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Topical bupivacaine and etidocaine analgesia following fallopian tube banding

The purpose of this study was to compare the effectiveness and safety of etidocaine and bupivacaine for postoperative analgesia after laparoscope sterilization. The study was performed in 22 healthy patients who received either one per cent etidocaine, 2 mg · kg⁻¹, or bupivacaine 1.5 mg · kg⁻¹ in a double-blind, randomized fashion. The local anaesthetic was dropped onto the fallopian tubes from uterus to fimbriae before tubal occlusion. To establish safety, blood concentrations of the parent drug and its metabolites were measured before application and at 1, 3, 6, 10, 15, 30, 60 and 120 min. The mean peak concentrations were 501.8 ± 71.3 (SEM) for etidocaine with a range of 225 to 905 ng · ml⁻¹. For bupivacaine, the mean peak concentration was 468 ± 73.8 SEM with a range from 191 to 1005 ng · ml⁻¹. The mean values are one eighth of the toxic convulsive dose for humans. Etidocaine was metabolized at a faster rate than bupivacaine with a rapid appearance of 2-amino-2'-butyroxylidide (ABX). The bupivacaine metabolite 2,6-pipecoloxylidide (PPX) was detected in low concentrations in the 60-minute samples. We conclude that the topical application of either etidocaine or bupivacaine is a safe procedure in the doses and concentrations used during general anaesthesia for laparoscopic tubal banding.

Key words

ANAESTHETICS, LOCAL: bupivacaine, etidocaine, metabolism; PAIN: postoperative; SURGERY: laparoscopy, tubal ligation.

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Lidocaine, bupivacaine, and etidocaine have been applied to the fallopian tubes to relieve the pain of tubal occlusion performed with the use of local anaesthesia, with intravenous sedation and with general anaesthesia.¹⁻³ The doses of local anaesthetics used vary widely. We reported a significant reduction in narcotic requirement in the recovery period when etidocaine was applied to the fallopian tubes before occlusion during laparoscopy.³ The frequency of overnight stay in hospital was also significantly reduced. The safety and effectiveness of etidocaine compared with other local anaesthetics used for this purpose have not been studied. We therefore designed a double-blind, randomized clinical trial to compare the clinical effectiveness of bupivacaine and etidocaine. The safety of topical application was evaluated by measuring the blood concentrations of the local anaesthetics along with their metabolites.

Methods

With the approval of our hospital human investigation committee, informed consent was obtained from 22 healthy outpatients having laparoscopic tubal occlusion under general anaesthesia. They were randomly assigned to one of two groups.

All patients received fentanyl 50 µg and droperidol 1.25 mg IV followed by preoxygenation and precurarization. Anaesthesia was then induced with thiamylal 5 mg · kg⁻¹, followed by succinylcholine, 100 mg, to facilitate tracheal intubation. Anaesthesia was maintained with 50 per cent nitrous oxide and oxygen with 0.5–2 per cent isoflurane. Following induction, a heparinized cannula was placed in a vein in the forearm not used for IV infusion, and a baseline blood sample was obtained. Nitrous oxide was insufflated to create the operative pneumoperitoneum needed for the surgery.

Patients in Group E had one per cent etidocaine, 2 mg · kg⁻¹, and patients in Group B had 0.75 per cent bupivacaine, 1.5 mg · kg⁻¹, applied to both fallopian tubes from uterus to fimbria. A 20 ml syringe containing the unknown local anaesthetic was attached to a Kiddy cannula and dripped onto the fallopian tube under direct vision via the laparoscope. We previously established the

FIGURE 1 Venous whole blood levels $\pm$ SEM of etidocaine $2 \text{ mg} \cdot \text{kg}^{-1}$ $\square$ and bupivacaine $1.5 \text{ mg} \cdot \text{kg}^{-1}$ $\blacksquare$ following intraabdominal, topical application during laparoscopy. $n = 11$ in each group.

clinical effectiveness of 1 per cent etidocaine³ and selected 0.75 per cent bupivacaine to obtain its maximum effect. Numbered syringes were prepared by one of the authors (AFV) according to the patient's weight. A 50 kg patient would require 10 ml of either drug in the syringe thereby precluding recognition of the solution and assuring double-blindness of surgical and anaesthetic personnel. The application of the unknown local anaesthetic was completed prior to tubal occlusion with Falope bands. At 1, 3, 6, 10, 15, 30, 60 and 120 min after application, 2 ml samples of venous blood were drawn.

