias present before anesthesia became infrequent (23 of 34 cases) or disappeared (11 of 34 cases) during anesthesia without using anti-arrhythmic drugs. The depth of anesthesia was adequate and no nitrous oxide inhalation was required in patients given TIVA plus epidural eptazocine (Table 3).

In patients given TIVA only, blood pressure and heart rate were frequently elevated ($P < 0.05$), during anesthesia and surgery (Fig. 1), and a vasodepressor in 25 (54.3%) patients ($P < 0.01$), and an anti-arrythmic drug in one (2.2%) were required, respectively. Nitrous oxide was inhalated in 18 (39.1%) patients whose depth of anesthesia was judged to be insufficient ($P < 0.01$) (Table 3).

SEPs and EEGs were recorded in five of the patients given TIVA plus epidural eptazocine. SEP latencies (N20, N32 and N60) in response to median nerve stimulation were significantly prolonged ($P < 0.05$), and the amplitudes were significantly ($P < 0.05$) decreased during anesthesia. EEGs showed a mixed pattern of slow

Table 3. Additional drugs required during and after anesthesia

	TIVA plus epidural eptazocine ($n = 115$)	TIVA only ($n = 46$)
Vasopressor	5 (4.3%)*	0 (0.0%)
Vasodepressor	0 (0.0%)	25 (54.3%)**
Diuretic	12 (10.4%)	5 (10.9%)
Nitrous oxide	0 (0.0%)	18 (39.1%)**
Postoperative analgesic	17 (14.8%)	45 (97.8%)**
Anti-arrhythmic drug	0 (0.0%)	1 (2.2%)

* $P < 0.05$ and ** $P < 0.01$ between groups.

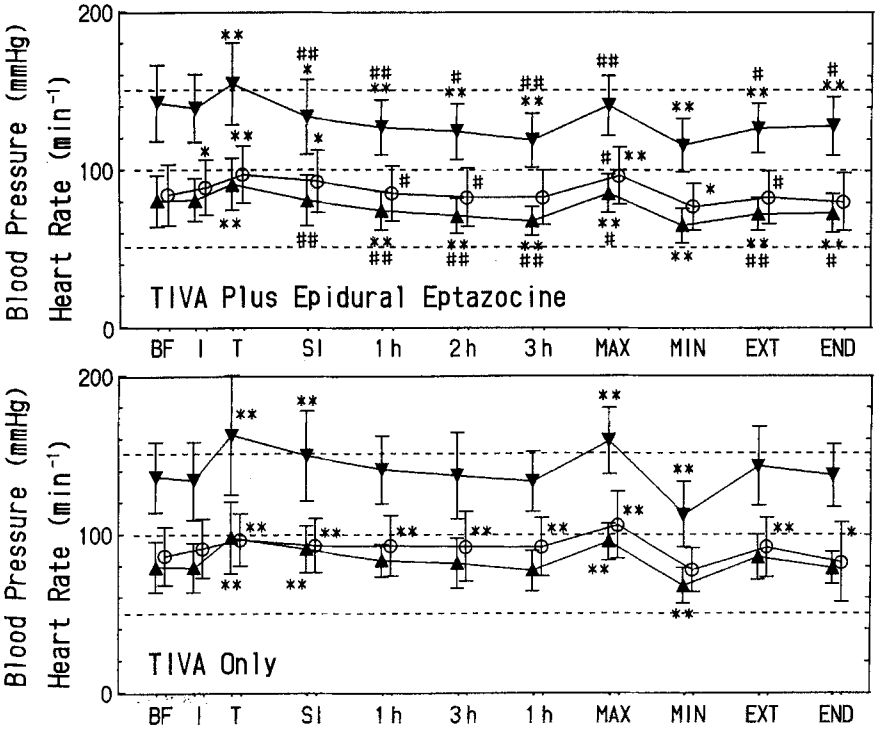

Fig. 1. Blood pressure and heart rate. *$P < 0.05$ and **$P < 0.01$ compared with the value before induction, and #$P < 0.05$ and ##$P < 0.01$ between the groups. Values are mean ± SD. *Inverted closed triangles*, systolic pressure; *closed triangles*, diastolic pressure; *open circles*, heart rate. BEF, before induction; IND, after induction of anesthesia; INT, after endotracheal intubation; SI, after skin incision; MAX, maximum value during surgery; MIN, minimum value during surgery; EXT, after extubation; END, end of anesthesia

