主　論　文

THE EFFECT OF EPIDURAL MORPHINE ON HUMAN INTESTINAL MOTILITY IN THE EARLY POSTOPERATIVE STATES

（術後早期におけるヒト腸管運動に対する硬膜外モルヒネの影響）

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Proposed running head : Effect of Epidural Morphine in postoperative motility.

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ABSTRACT

The early postoperative recovery of intestinal motility and the response of motility to epidural morphine were investigated in 20 patients. Periodic motor activities in the jejunum were recovered within 32 hours in all cases. The length of these cycles increased gradually from the 1st (23.2 min) to the 4th (41.7 min) postoperative day. Morphine and lignocaine were given through an epidural catheter. Morphine induced premature migrating motor complexes (MMC) in all cases, whereas lignocaine failed to evoke this response in every case. The mean duration (19.8 min) and maximal amplitude (62.8 mmHg) of the burst activities induced by morphine were significantly longer and higher than those which occurred spontaneously (7.7 min and 35.6 mmHg, respectively). The intervals between induced and the subsequent spontaneous contractions were the same as the intervals between spontaneous contractions. These observations indicate that epidural morphine induced premature MMC without interrupting recovery patterns from postoperative gastrointestinal paralysis.

Key words : Analgesia, Early postoperative state, Epidural anaesthesia, Gastrectomy, Intestinal motility, Morphine

INTRODUCTION

Abdominal pain and temporary gastrointestinal paralysis after general surgery have long been distressing for both patients and surgeons. Recently an epidural analgesia has been widely used to reduce postoperative pain and it has provided many benefits to patients and surgeons [*1, 2*]. On the other hand, the influence of epidural analgesia on the postoperative recovery of intestinal motility has been little reported [*3*]. Persson [*4*] and Burks [*5*] have reported that the intravenous administration of morphine delays gastrointestinal transit time, though opiates are known to be strong agents affecting gastrointestinal motility in rats [*6*] and pigs [*7*].

Although the recovery of the migrating motor complexes (MMC) [*8*] after abdominal surgery [*9, 10*] has been the subject of a few studies, the influence of epidural morphine on human MMC in the early postoperative period has not previously been reported. The purpose of the present study is to investigate the reappearance of periodic contractions and the influence of epidural morphine on these activities by measuring intestinal motility after abdominal surgery.

SUBJECTS AND METHODS

From August 1989 to September 1990, 204 abdominal operations were performed in the First Department of Surgery, Nagoya University Hospital. Among these, 38 out of 60 patients with gastric malignancies underwent partial distal gastrectomy. Excluding patients with preoperative complications (i.e., pyrolic stenosis, massive bleeding and/or protein loss), and aged patients (those more than 75 years old), 20 cases were chosen prospectively for the present study. They consisted of 12 males and 8 females with a mean age of 55.9 ± 2.8 years (a range of 30 − 73 years old). No liver metastasis or peritoneal dissemination was found at operation. This study was approved by the Ethical Committee of Nagoya University Hospital in June 1989 and informed consent was obtained in each case.

An epidural catheter was inserted in all patients 1 or 2 days before surgery. The tip of the catheter was placed at the level of Th6 − Th7 and the analgesic level was confirmed with 1% of lignocaine hydrochloride (50mg/10ml; Fujisawa Pharmoceutical Co, Osaka, Japan). Under general anaesthesia, using enflurane and nitrous oxide in oxygen, partial distal gastrectomy with regional lymphnode dissection and truncal vagotomy was performed. Gastrointestinal continuities were attained by Billroth first method in all patients. The mean operative time was 3.5 ± 0.1 hours, the mean blood loss was 325 ± 36 grams and no blood transfusion was performed in any of the cases. Before closing the abdominal cavity, a three-lumen silicon catheter, consisting of one drainage (3 mm in diameter) and two water-filled lumen (0.5 mm in diameter) with three side holes

located at 5 cm intervals oriented radially, was inserted via the nose through the residual stomach into the proximal jejunum. The tip of the tube was placed distal to the Treitz ligament, and each of the two pressure measuring orifice was positioned, respectively, at about 5 and 10 cm distal to the ligament, which was confirmed by palpation. The continuous recording of jejunal motility was started just after arrival in the recovery room. All the patients were given intravenous drip infusion and antibiotics (with components of penicillin or cephalosporin) after surgery.

The catheter was attached to a low compliance perfusion system (Medi-Quic, ACS－222, Terumo Corporation, Tokyo, Japan) with a low perfusion rate of 3 ml per hour, (measured at 200 mmHg in one second during occlusion of the distal side holes). Each perfusion channel was linked to a transducer (Statham transducer model P2310, Gould, Cleveland, OH) and the pressure was recorded on a polygraph pen recorder (RM－6100, Nihon－Koden, Tokyo, Japan). The zero reference was established at the mid-thoracic level in the 4th intercostal space. Records were made continuously from just after the surgery until the 4th postoperative day.

