Circulatory Stability and Plasma Lidocaine Levels during Continuous and Intermittent Thoracic Epidural Analgesia

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Circulatory stability and plasma levels of lidocaine were investigated in 20 patients who received thoracic epidural analgesia with plain lidocaine during elective abdominal surgery under general anesthesia. In one group, bolus injection of 8 ml of 2% lidocaine was followed by volumetric continuous pump-driven infusion (CPI) of 8 ml of 1.5% lidocaine per hour. In the other group, the same initial bolus injection was followed by repetitive intermittent bolus infusions (RII) of 6 ml of 1.5% lidocaine at a 45 min-interval. Circulatory stability was evaluated by a discriminant function. The results showed that epidural analgesia produced smaller circulatory fluctuations with CPI than with RII. Venous plasma lidocaine levels were consistently higher with CPI than with RII. Plasma levels increased stepwise with RII and kept constant with CPI. Differences in plasma levels were significant from 20 min after the initial injection to 135 min. We therefore conclude that epidural analgesia with CPI is superior to that with RII. However, it must be remembered that higher plasma levels may occur with CPI than with RII. (Key words: epidural analgesia, lidocaine, hemodynamics)

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Epidural analgesia combined with general anesthesia has some advantages. Analgesia and muscle relaxation are obtained with two different drugs. Smaller amounts of local and general anesthetics are required with this technique than with general anesthesia alone. This technique is suitable for patients undergoing abdominal and thoracic surgery[1]. However, the blood levels of local anesthetics could easily be increased with a repetitive intermittent bolus infusion (RII)[2,3], when epidural analgesia is maintained by repeated infusions at regular intervals. Following several infusions of local anesthetics, increased blood levels can become a clinical threat whenever an epidural analgesia is used[4].

Continuous pump-driven infusion (CPI) is applied to obstetric patients[5–7] and to postoperative pain relief [8], but no detailed study has yet appeared on this technique during surgery. It has been recently reported that blood levels of local anesthetics are significantly lower with CPI than with RII[9]. However, the effects on circulatory stability and blood levels of local anesthetics are not well defined. The purpose of this study was to elucidate the effects of CPI and RII on circulatory stability and on plasma lidocaine levels.

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Patients and Methods

Patients

Twenty ASA physical status I–II patients scheduled for elective abdominal surgery under combined general and epidural anesthesia were included in this study. The study was approved by the Ethics Committee of Hiroshima General Hospital. Informed consent was obtained before the study from all of the patients. Patients undergoing surgery that would require more than 3 hr were randomly assigned into two groups of equal number. Patients in groups A and B received epidural lidocaine with CPI and RII, respectively. None of the patients had a history of hepatic, renal or cardiac dysfunction. Plasma protein, hematocrit and electrolytes were within normal ranges.

Anesthesia

Intramuscular hydoxyzine 50 mg and atropine 0.5 mg were given one hour before induction of anesthesia. After a peripheral intravenous line and a central venous line into the internal jugular vein were secured, epidural catheterization was carried out in the lateral decubitus position. At the Th 8–9 or Th 9–10 interspace, a 17 G Tuohy needle was inserted and an 18 G epidural catheter was placed cephalad through the needle. The patient was then placed in the supine position. Neither blood nor cerebrospinal fluid were aspirated through the catheter in any of the patients. A test dose was not used.

Thereafter, endotracheal anesthesia was induced with fentanyl 0.2–0.3 mg, thiopental 5 $mg \cdot kg^{-1}$ and pancuronium 0.08 $mg \cdot kg^{-1}$, and maintained with nitrous oxide 4 $l \cdot min^{-1}$ and oxygen 2 $l \cdot min^{-1}$. Ventilation was adjusted to maintain $P_{ET_{CO_2}}$ between 35 and 40 mmHg with a capnometer. In group A, after circulation had stabilized, 8 ml of 2% lidocaine was injected through the epidural catheter, and CPI of 8 ml of 1.5% lidocaine per hour (120 $mg \cdot h^{-1}$) by a syringe pump (Terumo®, Japan) was started immediately and maintained until the completion of surgery. In group B, RII was maintained with 6 ml of 1.5% lidocaine at a 45 min-interval (120 $mg \cdot h^{-1}$). Surgery was started 10 to 15 min after the initial epidural administration of lidocaine. Blood pressure and heart rate were monitored and recorded throughout the study. Systolic pressure below 80 mmHg was treated with intravenous ephedrine 4 mg. No cases produced marked hypertension (systolic pressure above 180 mmHg) during the study. Rectal temperature was maintained within normal range. Lactated Ringer's solution was infused at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$ intravenously. Lidocaine was not used for local infiltration nor lubrication. Lidocaine used in the study did not contain epinephrine.