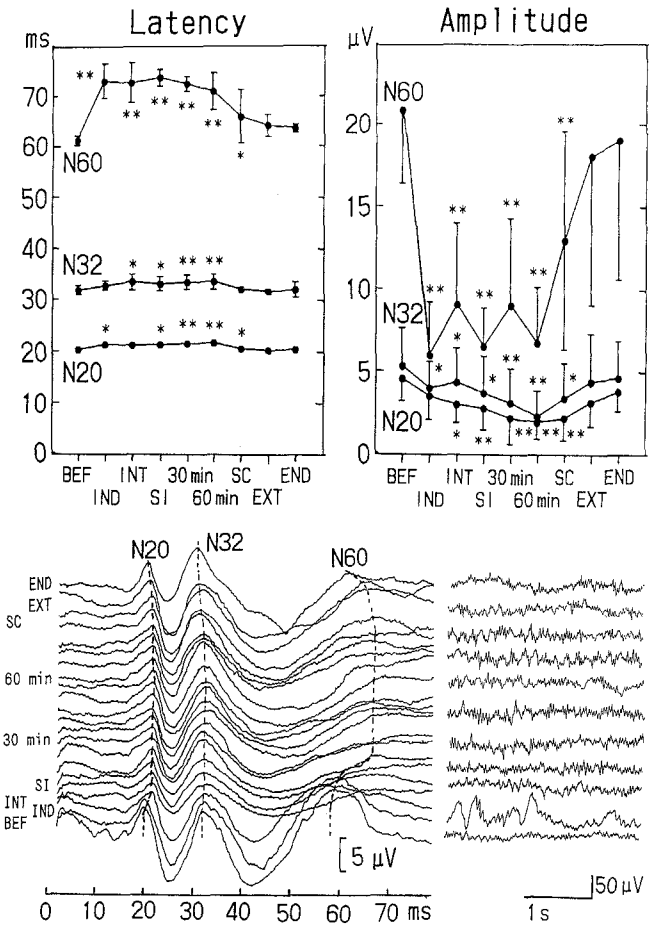

Fig. 2. Somatosensory evoked potentials (SEPs) and electroencephalogram (EEG) during TIVA plus epidural eptazocine. *Upper panels*: During TIVA plus epidural eptazocine ($n = 5$) significant increases in latency as well as significant decreases in amplitude of N20, N32, and N60 waves were observed. Values are means ± SD. Before induction; IND, after induction of anesthesia; INT, after endotracheal intubation; SI, after skin incision; EXT, after extubation; END, end of anesthesia. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the value before induction, and $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ between the groups. *Lower panels*: Specimen records of SEPs (*left sweep*) and spontaneous EEG (*right sweep*) during TIVA plus epidural eptazocine in a 55-year-old man undergoing cholecystectomy. The SEPs and EEGs from *bottom* to *top* were recorded at approximately 5 min and 5–10 min intervals, respectively

waves (6–9 Hz) plus spiky fast waves (20–30 Hz) during anesthesia. These recovered within 10 min of reversal after muscle relaxation (Fig. 2).

Shortly (5–10 min) after reversal of muscle relaxation, all patients in both groups responded to verbal commands and regained spontaneous respiration. All patients were extubated in less than 30 min (10.0 ± 5.9 min in patients given TIVA plus epidural eptazocine, and 12.8 ± 13.3 in patients given TIVA only) after the termination of surgery (not significant). Arterial gases were normal during and 30 min after TIVA with and without eptazocine (Table 4). Neither airway stimulation nor postanesthetic respiratory depression occurred. Endtidal CO_2 concentration was controlled between 4.5% and 5.0% during anesthesia. After anesthesia, oxygen, $3\,l \cdot min^{-1}$, was insuflated under spontaneous respiration.

No significant changes in blood glucose levels were observed during anesthesia and surgery in patients given TIVA plus epidural eptazocine, although there was a slight increase 30 min after the termination of anesthesia ($P < 0.05$). In patients given TIVA only, however, a significant elevation ($P < 0.01$) of blood glucose level during and after surgery was observed (Fig. 3). Serum Na and Cl in both groups significantly ($P < 0.01$) decreased 3 days after anesthesia in both groups. There were no significant changes in any other biochemical measurements (Table 5).

