Laboratory Investigation

Displacement of lidocaine from the lung after bolus injection of bupivacaine

Shigeo Ohmura MD,* Ken Yamamoto MD, Tsutomu Kobayashi MD, Seiitsu Murakami MD

The purpose of this study was to determine whether lidocaine was displaced from the lung after bolus injection of bupivacaine. Fourteen anaesthetized rabbits were randomly assigned to either a bupivacaine or a control group. Lidocaine was infused at a rate of 10 mg · kg^{-1} · hr^{-1}. After one hour of infusion, a bolus of bupivacaine (1 mg · kg^{-1}) in normal saline (0.2 ml · kg^{-1}) was injected into the central venous circulation in the bupivacaine group. The control group was injected with normal saline. After bolus injection, arterial blood samples were collected serially from an internal carotid artery at 1.2-sec intervals for 24 sec. The baseline concentration of lidocaine was 3.0 ± 0.1 μg · ml^{-1} in the bupivacaine group and 3.2 ± 0.1 μg · ml^{-1} in the control group (NS). Arterial concentrations of lidocaine increased to a maximum of 4.7 ± 0.2 μg · ml^{-1} in the bupivacaine group (P = 0.0001). No increases were seen in the control group. These findings indicate that lidocaine was displaced from the lung into the blood after bolus injection of bupivacaine. The amount of lidocaine displaced during the first passage of bupivacaine through the lung was calculated to be 92.3 ± 9.7 μg. It is concluded that lidocaine is displaced from the lung after bolus injection of bupivacaine.

Cette étude vise à déterminer si la lidocaïne est déplacée du poumon après un bolus de bupivacaïne. Quatorze lapins anesthésiés sont répartis au hasard entre un groupe bupivacaïne et un groupe contrôle. La lidocaïne est perfusée à la vitesse de 10 mg · kg^{-1} · hr^{-1}. Dans le groupe bupivacaïne, après une heure de perfusion, un bolus de bupivacaïne (1 mg · kg^{-1}) dans du soluté physiologique (0,2 ml · kg^{-1}) est injecté dans la circulation veineuse centrale. Le groupe contrôle ne reçoit que du physiologique. Après l'injection du bolus, on recueille des échantillons de sang artériel en série par la carotide interne à des intervalles de 1,2 sec pendant 24 sec. La concentration initiale de lidocaïne est de 3,0 ± 0,1 μg · ml^{-1} dans le groupe bupivacaïne et de 3,2 ± 0,1 μg · ml^{-1} dans le groupe contrôle (NS). Les concentrations artérielles de lidocaïne augmentent jusqu'à un maximum de 4,7 ± 0,2 μg · ml^{-1} dans le groupe bupivacaïne (P = 0,0001). On ne trouve pas d'augmentation dans le groupe contrôle. Ces résultats indiquent que la lidocaïne est déplacée du poumon vers le sang après un bolus de bupivacaïne. La quantité déplacée calculée lors du premier passage est de 92,3 ± 9,7 μg. On conclut que la lidocaïne est déplacée du poumon après une injection en bolus de bupivacaïne.

Key words
ANAESTHETICS, LOCAL: bupivacaine, lidocaine;
LUNG: drug uptake;
PHARMACOKINETICS.

From the Department of Anesthesiology and Intensive Care Medicine, School of Medicine, Kanazawa University, Kanazawa, Japan.

*Present address: Department of Anesthesiology, National Defense Medical College, Tokorozawa, Japan.

Address correspondence to: Dr. Shigeo Ohmura, Department of Anesthesiology, National Defense Medical College, 3-2 Namiki, Tokorozawa 359, Japan.

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The lung has important non-respiratory functions other than gas exchange.[1] This includes the uptake of a large number of drugs including local anaesthetics.[2-5] Because the lungs are uniquely situated in the circulatory system so that blood must pass through them before entering the systemic circulation, they prevent a sudden increase in the venous concentration of a local anaesthetic being transmitted directly to the systemic circulation and therefore may help to prevent toxic reactions.

Lidocaine and bupivacaine are often used in combination in clinical practice. Competition between them for binding to lung tissue has been demonstrated *in vitro*,[6] but not *in vivo*. Therefore it is important for the safe

management of anaesthesia to examine possible interactions between them *in vivo*.

The present study was performed to answer the following questions: (a) does bupivacaine displace lidocaine from the lung *in vivo*?, and (b) how much lidocaine is displaced during first passage of bupivacaine through the lung?

Methods

The experimental protocol was approved by the Animal Care Committee of Kanazawa University School of Medicine.