Epidural administration of agents was started on the 2nd or the 3rd postoperative day when premature periodic contractions appeared. Morphine hydrochloride (3mg／5ml of saline ; Takeda Pharmaceutical Co, Osaka, Japan), 1% of lignocaine hydrochloride (5ml ; Fujisawa Pharmaceutical Co, Osaka, Japan), or physiological saline (5ml) was injected during the period of quiescence. We also administered buprenorphine hydrochloride (0.1mg／5ml of saline ; Otsuka Pharmaceutical Co, Tokyo, Japan) to 12 of the twenty patients. The response

of motility to each drug was observed for more than 4 hours. The effects of the pain treatment method were evaluated either by pain evaluation made by the patients with a visual scale or by respiratory patterns.

Venous blood samples were withdrawn before and 5, 10, 15, 30, 45 and 60 min after the epidural administration of morphine. All blood samples were put into lithium heparin tubes and immediately centrifuged at 3000 rpm at 4 ℃. The plasma was stored at −80 ℃ until required for analysis. The plasma-morphine concentration was measured by high-performance liquid chromatography with amperometic detection [*11*]. The lower limit of detection was 0.4 ng/ml.

All the records were analyzed in terms of the overall cycle, intervals, durations and maximal amplitude of the burst contractions, which were defined as a series of rapid positive contractions followed by a period without contractions of more than 200 sec and a frequency of about 11 times per minute [*12*]. The mean of the cycle was determined as the duration of MMC ; that is, from the onset of the silent period to the end of burst contractions. The interval was measured as the time from the end of a period of burst contractions until the start of the next burst. Duration was regarded as the period during which burst contractions continued, and maximal amplitude was determined as the biggest wave during burst contractions. Each value was expressed as mmHg from the zero line or in minutes. The tracing speed was recorded at 5 mm/min.

Statistical analysis

Data were expressed as the mean ± SD. Statistical analyses of the data were carried out by one-way analysis of variance with Dunnet's procedure analysis, and the paired t test was used in comparing the evoked values of

contractions to each drug with the values of the spontaneous contractions for the same period. Significant differences were assumed to exist when $p < 0.05$.

RESULTS

Early Postoperative Motility : All patients received good analgesia by the epidural injection of analgetics during the study. Consequently, respiratory funcutions were not restricted, and patients could cough and breathe freely. No respiratory complications were observed. All subjects showed constant periodic contractions of the jejunum within 32 hours after surgery, with the earliest appearance at 5 hours postoperatively and the latest at 31.3 hours (mean = 9.39 ± 2.2 hours). There was no correlation between the appearance time and the type of drip infusion or antibiotics used. The contractions occurred spontaneously and rhythmically after a period without contractions.

The mean cycle of the burst contractions increased daily : 23.2 ± 1.9 min on the 1st postoperative day, 28.3 ± 1.1 min on the 2nd, and 41.7 ± 1.2 min on the 4th. By contrast, the mean duration of the burst contractions (7.7 ± 0.3 min) and the maximal amplitude of the contractions (35.6 ± 2.0 mmHg) were unchanged during this postoperative period (**Fig.1**).

Epidural Administration of Drugs : Epidural morphine caused additional burst contractions on jejunal motility at 3.0 ± 0.3 min (1.5 – 5 min) after administration. The mean duration of the induced burst contractions (19.8 ± 1.4 min) was significantly longer than the average of the durations of three spontaneous burst contractions (7.7 ± 0.3 min) recorded just before administration ($p < 0.01$) (**Fig.2**). The mean maximal amplitude of the contraction waves after morphine (62.8 ± 9.2 mmHg) was significantly higher than the average of the three maximal amplitudes previous to morphine administration

(35.6 ± 2 mmHg) ($p < 0.01$). However, the mean interval after the evoked bursts (15.0 ± 1.5 min) (i.e., between the end of the morphine－induced contractions and the onset of the next burst) was not significantly different from the average interval before (18.8 ± 1.4 min) or after (15.9 ± 1.2 min) the administration of morphine (**Table.I**).

In 7 out of 12 cases, buprenorphine induced the same responses on upper jejunal motility as morphine did, whereas no effect on motility was observed in the five cases in 7 out of 12 cases (**Fig.3**). One percent solution of lignocaine brought analgesia but no change in the periodic contractions of jejunal motility (**Fig. 4**). Saline did not affect analgesia or produce any changes on gut motility.