Sixty-one (53.0%) of the patients given TIVA plus epidural eptazocine and 22 (47.8%) of the patients given TIVA only reported that they dreamed during and after anesthesia, but were unable to recall whether this occurred during or after anesthesia. However, such patients stated that the content of the dreams either could not be recalled or was not unpleasant. Neither postanesthetic hypotension nor bradycardia was observed, and nausea, vomiting, headache, hallucination, and extrapyramidal signs did not occur. No adverse effects of long-term (72 h) opioid administration such as epidural infection were seen. Seventeen patients (14.8%) given TIVA plus epidural eptazocine and 45 (97.8%, $P < 0.01$) patients given TIVA only required additional analgesia postoperatively (Table 3).

Thus, in all 161 patients, surgical procedures were uneventful. It was later confirmed by interview that

Table 4. Arterial gas analyses during and after anesthesia

Group		pH	Pco_2 (kPa)	Po_2 (kPa)
TIVA plus epidural eptazocine	(During)	7.41 ± 0.05	5.29 ± 0.73	16.80 ± 4.51
	(After)	7.38 ± 0.06	5.42 ± 0.73	19.86 ± 12.46
TIVA only	(During)	7.40 ± 0.06	4.94 ± 0.89	16.05 ± 4.44
	(After)	7.39 ± 0.06	5.53 ± 0.71	21.41 ± 5.73

Values are means ± SD. There are no significant differences between groups.

Table 5. Blood chemistry before and after anesthesia

Group		Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	BUN (mmol/l)	Creatinine (μmol/l)	GOT (U/l)	GPT (U/l)
TIVA plus epidural eptazocine	(Before)	139 ± 3	4.3 ± 0.5	105 ± 5	10.7 ± 3.4	67.2 ± 14.1	20 ± 5	21 ± 26
	(After)	135 ± 4**	4.2 ± 0.5	101 ± 4**	10.1 ± 3.4	62.8 ± 18.6	22 ± 10	20 ± 15
TIVA only	(Before)	139 ± 4	4.2 ± 0.4	105 ± 4	10.8 ± 3.9	57.5 ± 8.0	19 ± 5	15 ± 8
	(After)	136 ± 3**	4.3 ± 0.4	101 ± 5**	10.1 ± 4.1	59.2 ± 9.7	17 ± 10	14 ± 7

Values are means ± SD.
** $P < 0.01$ between the values before and after anesthesia.
BUN, blood urea nitrogen; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; TIVA, total intravenous anesthesia.

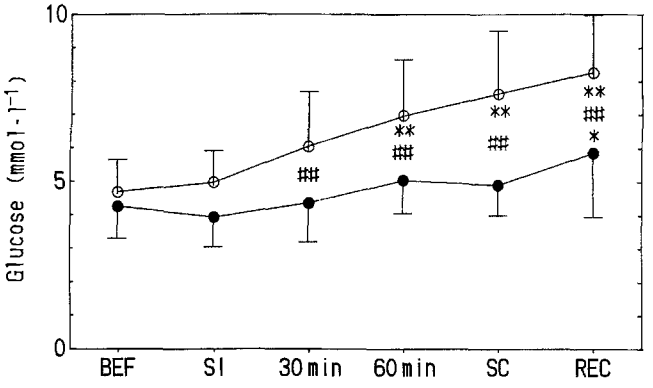

Fig. 3. Blood glucose concentration. *Closed circles*, TIVA plus epidural eptazocine; *open circles*, TIVA only values are means ± SD. BEF, before induction; SI, skin incision; SC, after skin closure; REC, during recovery 30 min after anesthesia. *$P < 0.05$ and **$P < 0.01$ compared with the value before induction, and #$P < 0.05$ and ##$P < 0.01$ between the groups

none of the patients in either group had been intraoperatively aware. There were no differences between the groups in infusion rate, urine output, blood loss, and blood transfusion during anesthesia (Table 1). The effect of the regime on urinary retention, if any, could not be assessed because all patients in both group were catheterized.