Whole blood was analyzed in triplicate by high-pressure liquid chromatography (HPLC) for etidocaine and its metabolites, 2-amino-2'-butyroxylidide (ABX), 2-N-propylamino-2'-butyroxylidide (PBX), and 2-N-ethylamino-2'-butyroxylidide (EBX) in Group E and for bupivacaine and its metabolite 2,6-pipecoloxylidide (PPX) in Group B. The samples were collected using nonheparinized syringes and immediately placed in a borate solution buffered to pH 9.5. The extraction was a two-step technique. The samples were first extracted into 10 ml of 30 per cent methylene chloride and then back extracted into 150 μl of 0.1 N HCl. All samples were frozen and later analyzed by HPLC using a reversed-phase technique described by Kennedy *et al.*⁴ Bupivacaine was used as the internal standard for the etidocaine and metabolite analyses, and etidocaine as the internal standard for the bupivacaine and PPX analyses. Ultraviolet detection was used with a wavelength of 210 nm for maximum absorbance. Detection limits were etidocaine, 10 $\text{ng} \cdot \text{ml}^{-1}$; bupivacaine, 15 $\text{ng} \cdot \text{ml}^{-1}$; ABX, 5 $\text{ng} \cdot \text{ml}^{-1}$; PBX, 5 $\text{ng} \cdot \text{ml}^{-1}$; EBX, 5 $\text{ng} \cdot \text{ml}^{-1}$; and PPX, 5 $\text{ng} \cdot \text{ml}^{-1}$. Standard curves were constructed and validated daily; they were found to be linear, $r^2 \geq 0.99$, for all compounds of interest.

On arrival at the recovery room and at 0.5, 1 and 2 hr after termination of anaesthesia, the degree and site of pain, occurrence of nausea or vomiting, and medication(s) administered were recorded by an anaesthetist (RMCK or BMM) blinded to the local anaesthetic used. Subjective abdominal pain was assessed by the anaesthetist by asking the same questions of each patient. "Are you comfortable?" With a positive response, the patient was then asked specifically, "Are you having any abdominal pain?" If so, she would classify the pain as mild, moderate or severe. With a negative response to the first question, the specific follow-up question on abdominal pain was asked. Nausea and vomiting were evaluated as 0 = nil, 1 = nausea, and 2 = vomiting. A follow-up telephone call was made the next day to record persistent or new complications.

Data were analyzed for statistical significance using the Fisher exact probability test. Level of $P \leq .05$ was considered statistically significant.

Results

The two groups were similar in age, weight, height, haematocrit and duration of operation. With Group E, the mean peak whole blood concentration ($\pm$ SEM) was $501.8 \pm 71.3 \text{ ng} \cdot \text{ml}^{-1}$; with a range of 222–905 $\text{ng} \cdot \text{ml}^{-1}$ (Figure 1). Corresponding values for Group B were $468.8 \pm 73.8 \text{ ng} \cdot \text{ml}^{-1}$ with a range of 191–1005 $\text{ng} \cdot \text{ml}^{-1}$. Mean peak concentrations occurred at 17.7 min (range 6–30 min) with etidocaine and at 33.2 min (range 10–60 min) with bupivacaine (Table I). There were rapid, parallel increases in blood concentrations of both parent drugs during the first 15 min. After 20 min, etidocaine levels began to decrease. Bupivacaine levels reached a plateau from 20–60 min before slowly declining. Blood concentrations of both drugs decayed at a similar rate (Figure 1). The metabolic degradation products of etidocaine, ABX, PBX, and EBX, were all present in the 1-min sample (Figure 2). The major metabolite of bupivacaine, PPX, did not consistently appear until the 60-min sample (Figure 3).

In the recovery room, pain was significantly less in Group E patients (Table II), $P < 0.05$. No subjective abdominal pain was reported in 28 of 42 observations (66.6 per cent), mild pain 13 of 42 (31 per cent) and moderate pain one of 42 (2.4 per cent). In Group B, no subjective abdominal pain was reported in 13 of 42 (40.5 per cent) and moderate pain 12 of 42 (28.5 per cent). No patient in either group had severe abdominal pain. Statistical significance $P < 0.5$ was reached for patients with no pain and moderate pain. Group E patients had less moderate pain and more patients reported no pain compared with group B ($P < 0.5$). Intravenous fentanyl 50 μg in divided doses was necessary in one patient in Group B.