Plasma Morphine Levels: Before the administration of morphine, the basal value of plasma morphine was 1.4 ± 0.6 ng／ml. After the epidural administration of 3 mg of morphine, the plasma concentration of morphine quickly exceeded the basal value and reached a peak in 5 min (43.3 ± 4.5 ng／ml) after injection. It then decreased gradually, approaching to the basal level in 45 min (**Fig.5**).

DISCUSSION

The present study confirms that the periodic contractions (i.e., premature migrating motor complexes [*13*]) reappeared early in the postoperative period (within 32 hours) and that epidural morphine induces periodic contractions in man. The longer-than-average duration and higher maximal amplitude of induced bursts noted in our study were likely due to the rather high dosage of morphine given in the epidural spaces. On the other hand, the intervals between induced contractions and subsequent spontaneous contractions were the same as for spontaneous contractions. The measurement of the plasma morphine concentration indicated that those responses were due to the direct effects of the morphine itself via the peripheral opioid receptor of the intestinal wall. Because epidural-administrated morphine penetrates the dura with an onset of action of more than fifteen min [*14*], we injected 3 mg of morphine via the epidural catheter, causing the plasma morphine level to show 43.3 ± 4.5 ng/ml within 5 min.

Szurszewski first demonstrated the migrating myoelectric motor complexes in dogs in 1969 [*8*]. These were then closely investigated [*15*] and found to be present in man by Vantrappen et al.[*16*] using the manometric method. These complexes consist of three different phases : no motility (phase I) ; irregular but weak contractions (phase II) ; and burst rhythmic contractions of about 11 times per minute, continuing about 4 min or more (phase III). The mean cycle of MMC in healthy man was 80 − 110 min, though it has been reported to be 40 − 50 min in the early postoperative period [*17*]. Our data showed that the cycle of periodic contractions grew longer after surgery : 23.2 ± 1.9 min on

the 1st postoperative day and 41.7 ± 1.2 min on the 4th day. We could not detect how long it would take to recover regular cycles because the patients were required to start their oral intake around the 4th postoperative day and the manometric tubes had to be withdrawn. But the cycles might prolong gradually to a normal level.

It has been reported that intravenous morphine increased the number of intestinal contractions and prolonged the transit time due to intestinal spasms [*18,19*]. On the other hand, morphine administration has been recognized to initiate MMC and shorten the intestinal transit time in mice [*20*], pigs [*21*] and dogs [*22*]. However, there are little human data on the effects of epidural morphine on gastrointestinal motility in the early postoperative state. Our results revealed that morphine initiated MMC and might accelerate the intestinal transit time in man during the early postoperative period. Different effects of morphine on gut motility may occur at different dosages: e.g., 0.2 − 1.0 mg/kg interrupted the transit time and 20 − 80 μg/kg accelarated it. When a smaller dose (2 mg) of morphine was injected in two patients, induced contractions occured which were of average duration but high maximal amplitude. These data suggest that some patterns of gut motility affected by morphine were dosage dependent. In the present study, epidural morphine induced premature MMC, but had no effect on the recovery pattern of intestinal motility after gastric surgery.

The effects of epidural anaesthesia on gut motility have rarely been reported. Our data indicate that epidural administration of lignocaine does not influence the periodic contractions of small intestine. These data support the observation that an epidural bupivacaine dose not change the intestinal transit

time in man [*24*]. They indicated that epidural administration of opiates stimurated contractility in the small intestine, but local anaesthetic agents did not. Therefore, we suggest that these phenomena do not occur as a result of a block of sympathetic activity.

Myoenteric plexus and muscle cells of the human small intestine are known to have three kinds of opiate receptors – – mu, delta and kappa – – that interact with each ligand of morphine, enkephalin and ketocyclazocine, respectively. Recently it has been reported that mu and delta, but not kappa, agonists induced intestinal contraction in vivo in dogs [*23*]. Naloxone (Kodama Pharmaceutics Co, Tokyo, Japan), a selective mu antagonist, was injected intravenously (0.2 mg in clinical value) before epidural morphine administration in 2 patients. However, the phasic contractions induced by morphine failed to be suppressed. In pharmacological experiments, it has been common to use more than 1 mg in dogs to block the morphine activities [*13*]. It might be that a larger dose is necessary for the appearence of antagonistic activity. When buprenorphine was administrated to 12 of the 20 patients, phasic contractions were initiated in 7 of those 12. These findings suggest that the induction of contractile activity by epidural opioid was induced via gut opioid receptors.

It is well known that motilin is a main peptide for regulating MMC in dogs [*25*]. Recently, morphine has been reported to release motilin and consequently to induce MMC [*26*]. In our study plasma motilin levels were not measured, but the fact that a high dosage of morphine induced spasms of the gut and delayed the gastrointestinal transit time [*18 – 22*] is not adequately explained by the idea that motilin induced by morphine mediates gut motility.