Discussion

The present study demonstrated that analgesia of TIVA plus epidural eptazocine is more effective than TIVA only: the depth of surgical anesthesia was sufficient, a vasodepressor was used during anesthesia in only two patients, and the additional use of an analgesic for postoperative pain relief was infrequent (Table 3). The results also demonstrated that patients given TIVA plus epidural eptazocine had stable hemodynamics (Fig. 1) and glucose levels during and after surgery (Fig. 3). Postanesthetic respiratory disturbance was not noted (Table 4), and recovery from anesthesia was rapid in these patients. Furthermore, the SEP and EEG findings suggest that central nervous system (CNS) function during TIVA plus epidural eptazocine was stable and surgically deep (Fig. 2). Furthermore, the total doses of intravenous anesthetics required were low during anesthesia compared with other author's descriptions [1,2].

Eptazocine has been demonstrated to have κ-stimulating an σ-blocking action without a μ effect (sodium index, 3.89) [6]. Most κ-receptors are found in the spinal cord, whereas μ-receptors are expressed widely in the brain and spinal cord [5]. Eptazocine is therefore a powerful analgesic when given epidurally with minimal effects on the brain via μ-receptors. Therefore, the effects of epidural eptazocine are considered to enhance anesthesia and reduce the does of anesthetic needed. These effects may account for the adequate anesthesia depth, stable hemodynamics and blood glucose level, rapid recovery from anesthesia, absence of respiratory depression, and neurological signs after anesthesia.

No anti-arrhythmic drugs were required during the study, and this is probably due to the anti-arrhythmic effect of ketamine [9–11]. On the other hand, the sympathomimetic action of ketamine is considered to be mediated via the CNS [9,12,13], which was blocked by the preceding administration of CNS depressants such as diazepam [14], droperidol [15,16], or opiates [15]. In the present study, the rise in blood pressure due to ketamine administration was thought to be blocked by the preceding administration of these drugs (Fig. 1). Thus, TIVA plus epidural eptazocine was uneventful even in 15 patients with complete right bundle branch block, 55 with coronary ischemia, 16 with atrial fibrillation, 2 with hypertrophic cardiomyopathy, and 2 patients over the age of 90 years, in patients given TIVA plus epidural eptazocine.

SEPs showed a significant prolongation of latency and a decrease in amplitude. However, the changes in an early component, N20, were small, and were likely to be due to ketamine, since changes in early components of auditory evoked potential (AEP) during ketamine anesthesia have also been found to be small [17]. In the present study, we also observed a sustained depression in a later component, N60, and EEGs showed slow waves with spiky fast waves, another

characteristic of ketamine anesthesia (Fig. 2) [18]. Our regime of TIVA plus epidural eptazocine probably owes its effects to the balanced effects of ketamine, diazepam, droperidol, and eptazocine on *N*-methyl-D-aspartate (NMDA) receptors, γ-aminobutyric acid (GABA) receptors, catecholamine receptors, and κ-receptors, respectively, with a dominant cortical effect of ketamine.

In the present study, muscle relaxation was achieved by a very low maintenance dose of vecuronium, $0.08\,mg \cdot kg^{-1} \cdot h^{-1}$ (Table 1). The need for such a low dose may be due to the fact that ketamine enhances the effect of nondepolarizing muscle relaxants [19–21]. No significant depression of respiration by ketamine [22,23], diazepam [23], droperidol [24] and eptazocine [25] in the respective clinical doses has been demonstrated. In addition, ketamine [26–29], opioids [5,30], diazepam [31], droperidol [24], and vecuronium [32] have been shown not to stimulate bronchial smooth muscle in the clinical doses used in this study, and this accounts for the lack of significant effects on respiration of our TIVA regime. In fact, a 72-year-old woman with a recent history of several complicated asthmatic attacks underwent uneventful subtotal gastrectomy under TIVA plus epidural eptazocine.

No significant increases in blood glucose were found during anesthesia and surgery in patients given TIVA and epidural eptazocine (Fig. 3). A saline diuresis by ketamine, which is long-lasting and mild, has been suggested [33,34]. In the present study, urine output during anesthesia was also adequate in most cases, and significant falls in serum Na and Cl occurred after anesthesia. Other biochemical tests did not change significantly after anesthesia (Table 5), suggesting that TIVA plus epidural eptazocine does not disturb renal or hepatic function.

In conclusion, we suggest that TIVA plus epidural eptazocine has advantages, due to the balanced effects of intravenous ketamine, diazepam and droperidol, and epidural eptazocine on the brain and spinal cord.

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