Surgical procedures

Fourteen male rabbits weighing 2.9 – 3.7 kg were used for the experiment. They were randomly assigned to either a bupivacaine ($n = 7$) or a control group ($n = 7$). A posterior auricular vein was cannulated and anaesthesia was induced with 750 $mg \cdot kg^{-1}$ urethane *iv*. Tracheostomy was performed and the lungs were ventilated mechanically with air and oxygen after pancuronium 1 mg *iv*. The $PaCO_2$ was maintained between 30 and 40 mmHg and the PaO_2 between 100 and 200 mmHg. An internal carotid artery was cannulated to monitor arterial pressure and for blood sampling. An external jugular vein was cannulated for bolus drug administration.

Experimental protocol

Following a stabilization period of approximately 20 min, arterial blood was obtained for blood gas analysis and for preparation of standard curves for sample analysis. Then lidocaine was infused into the posterior auricular vein at a rate of 10 $mg \cdot kg^{-1} \cdot hr^{-1}$ and was continued until the end of the study. One hour after the beginning of the lidocaine infusion, arterial pressure was measured and arterial blood gas analysis was repeated. Then a solution containing bupivacaine (1 $mg \cdot kg^{-1}$) and the intravascular indicator, indocyanine green (ICG, 0.1 $mg \cdot kg^{-1}$) in 0.2 $ml \cdot kg^{-1}$ normal saline was injected rapidly into the external jugular vein of rabbits in the bupivacaine group. Animals in the control group were injected with only ICG (0.1 $mg \cdot kg^{-1}$) in 0.2 $ml \cdot kg^{-1}$ normal saline. Arterial blood samples were withdrawn simultaneously from the internal carotid artery at a rate of 15 $ml \cdot min^{-1}$ by means of a peristaltic pump (Minipuls 3®, Gilson, Middleton, U.S.A.) and collected in 1.2-sec fractions in a fraction collector (Type 203, Gilson). Tubes in the fraction collector contained 8 μl of heparin (1,000 units $\cdot ml^{-1}$). A total of 20 blood samples were collected from the time of injection.

Sample analysis

After collection, 250 μl of each blood sample was diluted with 2.75 ml of water and vortexed vigorously to lyse the red cells. After centrifugation at 3000 rpm for ten minutes, the supernatant was decanted. The ICG concentration in the diluted blood sample was determined by spectrophotometry from its absorbance at 805 nm. A linear standard curve was obtained for ICG concentrations of 0–9.60 $\mu g \cdot ml^{-1}$. The diluted blood samples were frozen at −80°C until lidocaine analysis.

Lidocaine blood concentration was determined by high-performance liquid chromatography based on the method of Adams *et al.*[7] A Model ALC/GPC 204 High-performance Liquid Chromatograph equipped with a Model 441 fixed-wavelength absorbance detector (214 nm) and μ Bondapak C_{18} reversed-phase column (all from Waters, Milford, U.S.A.) was used. Five hundred microlitres of each diluted blood sample was placed in a screw-cap centrifuge tube, followed by the addition of 40 μl of internal standard solution (procaine 5 $\mu g \cdot ml^{-1}$), 100 μl, 1 N NaOH and 5 ml, diethylether. The contents were mixed by vortexing and then shaken for 20 min on a reciprocating shaker. After centrifugation at 3000 rpm for five minutes, the supernatant was transferred to another tube and evaporated to dryness under a gentle stream of nitrogen at 25°C. The residue was dissolved in 50 μl of methanol and 20 μl was injected into the chromatograph under the following conditions: flow rate of 2.0 $ml \cdot min^{-1}$; mobile phase of 20% acetonitrile in 0.2 M phosphate buffer adjusted to pH 5.5. The peak-height ratio between the internal standard and lidocaine was used to quantify the amount of lidocaine by comparison with the standard curve. A linear standard curve was obtained for lidocaine concentrations of 0.24–9.60 $\mu g \cdot ml^{-1}$. The minimum sensitivity was 0.24 $\mu g \cdot ml^{-1}$ lidocaine in whole blood with a coefficient of variation for the assay of 2.7%.

Calculations

Cardiac output (CO) was measured by dye dilution from the ICG curves for each subject, as described by Ross.[8] It was calculated by the formula:

$$CO = \frac{T_{ICG}}{AUC_{ICG}} \times 60,$$

where T_{ICG} is the total amount of the injected ICG, and AUC_{ICG} is the area under the curve of ICG corrected for recirculation (Figure 1).