However, there must be another pathway to the stimulation of intestinal motility. Correlation and interaction between morphine and motilin on gut motility in man await further study.

In conclusion, this study has demonstrated that morphine administered epidurally initiates premature MMC - - bursts of longer duration and higher amplitude than occur spontaneously - - on the human intestine during the early postoperative period following gastrectomy. We found that these phenomena did not eliminate or inhibit the return of intestinal motility from postoperative gut paralysis.

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FIGURE LEGENDS

Fig.1 Motility patterns of the proximal jejunum in the early postoperative periods. Note the reappearence of prolonged clusterd phasic activity of the jejunum. MMC intervals increased daily after surgery. ＊J1 : placed at 5 cm distally to the Treitz ligament. J2 : placed at 10 cm distally to the Treitz ligament. ＊＊POD : post operative day.

Fig.2 Effect of epidural administration of morphine hydrochloride (3mg／5ml) on the upper jejunum in the early postoperative state. An arrow indicates morphine injection via a catheter into the epidural space. Induced phase－Ⅲ contractions were observed in all cases.

Fig.3 Effect of epidural administration of buprenorphine hydrochloride (0.1mg ／5ml) on the upper jejunum in the early postoperative state. An arrow indicates buprenorphine injection via a catheter into the epidural space. Induced phase －Ⅲ contractions were observed in seven cases out of 12, but no effects on motility were noticed in the remaining five.

Fig.4 Effect of epidural administration of 1％ of lignocaine hydrochloride (5 ml) on the upper jejunum in the early postoperative state. An arrow indicates lignocaine injection via a catheter into the epidural space. No changes in the cycles of a migrating motor complex or the characteristics of phase－Ⅲ contractions were indicated.

Table I

Comparison of spontaneous phase－Ⅲ contractions and phase－Ⅲ contractions induced by epidural administration of morphine

	spontaneous phase Ⅲ (before morphine)	morphine－induced phase Ⅲ	spontaneous phase Ⅲ (after morphine)
duration (min)	7.7 ± 0.3	19.8 ± 1.4 **	7.9 ± 0.3 NS
amplitude (mmHg)	35.6 ± 2.0	62.8 ± 9.2 **	36.2 ± 2.8 NS
interval (min)	18.8 ± 1.4	15.0 ± 1.5 NS	15.9 ± 1.2 NS

(mean ± S.D. , n = 20)

** significantly different from each spontaneous phase Ⅲ before epidural administration of morphine : $p < 0.05$; NS : not significant

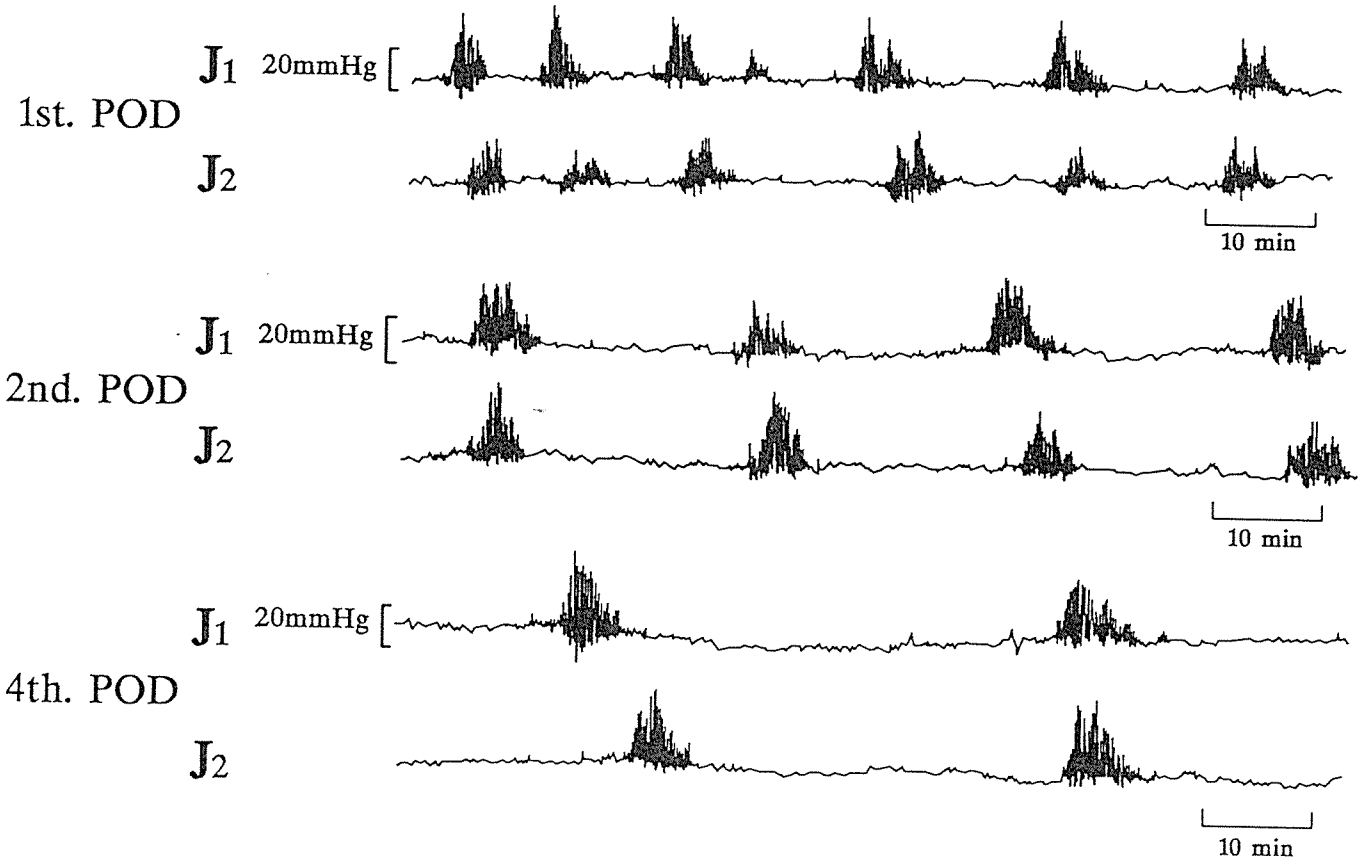
1st. POD
J1
20mmHg
J2
10 min
2nd. POD
J1
20mmHg
J2
10 min
4th. POD
J1
20mmHg
J2
10 min

