Plasma lidocaine concentrations during continuous epidural infusion of lidocaine with and without epinephrine

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Plasma lidocaine concentrations were measured over a five-hour period in 20 patients following continuous epidural infusion of lidocaine for surgical anaesthesia. Patients were divided into two groups: Group I received plain lidocaine; Group II received lidocaine with epinephrine. Patients initially received 10 ml followed by a constant infusion of 10 ml · hr^{-1} of two per cent lidocaine. The mean plasma concentrations of lidocaine were significantly higher for the first 40 min in Group I than in Group II. However, from one to five hours, there was no significant difference between the groups. These results demonstrate that the addition of epinephrine to lidocaine does not decrease the plasma concentration of lidocaine during continuous epidural infusion for long operations.

Des concentrations plasmatiques de lidocaïne ont été mesurées pour une période de cinq heures chez 20 patients après une perfusion continue dans l'espace épidural de lidocaine pour une anesthésie chirurgicale. Les patients furent divisés en deux groupes: Le groupe I a reçu de la lidocaïne simple, le groupe II a reçu de la lidocaine avec épinéphrine. Les patients initialement ont reçu 10 ml suivi d'une perfusion continue de 10 ml · hr^{-1} de deux pour cent de lidocaïne. La concentration plasmatique moyenne de lidocaïne était significativement supérieure pour les premières 40 minutes dans le groupe I comparativement au groupe II. Cependant si on compare la première à la cinquième heure, il n'y avait aucune différence significative entre les deux groupes. Ces résultats démontrent que l'addition d'épinéphrine à la lidocaïne ne diminue pas la concentration plasmatique de lidocaïne lors de la perfusion continue dans l'espace épidural de lidocaïne pour des longues opérations.

Key words
ANAESTHETICS, LOCAL: lidocaine;
ANAESTHETIC TECHNIQUE: epidural;
PHARMACOKINETICS: absorption, plasma concentration.

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Epidural anaesthesia following continuous infusion of local anaesthetics into the epidural space or in combination with light general anaesthesia has been employed for upper or lower abdominal surgery. The effects of epidural analgesia following continuous epidural infusion of local anaesthetics on the extent of sensory block and the degree of motor block are very similar to those following multiple intermittent injections,[1] but the blood concentrations of local anaesthetics using continuous epidural infusion are lower than those using intermittent injections.[2] The reduction in blood levels of local anaesthetics is important in preventing systemic toxicity.

Epinephrine is frequently added to local anaesthetic solutions for epidural administration to enhance the efficacy of epidural block and to decrease the rate of vascular absorption.[3] The peak blood concentration of local anaesthetics following intermittent epidural injections is reduced by the addition of epinephrine.[4,5] However, the effects of epinephrine on the systemic levels of local anaesthetics have not been studied when continuous epidural infusion is used for prolonged epidural anaesthesia.

The present study was designed to compare the blood concentrations of lidocaine following continuous epidural infusion of lidocaine with or without epinephrine.

Methods

Twenty patients, aged between 38 and 67 yr, scheduled for epidural plus general anaesthesia that would last more than five hours were selected for this study. The study was approved by our institution's human research review committee and informed consent was obtained from each

TABLE I Operative procedures performed with epidural plus general anaesthesia

Procedure	*Number of patients*
Gastrectomy	9
Jejunectomy	1
Colectomy	1
Proctectomy	1
Pancreato-duodenectomy	1
Pancreatectomy	1
Cystectomy	2
Hysterectomy	4

patient. The operations performed are presented in Table I. Patients were randomly divided into two groups of ten: patients in Group I received plain lidocaine solution into the epidural space; patients in Group II received epinephrine-containing lidocaine solution.