Assessment of circulatory stability

Circulatory stability was assessed by a discriminant function, Z, which was proposed by Momose and associates[10] to assess circulatory fluctuations during general anesthesia.

$$Z = 6 \cdot R + 5 \cdot R' + 4 \cdot R''$$

where R (mmHg) and R' (bpm) are the differences between the maximum and minimum systolic pressure and the heart rates, respectively, throughout the subjected period. R" (mmHg) is the difference between the maximum and minimum systolic pressures during the latter half of the subjected period. The critical value of Z, which discriminates "stable" from "fluctuated", is 527. Circulation is considered highly stable when Z is less than 400. This function has an error rate of less than 0.033 in discrimination[10]. This function shows a normal distribution in randomly assigned patients (unpublished observation).

Blood samples and analysis

Venous blood was sampled from the central venous line and placed in EDTA-containing test tubes before epidural infusion and at 10, 20, 45, 65, 90, 110, 135, 155, 180, 200, 225, 245, 270, 290, and 315 min after the initial administration of lidocaine in both groups. Plasma was separated by centrifugation at 2800 g for 5 min, stored at −24°C, and assayed using a fluorescence polarization immunoassay system (DAINABOT®, Japan). We previously confirmed the accuracy of this system[11]. Based on the characteristics of the data, either paired or unpaired t-tests, Mann-

Table 1. Surgical procedures

	Procedure	No. of patients
Group A	Gastrectomy	7
	Cholecystectomy	2
	Hemicolectomy	1
Group B	Gastrectomy	5
	Cholecystectomy	4
	Hemicolectomy	1

Table 2. Patient characteristics

	Sex M/F	Age (year)	Weight (kg)	Height (cm)
Group A	5/5	55 ± 10	53 ± 5	156 ± 6
Group B	5/5	56 ± 9	54 ± 6	160 ± 6

Mean ± SD. No significant differences were observed between the groups.

Table 3. Values determined by discriminant function

	Group A	Group B
Z value	451 ± 148	626 ± 116#

Mean ± SD. # $P < 0.01$

Whitney U-test, or chi-square test were used for statistical analysis. Statistical significance was determined at $P < 0.05$.

Results

The surgical procedures performed are listed in table 1. Age, weight and height did not differ between the groups (table 2). The Z values were different between the groups ($P < 0.01$) (table 3). Frequencies of repetitive administrations of intravenous ephedrine were 3.4 ± 2.3 and 9.1 ± 5.3 (times/case) in groups A and B, respectively ($P < 0.05$). Blood loss was 357 ± 322 g and 300 ± 231 g, the dosage of lidocaine was 592 ± 145 mg and 535 ± 83 mg, and the duration of surgery was 228 ± 78 min and 240 ± 54 min in groups A and B, respectively. These values were not different. Plasma lidocaine levels in group B were significantly lower than those in group A at 20, 45, 90, and 135 min after the initial injection (fig. 1). Although the highest level was 6.3 $\mu g \cdot ml^{-1}$, no signs of toxicity were observed in the central nervous system or the circulatory system. Postoperative analgesia was was satisfactory in all the patients in the two groups.

Discussion

In this study, hemodynamic alterations are evaluated with the discriminant function proposed by Momose and his coworkers, and this function clearly revealed the circulation more stable with CPI than with RII. Continuous epidural infusion with CPI has been recently used for obstetric analgesia[5–7] and for postoperative pain relief[8], since hemodynamic alterations are minimal with CPI. However, no detailed studies have been carried out to show the definite advantages of CPI. Our study confirmed that CPI technique was superior to RII to minimize circulatory alterations. Circulatory stability during epidural analgesia depends on altered sympathetic tone. The changes in blood pressure, heart rate, and cardiac performance are related to the extent of sympathetic blockade[1,8] produced by epidural analgesia. Therefore, to maintain sympathetic blockade constant seems to be essential to keep circulation stable. In this study, circulation was significantly stable with RII, but not with