Fig.1

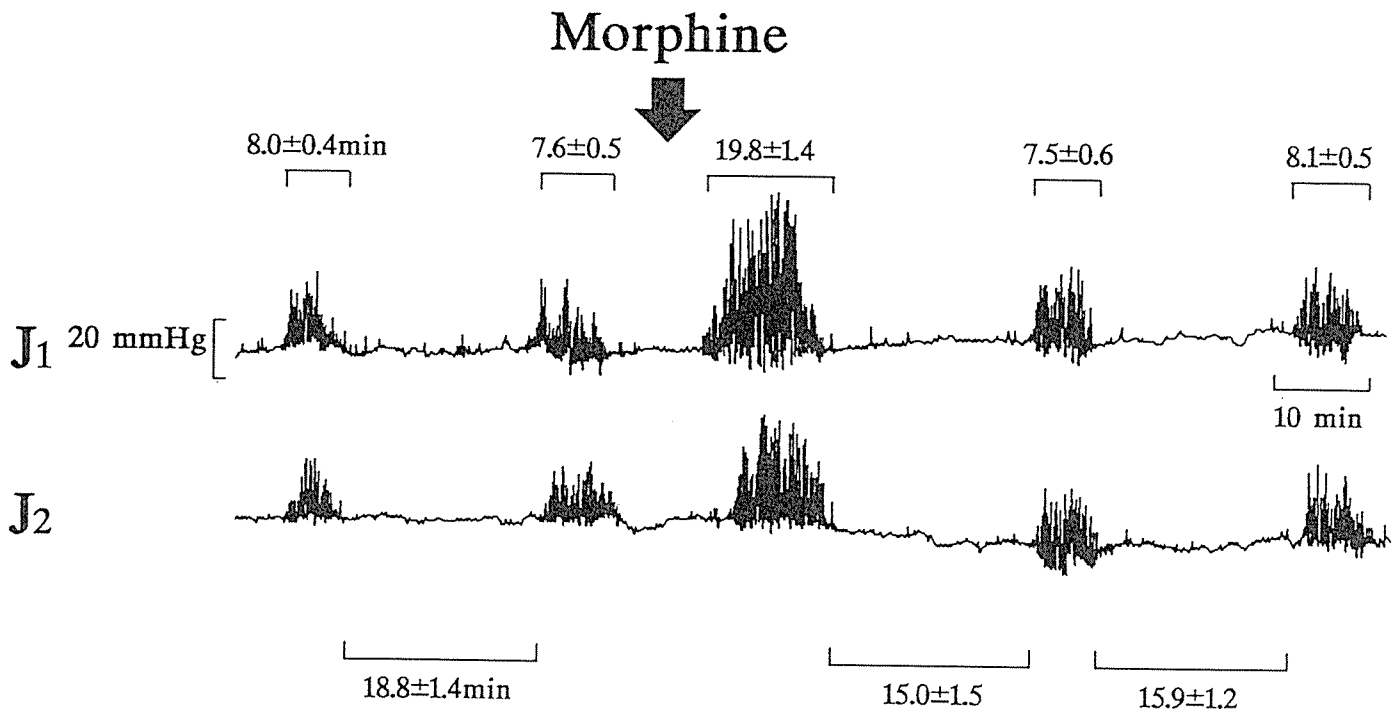
Morphine
8.0±0.4min
7.6±0.5
19.8±1.4
7.5±0.6
8.1±0.5
J1
20 mmHg
10 min
J2
18.8±1.4min
15.0±1.5
15.9±1.2