The displaced lidocaine (D_{LID}) was defined as the amount of lidocaine displaced during the first passage of the injectate through the lung. It was calculated by the formula:

$$D_{LID} = \int_0^t \Delta C_{LID}\, dt \times CO,$$

where ΔC_{LID} is the difference in lidocaine concentration

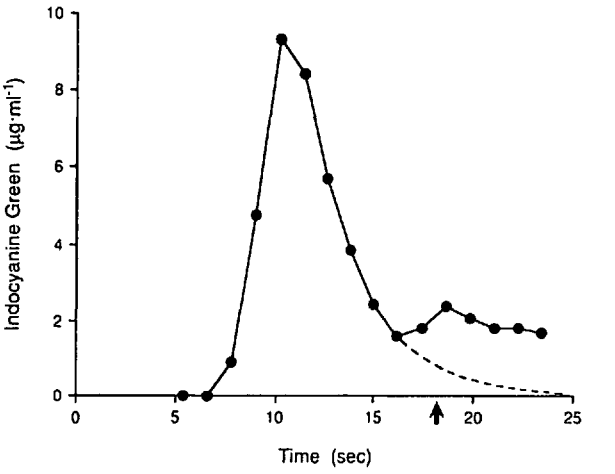

FIGURE 1 Typical concentration *versus* time curve of indocyanine green (ICG) after bolus injection (solid line). Two peaks are observed in the curve. The first corresponds to the first pass of ICG through the lung. The second corresponds to the recirculation of ICG through the lung. The dashed line represents concentration *versus* time curve of ICG corrected for recirculation. The correction for recirculation was performed by monoexponential extrapolation of the early part of the downward slope to infinity. The arrow indicates the time at which 95% of the total amount of ICG had passed through the lung.

between each sample and the baseline sample, *0* is the time of bolus injection, and *t* is the time when 95% of the total amount of ICG had passed through the lung.

Statistical analysis

Data were analyzed using the Mann-Whitney U test for between-group comparisons and the Friedman test for intra-group comparisons. A P value of less than 0.05 was considered to be statistically significant. All results were expressed as mean ± SEM.

Results

The physiological data at the time of bolus injection are shown in the Table. There were no differences in body weight, arterial pH, $PaCO_2$, PaO_2, systolic blood pressure, diastolic blood pressure and CO between the groups.

The baseline concentration of lidocaine was 3.0 ± 0.1 $\mu g \cdot ml^{-1}$ in the bupivacaine group and 3.2 ± 0.1 $\mu g \cdot ml^{-1}$ in the control group (NS). The lidocaine concentration increased to a maximum of 4.7 ± 0.2 $\mu g \cdot ml^{-1}$ in the bupivacaine group ($P = 0.0001$). In contrast, no increase was seen in the control group (Figure 2). The lidocaine concentration was higher in the bupivacaine group than in the control group from 9.6 sec to 18.0 sec after bolus injection ($P < 0.05$).

The DLID was 92.3 ± 9.7 μg in the bupivacaine group and −5.4 ± 4.5 μg in the control group ($P < 0.01$).

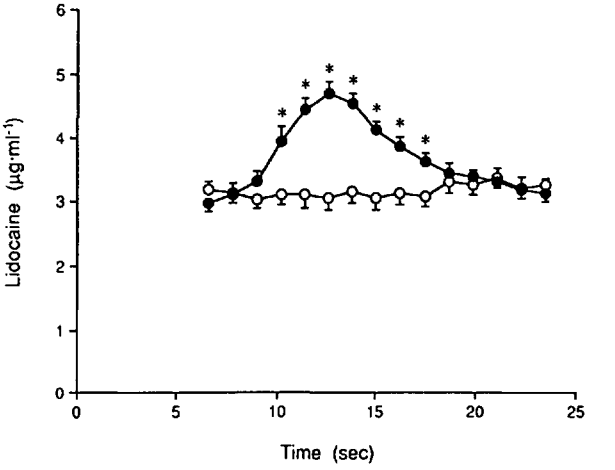

FIGURE 2 Concentration *versus* time curves of lidocaine after bolus injection. O—O: control; ●—●: bupivacaine. $n = 7$. *$P < 0.05$ compared with control.

TABLE Physiological data

	Control ($n = 7$)	*Bupivacaine* ($n = 7$)
Weight (kg)	3.4 ± 0.1	3.3 ± 0.1
pH	7.39 ± 0.02	7.38 ± 0.02
$PaCO_2$ (mmHg)	33.5 ± 0.8	33.9 ± 0.9
PaO_2 (mmHg)	159.3 ± 7.7	170.5 ± 8.9
SBP (mmHg)	116 ± 3	114 ± 3
DBP (mmHg)	92 ± 2	87 ± 3
CO ($ml \cdot min^{-1}$)	505.4 ± 31.0	506.3 ± 12.5

$PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; SBP: systolic blood pressure; DBP: diastolic blood pressure; CO: cardiac output.