TABLE I Venous blood concentrations after topical application of etidocaine and bupivacaine

Group	n	Peak concentration (ng·ml ⁻¹)		Time to maximum concentration (min)		
		Mean*	Range	Mean*	Median	Range
Etidocaine	11	501.8 ± 71.3	222–905	17.7 ± 1.8	20	10–30
Bupivacaine	11	468.0 ± 73.8	191–1005	33.2 ± 5.7	30	6–60

*± SEM.

Values obtained by high pressure liquid chromatography and time to maximum peak concentrations of etidocaine and bupivacaine.

FIGURE 2 Whole blood levels of etidocaine □ and major metabolites ABX, PBX and EBX following intraabdominal, topical application during laparoscopy. (Note the rapid appearance and amount of 2-amino-2'-butyroxylidide (ABX) △ and the small amount of 2-N-propylamino-2'-butyroxylidide (PBX) ○ and 2-N-ethylamino-2'-butyroxylidide (EBX) ●.) n = 11.

An equal number of patients in both groups required oral analgesics (acetaminophen – oxycodone – acetaminophen [Percoset], or ibuprofen).

Nausea occurred in three patients in Group E and in two patients in Group B. Vomiting occurred three times in two patients given bupivacaine. There was no significant difference in the incidence of nausea or vomiting in the two groups. At 24 hr one patient in each group complained of lower abdominal pain.

TABLE II Abdominal pain reported after topical application of etidocaine and bupivacaine during tubal occlusion

Group	n	Degree of pain				# Observations†
		Nil*	Mild	Moderate*	Severe	
Etidocaine	11	28	13	1	0	42
Bupivacaine	11	13	17	12	0	42

*P < 0.05.

†Four observations could not be obtained: in group E, one on arrival at recovery room and one at 2 hr; in group B, two on arrival at recovery room.

FIGURE 3 Whole blood levels of bupivacaine ■ and its major metabolite 2,6-pipecoloxylidide (PPX) ○ following intraabdominal, topical application during laparoscopy. (Note the slow metabolism of parent drug bupivacaine ■ to 2,6-pipecoloxylidide (PPX) ●.) n = 11.

Discussion

The intraoperative, intraperitoneal instillation of local anaesthetic agents to reduce pain has been used for many years. In 1950, Hanson and Hingson reported on seven patients who successfully underwent laparotomy with 500–1200 mg intraperitoneal lidocaine.¹ The average duration of action was 45 min. Cruikshank *et al.* found that nonconvulsive blood levels were attained with 1000 mg lidocaine in nonpregnant women having tubal occlu-

sion under local anaesthesia supplemented with preoperative IV alphaprodine and diazepam.² For postpartum tubal ligation using the same analgesic and sedative drugs, subconvulsive blood levels of lidocaine were also found when 500 mg lidocaine was used.²

Abdominal pain after laparoscopic tubal occlusion is severe in most patients, lasts from 4–6 hr, and may delay discharge from day surgery units.³ Postoperative pain is more severe following laparoscopic sterilization than when diagnostic laparoscopy alone is performed, and for this reason studies of morbidity from laparoscopy patients having laparoscopic sterilization may be excluded.⁵ Davis and Millar found that the laparoscopic sterilization patients have significantly more pain in the first 4 hr after surgery than diagnostic laparoscopy patients ($P < 0.02$).⁶

Etidocaine and bupivacaine were selected in the present study because extended duration of action is needed to provide postoperative comfort. However, both drugs have been implicated in cases of cardiac arrest following epidural and probably inadvertent intravascular administration.⁷ Topical application avoids intravascular injection, but rapid absorption of the drug could still lead to toxic blood levels with convulsion and/or cardiac arrest. Although the clinical effectiveness of etidocaine one per cent and bupivacaine 0.5 per cent has been reported independently, blood analyses to verify the safety of intraabdominal instillation have not.^{3,8}

In the doses and concentrations that we compared, the patients in Group E complained of less severe abdominal pain than those in Group B. Although there were only 11 patients in each group, 84 spoken subjective pain assessments were made. Without valid dose-response curves for each drug, the difference in effectiveness is not easily explained. Etidocaine differs from bupivacaine in physical properties, especially pKa and lipid solubility. At body pH etidocaine ($pK_a = 7.74$) is less ionized than bupivacaine ($pK_a = 8.01$). Etidocaine has a partition coefficient of 141 and is approximately five times as soluble in fat as bupivacaine.²⁸ Both drugs are 90–96 per cent protein bound. If more etidocaine is available to penetrate nervous tissue there may be more active ionized drug to account for superior pain relief.