Fig. 2

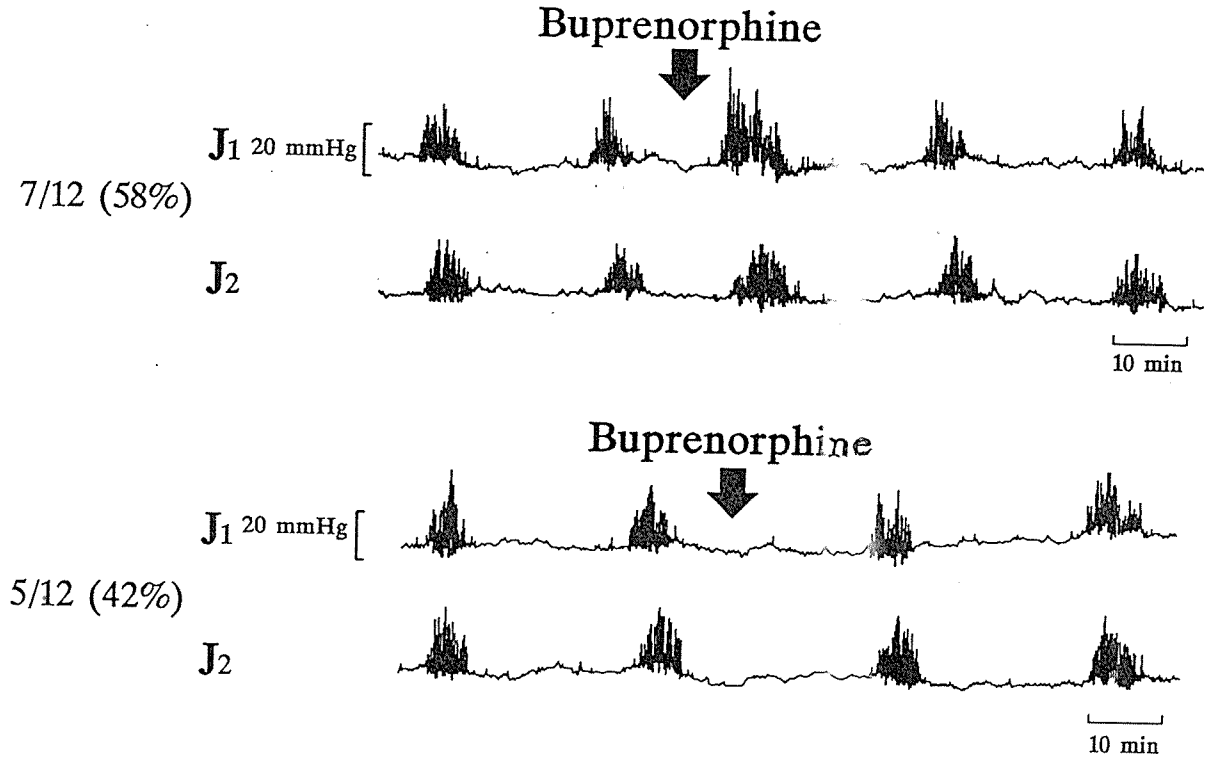
Buprenorphine
J1 20 mmHg
7/12 (58%)
J2
10 min
Buprenorphine
J1 20 mmHg
5/12 (42%)
J2
10 min