All patients received premedication with 50–100 mg of hydroxyzine and 0.5 mg of atropine IM, one hour before induction of anaesthesia. An IV cannula was placed for fluid administration and a radial artery cannula was placed for continuous monitoring of the arterial pressure and blood sampling. With the patient in the lateral decubitus position and with 2–3 ml of one per cent lidocaine solution for local anaesthesia, a 17-g Tuohy needle was inserted into the epidural space at the T_7-T_8 to L_2-L_3 interspace and a catheter was inserted.

General anaesthesia was induced with 4–5 $mg \cdot kg^{-1}$ thiamylal IV, preceded by 1 mg pancuronium, and followed by 1 $mg \cdot kg^{-1}$ succinylcholine to facilitate tracheal intubation. Maintenance of anaesthesia consisted of nitrous oxide, oxygen (4:2 $L \cdot min^{-1}$) and 0.2–0.5 per cent halothane. Epidural anaesthesia was produced by injection through the epidural catheter of 10 ml two per cent lidocaine hydrochloride without epinephrine in Group I and with epinephrine in Group II. A test dose was not used. Immediately following the initial injection, two per cent lidocaine with or without epinephrine was continuously infused at a rate of 10 $ml \cdot hr^{-1}$ for five hours or more. Epinephrine 1:200,000 was freshly added to the lidocaine solution. Pulmonary ventilation was adjusted to control $PaCO_2$ between 35 and 42 mmHg and arterial pH between 7.35 and 7.45. Arterial blood gases were measured one, three and five hours after the initial injection of lidocaine. The ECG, radial artery pressure, rectal temperature, and urinary volume were monitored in all patients, and central venous pressure was measured in ten patients throughout the operation. Blood loss was replaced as necessary.

Arterial blood samples of 1 ml were taken with a heparinized syringe at 5, 10, 15, 20 min and then 20-min intervals after the initial injection of lidocaine for five hr. Plasma lidocaine concentrations were measured by enzyme immunoassay (EMIT) technique (Du Pont ACA Discrete Clinical Analyzer). The EMIT technique for lidocaine assay has proved to be accurate with a high degree of specificity and precision.[6,7] In our measurements, the coefficient of variation at one, five or ten $\mu g \cdot ml^{-1}$ was less than ten per cent. The principal metabolites of lidocaine, monoethylglycinexylidide (MEGX), and glycinexylidide (GX) were not measured. Plasma lidocaine concentrations less than 1.0 $\mu g \cdot ml^{-1}$ were not precise.

The results of repeated measurements in arterial pH, $PaCO_2$ and lidocaine concentration were analyzed by an analysis of variance for repeated measures. Pairwise comparisons of the mean values between the two groups were assessed by Student's t-test for unpaired data. $P < 0.05$ was considered significant. All data are presented as mean ± SEM.

Results

There were no significant differences between the two groups in patient characteristics, arterial pH, $PaCO_2$ and blood loss (Tables II and III). No significant changes in arterial pH and $PaCO_2$ during the five-hour period of this study were observed in either group (Table III). No patients had signs of local anaesthetic toxicity during or after surgery.

The mean plasma lidocaine concentration was significantly higher for the first 40 min in Group I than in Group

TABLE II Patient characteristics and blood losses

	Group I without epinephrine (n = 10)	*Group II with epinephrine (n = 10)*
Sex (M/F)	5/5	5/5
Age (yr)	55.7 ± 2.8	51.5 ± 2.7
Weight (kg)	56.1 ± 2.8	54.8 ± 1.7
Height (cm)	159.7 ± 1.9	157.7 ± 2.6
Blood loss (ml)	752 ± 168	891 ± 122

Values are expressed as mean ± SEM.

TABLE III Arterial pH and $PaCO_2$

		Time (hr)		
		1	*3*	*5*
pH	Group I	7.40 ± 0.01	7.39 ± 0.01	7.38 ± 0.01
	Group II	7.39 ± 0.01	7.38 ± 0.01	7.37 ± 0.01
$PaCO_2$ (mmHg)	Group I	37.3 ± 0.6	36.8 ± 0.7	37.6 ± 0.9
	Group II	38.0 ± 0.9	37.0 ± 0.7	38.4 ± 0.9

Values are expressed as mean ± SEM.