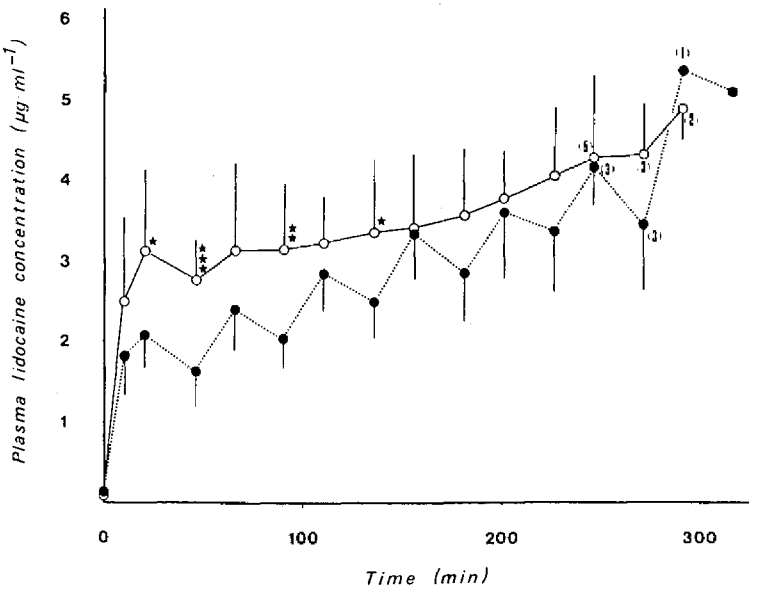

Fig. 1. Serial changes in plasma lidocaine levels

Serial changes in plasma lidocaine levels (mean ± SD) are shown. The bolus injection of 8 ml of 2% lidocaine was followed by volumetric continuous pump-driven infusion (CPI) of 8 ml of 1.5% lidocaine per hour in group A (○—○). The same dose of bolus injection was followed by the repetitive intermittent infusions (RII) of 6 ml of 1.5% lidocaine at a 45 min-interval in group B (●—●). The plasma lidocaine levels were consistently higher in group A than in group B. Statistically significant differences ($^{\star}P < 0.05$, $^{\star\star}P < 0.01$, $^{\star\star\star}P < 0.001$) were observed at 20, 45, 90 and 135 min after the initial injection. Each group consisted of 10 patients. Numbers of patients analyzed are presented in parentheses, because some of the patients were not available.

CPI. Required intravenous vasopressors were smaller with CPI than with RII, since RII easily produced serious hypotension at every injection.

Epidural analgesia combined with general anesthesia has the advantage of reducing the dose of general anesthetics. This technique is suitable for patients undergoing abdominal or thoracic surgery[1]. However stepwise elevations in the blood levels of local anesthetics are seen when epidural analgesia with RII is used[12–14], and high blood levels are reported with lidocaine[15], mepivacaine[16] and bupivacaine[17] with this technique. In this study, plasma levels with RII increased stepwise but significantly lower than with CPI from 20 to 135 min after the initial injection. No serious adverse reactions were observed throughout the study. On the contrary, it has been reported that lower blood levels of lidocaine and bupivacaine are obtained with CPI than with RII, although the overall average dose of plain solutions required is higher with CPI than with RII[6,18,19]. Epinephrine-containing local anesthetics can also yield lower blood levels with CPI than with RII[9], since they can diminish their absorption by suppressing the local circulation to decrease blood levels[2,4]. Therefore, It is still uncertain which technique is more favorable in aspect of blood levels.

An absorption rate of local anesthetics from the epidural space into blood stream is determined by a variety of factors[4]: vascularity, fat, pH of local anesthetic solutions, tissue-plasma anesthetic partition coefficient and diffusibility in the epidural space. With chloroprocaine, CPI resulted in lower blood

levels than RII. Rapid hydrolysis of chloroprocaine by plasma cholinesterase was estimated in obstetric patients[20]. This mechanism, however, does not work for lidocaine and mepivacaine, since they are not metabolized in blood stream. No appropriate explanation was available to clarify the reason of different blood levels in this study.

In clinical settings, CPI technique is superior to RII, since CPI can keep circulation more stable than RII does. It must be remembered that plasma levels are higher with CPI than with RII, when plain lidocaine is applied.

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