Fig.3

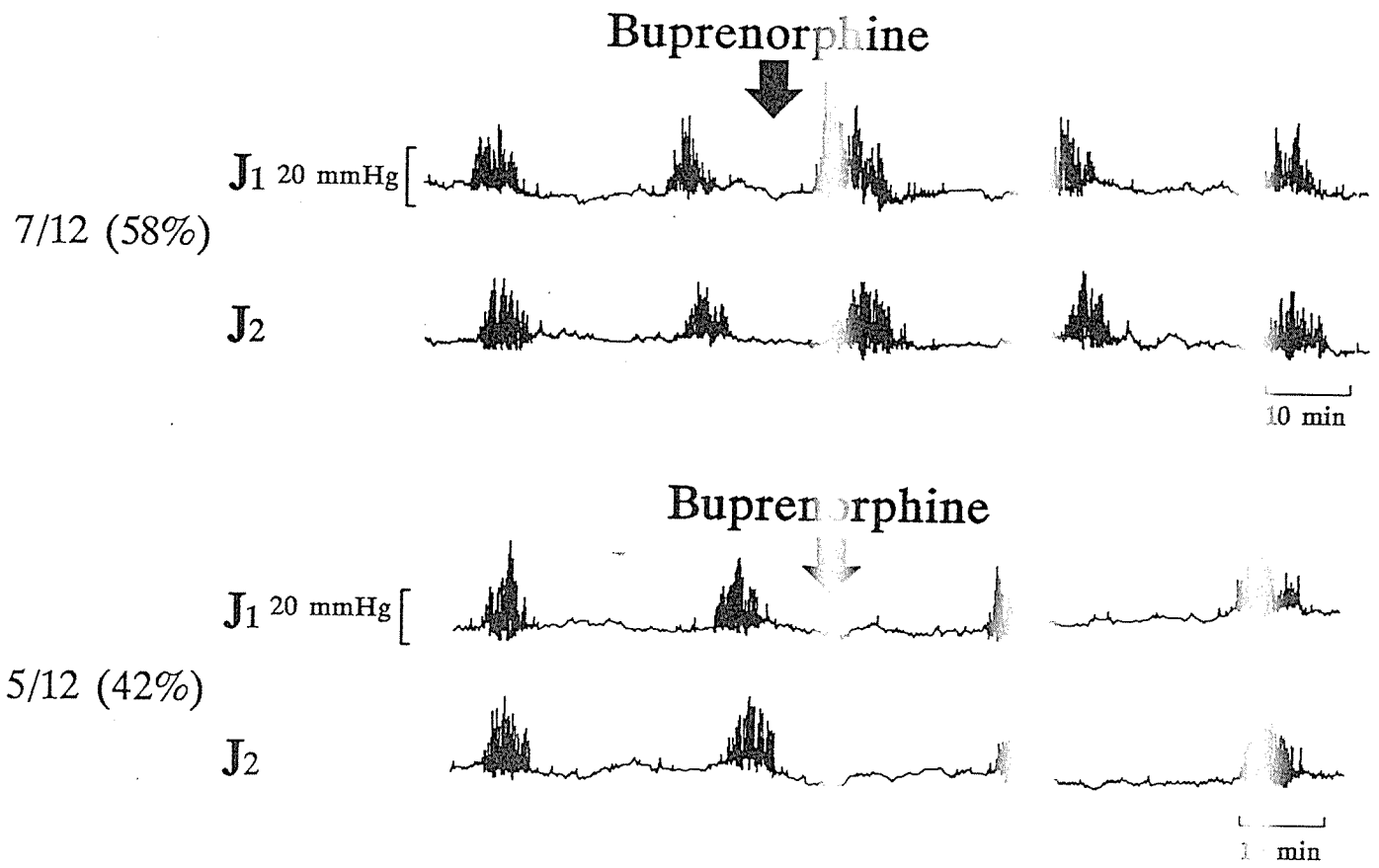
Buprenorphine
J1 20 mmHg
7/12 (58%)
J2
10 min
Buprenorphine
J1 20 mmHg
5/12 (42%)
J2
min