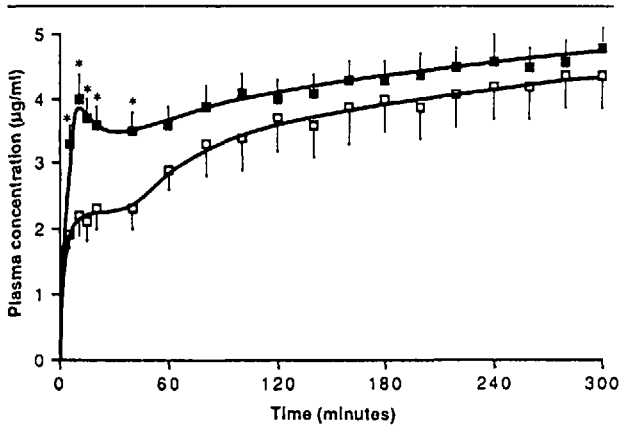

FIGURE Mean plasma concentrations of lidocaine during epidural anaesthesia induced by continuous infusion of two per cent lidocaine solution without epinephrine (■, Group I) or with epinephrine (□, Group II). Values represent mean ± SEM. An asterisk denotes significant differences ($P < 0.05$).

II (Figure). However, from one to five hours, there were no significant differences between the groups. The increases in plasma lidocaine concentrations following continuous epidural infusion of lidocaine were very slow after the initial rise in the two groups. The mean maximum concentrations were 4.8 ± 0.4 and 4.4 ± 0.5 $\mu g \cdot ml^{-1}$ at five hours in Groups I and II, respectively.

Discussion

The present study shows that the addition of epinephrine to lidocaine does not decrease the mean plasma lidocaine concentration, except during the first 40 min, when lidocaine is continuously infused into the epidural space.

The blood concentrations of local anaesthetics following continuous epidural infusion are lower than those following multiple intermittent injections of local anaesthetics.[2] We have recommended the use of the continuous infusion technique for long operations to decrease the blood concentrations and to prevent systemic toxicity of local anaesthetics. However, an initial bolus injection of local anaesthetic is necessary to induce epidural block quickly,[1] although the blood concentrations increase rapidly following the bolus injection of local anaesthetics without epinephrine.

There was no difference in the mean plasma lidocaine concentrations between the two groups after one hour. The plasma concentration of lidocaine under steady-state conditions of infusion is primarily determined by the ratio of the steady-state infusion rate to the plasma clearance of lidocaine.[8] If the factors which determine the clearance are constant, the plasma concentration is determined by the infusion rate, regardless of the absorption rate influenced by epinephrine. We used the same infusion rate for five hours in the two groups. Therefore, the mean plasma lidocaine concentrations in the two groups may be similar with prolonged infusions, although a true steady-state is not achieved in a five-hour period and the clearance of lidocaine is slightly changed during surgical anaesthesia.

There are no reports of the blood concentrations following continuous epidural infusion of local anaesthetics during surgery, apart from our previous reports,[1,2] although there are some studies which describe blood concentrations during continuous epidural infusion of bupivacaine for postoperative pain relief.[9–11] In our previous study,[2] an initial volume of 10 or 15 ml of two per cent mepivacaine with epinephrine was injected. Immediately after the initial injection, the same mepivacaine solution was infused continuously at a rate of 10 $ml \cdot hr^{-1}$ for five hours. The mean maximum blood concentration of mepivacaine was 4.65 ± 0.55 $\mu g \cdot ml^{-1}$ at five hours. The blood levels of mepivacaine during continuous epidural administration were similar to those of lidocaine observed in this study. The cumulative dose used in this study amounted to 1200 mg but the plasma lidocaine concentrations did not exceed 8 $\mu g \cdot ml^{-1}$. None of the patients, under light general anaesthesia, had signs of local anaesthetic toxicity.

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