Discussion

The present study demonstrates that bupivacaine displaces lidocaine from the lung *in vivo*. Displacement of one bound drug by another reflects competition between the two drugs. Post *et al.* reported displacement of nortriptyline from the swine lung by lidocaine,[9] and Jorfeldt *et al.* reported displacement of mepivacaine from the human lung by lidocaine.[10] But, in these reports, it was not clear whether displacement was a result of competition, because they were uncontrolled studies. We performed this controlled experiment, in which the control group received a bolus injection of saline after one hour of lidocaine infusion, and demonstrated that displacement was the result of competition.

The competitive displacement indicates that drug binding to the lung is not particularly specific. Drugs most effectively bound to lung tissue are basic amines with high lipophilicity.[11] For example, among analgesics, morphine with lower pKa and less lipophilicity is hardly af-

fected by passage through the human lung, but more lipophilic drugs with higher pKa, such as meperidine and fentanyl, are extensively taken up in the lung during the first passage.[12] Local anaesthetics are also basic amines with high lipophilicity,[13] and are extensively taken up in the lung.[2-5] The total uptake during first passage through the lung for lidocaine and bupivacaine was reported to be 64%[4] and 81%[5] of the injected dose, respectively.

In vitro studies using lung slices have previously shown that the uptake of lidocaine in lung tissue is inhibited by the presence of bupivacaine.[6] This type of competition has also been demonstrated *in vivo*; Roerig *et al.* reported decreased first pass uptake of fentanyl in patients receiving chronic propranolol therapy.[14] But Jorfeldt *et al.* reported that uptake of lidocaine in the lung was not affected by mepivacaine infusion.[10] The latter suggested that the concentration of mepivacaine in blood was not sufficient to compete with binding of lidocaine to lung tissue. We employed a higher dose of lidocaine infusion (10 $mg \cdot kg^{-1} \cdot hr^{-1} \times 1$ hr) than the dose of mepivacaine infusion in Jorfeldt's study (0.25 $mg \cdot kg^{-1} \cdot hr^{-1} \times 10$–12 min). The concentration of lidocaine in blood at the time of bupivacaine injection (3.0 ± 0.1 $\mu g \cdot ml^{-1}$) was also higher than the mepivacaine concentration in their study (about 2 $\mu g \cdot ml^{-1}$).

We employed the time when 95% of the total amount of ICG had passed through the lung for the calculation of DLID. It was impossible to determine the time when the injectate first passed through the lung because of recirculation. The time for 95% of the ICG to pass through the lung has been employed previously to calculate first pass uptake of some drugs through the lung.[3-5,12] First pass uptake could be compared regardless of cardiac output. Employing this time to calculate DLID, this could also be compared regardless of cardiac output. Post *et al.* calculated the amount of nortriptyline displaced after bolus injection of lidocaine[9] but their calculation was confined to the 9.5-sec period after the start of the increase of nortriptyline concentration.

The amount of lidocaine displaced during the first passage of bupivacaine through the lung was 92.3 ± 9.7 μg. This is small compared with the rate of lidocaine infusion (10 $mg \cdot kg^{-1} \cdot hr^{-1}$) and with the bolus dose of bupivacaine (1 $mg \cdot kg^{-1}$) probably because the volume of rabbit lung tissue is so small that the capacity for lidocaine in the lung is also small. The average weight of the lung is about 5 $g \cdot kg^{-1}$ in rabbit,[15] and about 20 $g \cdot kg^{-1}$ in man.[16] Therefore human lung would take up more lidocaine than the rabbit lung, and the amount of lidocaine displaced, under the same conditions, would be large.

In clinical practice, displacement of lidocaine from the lung may occur when bupivacaine is administered epidurally after continuous epidural injection of lidocaine, because large amounts of local anaesthetics are used to produce epidural block and their absorption is rapid. Attention should be paid to the potential risk of toxic reactions not only to injected bupivacaine but also to lidocaine displaced from the lung. Further investigation is indicated.

In conclusion, bupivacaine was found to displace lidocaine from the lung *in vivo*. Although the amount of lidocaine displaced during the first passage of bupivacaine through the lung was small in rabbits, attention should be paid to the potential hazard of an unexpected rise of lidocaine concentration in the blood when bupivacaine is used in combination with lidocaine in man.

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