Fig.3

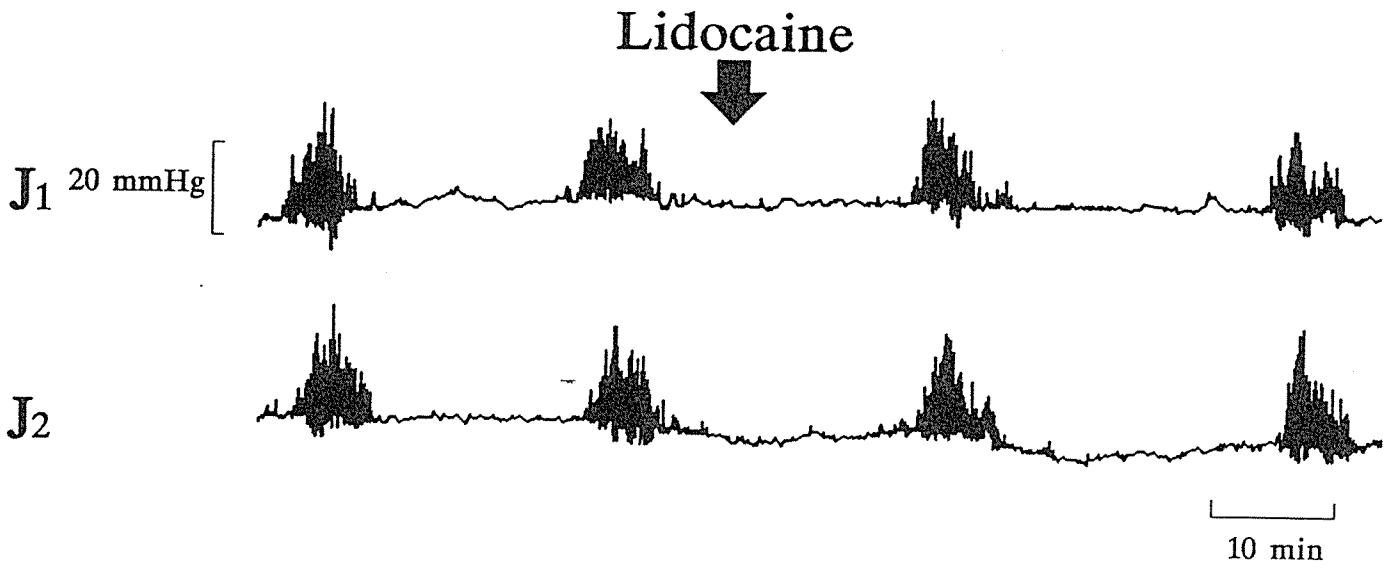

Fig.4

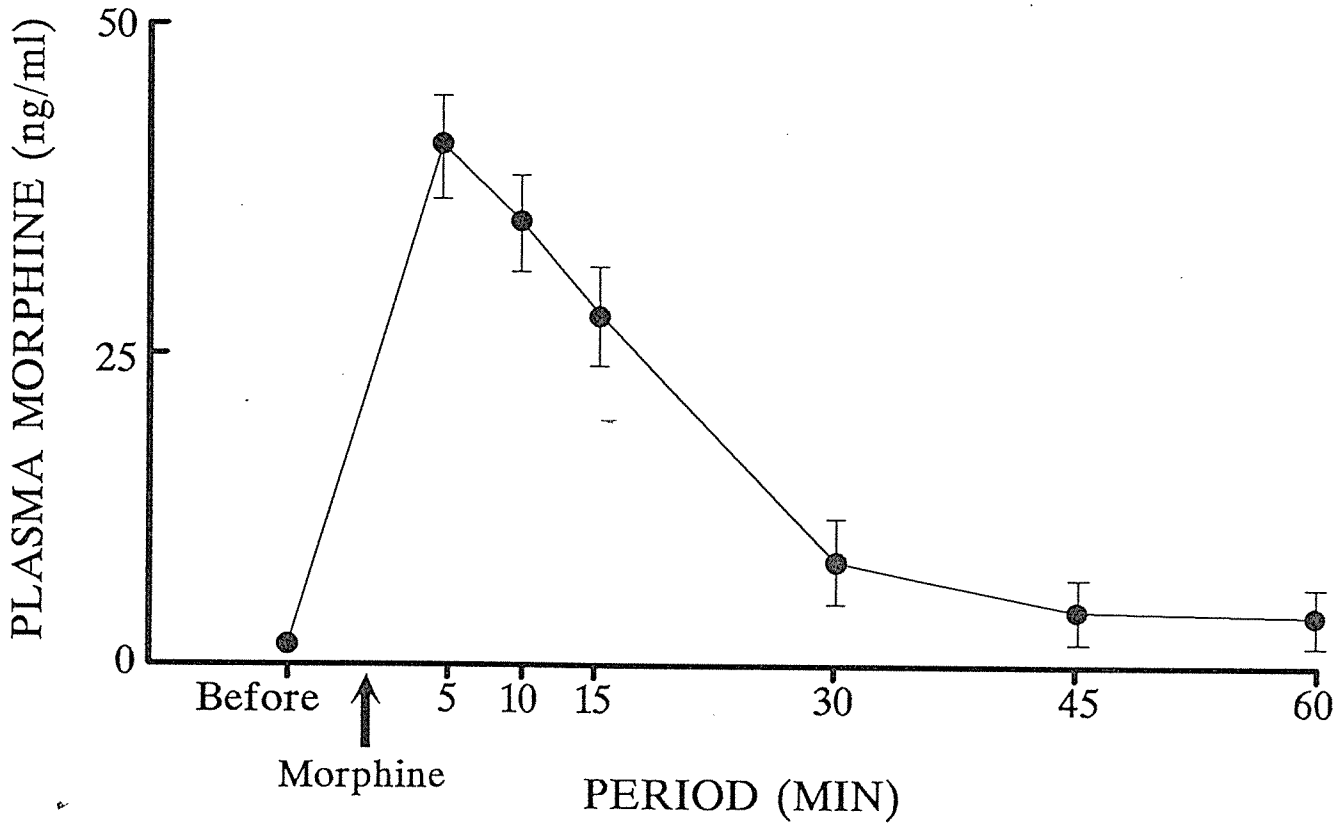
PLASMA MORPHINE (ng/ml)
50
25
0
Before
Morphine
5
10
15
30
45
60
PERIOD (MIN)

Fig.5