The weight-normalized dose that produces seizures in rhesus monkeys is higher for etidocaine than for bupivacaine; etidocaine is therefore considered less toxic.⁹ Plasma concentrations at seizure of these two drugs are similar. Having established an effective dose of etidocaine,³ we chose a dose of bupivacaine estimated to result in similar blood levels. To maximize the effectiveness of topical bupivacaine, the highest concentration was chosen. The similar peak blood concentrations may be attributable to the higher lipid solubility and more rapid metabolism of etidocaine. A high metabolite concentra-

tion would imply greater safety for system toxicity by reducing the concentration of parent drug.

The earliest peak concentration for etidocaine at six minutes and for bupivacaine at ten minutes demonstrated that drugs placed intraabdominally may be absorbed rapidly into the bloodstream. Close patient surveillance is necessary for one hour because the latest peak concentrations occurred at 30 min for Group E and 60 min for Group B. The blood level of a local anaesthetic parent drug is altered by the rapidity of metabolites produced. Etidocaine has three metabolites which appear quickly, indicating rapid metabolism by the liver. The early appearance of ABX, PBX and EBX and the increase in concentration over time account for the decrease in etidocaine level. Similarly, bupivacaine levels remained high throughout the study with a low metabolite level for PPX. It is believed that none of these metabolites adds to the toxicity of the parent drugs. Our doses avoided toxicity as confirmed by serial blood analyses. The mean peak blood concentration was one-quarter of the reported minimal convulsive level of $2 \mu\text{g} \cdot \text{ml}^{-1}$ in monkeys⁹ and one-eighth of the arterial plasma levels that caused convulsions in humans.¹⁰

Reduction of etidocaine concentrations, and hence its safety, appears to be related to metabolism. There is a possibility that absorption may in part be into the portal circulation rather than systemic, but this study could not determine differential absorption. Wide variations were noted in the venous blood levels. For etidocaine the range was from 222 to $905 \text{ ng} \cdot \text{ml}^{-1}$, while bupivacaine values were 191 to $1005 \text{ ng} \cdot \text{ml}^{-1}$. Doubling the dose might achieve convulsive levels in some patients. These results do not apply to procedures carried out under local anaesthesia, because possible cumulative effects of additional local anaesthetic agent could reach a convulsive level.

In summary, topical application of either etidocaine or bupivacaine was a safe procedure in the dose and concentration used. Furthermore, intravascular injection is impossible with topical application. The venous blood concentrations of etidocaine and bupivacaine were similar, although quantitatively 33 per cent more etidocaine was applied. The doses used were effective, and peak blood concentrations were below toxic levels despite wide individual variation.

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Résumé

Le but de cette étude est de comparer l'efficacité et la sécurité de l'étidocaïne et de la bupivacaïne pour l'analgesie postopératoire après ligature tubaire par laparoscopie. Cette étude comprend 22 patientes en bonne santé ayant reçu soit un pour cent d'étidocaïne, 2 mg · kg⁻¹, ou de la bupivacaïne 1,5 mg · kg⁻¹ d'une façon randomisée à double insu. L'anesthésique fut mis sur les tubes de fallope à partir de l'utérus jusqu'aux franges avant la ligature tubaire. Afin d'établir la sécurité, les concentrations sanguines du médicament et de ses métabolites ont été mesurées avant l'application et à 1, 3, 6, 10, 15, 30, 60 et 120 minutes. Les concentrations maximales moyennes étaient de 501,8 ± 71,3 (SEM) pour l'étidocaïne avec un écart de 225 à 905 ng · ml⁻¹. Pour la bupivacaïne, la concentration maximale moyenne était de 468 ± 73,8 SEM avec un écart de 191 à 1005 ng · ml⁻¹. Les valeurs moyennes étaient de 1/8 de la dose toxique provoquant des convulsions chez les humains. L'étidocaïne était métabolisée à un taux supérieur à la bupivacaïne avec une apparition rapide de la 2-amino-2'-butyroxylidide (ABX). Le métabolite de la bupivacaïne 2,6-pipécoloxylidide (PPX) était détectée à des concentrations basses aux échantillons de 60 minutes. On conclut que l'application topique de l'étidocaïne ou de la bupivacaïne est sécuritaire à des doses et des concentrations utilisées en anesthésie générale pour ligature tubaire.