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REGIONAL DISTRIBUTION OF ^{11}C-LABELED LIDOCAINE, BUPIVACAINE, AND ROPIVACAINE IN THE HEART, LUNGS, AND SKELETAL MUSCLE OF PIGS STUDIED WITH POSITRON EMISSION TOMOGRAPHY

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ABSTRACT

The regional myocardial uptake and kinetics of ^{11}C-lidocaine, ^{11}C-bupivacaine, and ^{11}C-ropivacaine were examined in the pig, utilizing positron emission tomography to determine whether disproportionate distribution exists among these agents.

The three drugs were rapidly distributed to the myocardium and lung with mean peak radioactivities occurring between 0·35 and 0·48 min post-injection in myocardium and 0·35 and 0·65 min in lung. Radioactivities peaked later in skeletal muscle than in the myocardium and lung, occurring between 1·1 and 2·7 min post-end injection. Blood radioactivities for bupivacaine and ropivacaine were significantly higher than those of lidocaine, whereas myocardial, lung, and muscle uptakes for the three agents were not significantly different. Myocardium–blood partition coefficients were similar for bupivacaine and ropivacaine (0·55 and 0·49 respectively), while it was three times higher for lidocaine (1·4). A similar relationship existed for skeletal muscle– and lung–blood partition coefficients. Bupivacaine and ropivacaine $t_{1/2z}$ in skeletal muscle were significantly longer than those of lidocaine.

The results of this study indicate that the increased cardiotoxicity associated with bupivacaine does not appear to be related to disproportionate distribution in the myocardium when compared to lidocaine and ropivacaine.

KEY WORDS: local anesthetics; lidocaine; bupivacaine; ropivacaine; myocardial uptake; tissue distribution; positron emission tomography (PET)

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INTRODUCTION

The advent of techniques such as positron emission tomography (PET) has created the opportunity to study significant theoretical and practical issues related to the pharmacokinetics and toxicokinetics of various drugs. For example, a comprehensive physiologic pharmacokinetic model was developed to describe lidocaine pharmacokinetics over 20 years ago.[1] This model was used to predict the time course of lidocaine in tissues such as lung, blood, and muscle. The methodologies available when this model was developed essentially precluded repeated sampling of any tissue, and thereby the experimental verification of the time course of tissue levels of drug was not practical. PET scanning techniques provide a state of the art method to approach this issue, since it allows the evaluation of the time course of drug distribution simultaneously in several tissues.

Research examining the acute systemic toxicity of local anesthetics has recently focused on the long-acting amino-amide agents, in particular bupivacaine. Substantial evidence in the form of clinical reports[2–6] and studies in laboratory animals indicate that bupivacaine is more cardiotoxic than other amino-amide local anesthetic agents such as lidocaine, mepivacaine, and the new agent ropivacaine.[7–16] Acute systemic toxicity in humans is generally associated with the accidental intravascular injection of local anesthetic during a regional anesthetic procedure, such as epidural blockade. The resultant sudden cardiovascular collapse and ventricular arrhythmias, including ventricular fibrillation, are sometimes associated with difficult and prolonged resuscitations.[4]

The mechanisms underlying the increased cardiovascular toxicity and arrhythmogenicity of bupivacaine is unclear. There is, however, substantial evidence indicating a direct myocardial effect.[15–20] Factors that may result in increased cardiotoxicity and difficult, prolonged resuscitations include the possibility that bupivacaine has a higher affinity for the myocardium and slower washout than other amino-amide local anesthetics. The current study was initiated to examine the regional distribution and kinetics in the heart, blood, skeletal muscle, and lung of N-[^{11}C-ethyl]-lidocaine, N-[^{11}C-butyl]-bupivacaine, and N-[^{11}C-propyl]-ropivacaine after an intravenous bolus injection in the anesthetized pig, utilizing PET technology. This technique has been successful in examining the distribution of radiolabeled compounds in the brain and spinal cord of the monkey[21,22] and myocardial energy metabolism in swine.[23]

METHODS AND MATERIALS

Radionuclide production and organic synthesis

The radionuclide, ^{11}C, was produced at the Tandem accelerator, the Svedberg Laboratory, University of Uppsala, by bombarding nitrogen gas

with a 10 MeV beam of protons. The ^{11}C was obtained as ^{11}C-carbon dioxide which, after trapping in a 4 Å molecular sieve, was used in a series of steps to give 1-^{11}C-ethyl iodide, 1-^{11}C-butyl iodide, and 1-^{11}C-propyl iodide. These were used to alkylate the corresponding N-dealkylated analogues of lidocaine, bupivacaine, and ropivacaine respectively in solvent mixtures of dimethyl sulfoxide and dimethyl formamide. After purification by liquid chromatography, the appropriate fractions were collected and analyzed for identity, and chemical, and radiochemical purity ($>95\%$) using reversed phase liquid chromatography with a combination of radiochemical and UV detection. The ^{11}C-labeled local anesthetics were dissolved in saline and filtered through a 0·22 μm filter unit. The radioactive dose varied from 21·4 to 130·0 MBq for the three agents. The total dose of actual local anesthetic administered to the pig was in the range of 50–200 μg. This dose is far less than the clincial dose and was chosen because it provided sufficient radioactivity to study distribution, without drug-induced physiologic changes. The half life of ^{11}C is 20 min, and meaningful measurements of radioactivities utilizing PET can be made for 40–60 min.

Animals

Approval of the Regional Animal Ethics Committee was obtained. Five healthy swine, having a mean weight ($\pm$SD) of 17·5 ($\pm$3·1) kg, were used. Animals were sedated with 300 mg pentobarbital ip, and anesthesia was induced with 500 mg ketamine iv. A continuous iv infusion consisting of chlormethiazole 8·0 mg mL^{-1} and pancuronium bromide 0·04 mg mL^{-1} was administered at a rate of 144 mL h^{-1} via an adjustable-rate infusion pump. Fentanyl 0·2 mg was given iv prior to surgery. The abdominal aorta and inferior vena cava were catheterized via the femoral vessels and used for arterial blood pressure monitoring and venous blood sampling. A jugular vein was also catheterized for drug administration. A urinary bladder catheter was surgically implanted for continuous bladder drainage. Leader II electrocardiogram, heart rate, and arterial blood pressure were continually monitored on a visual display oscilloscope. All animals were intubated and mechanically ventilated with oxygen-enriched air. A sternotomy was performed to allow exact location of the heart for positioning of the pig in the PET apparatus. Arterial blood gases were frequently measured to assure normal pH and blood gas values.

Experimental procedure

After the pig had been fixed in a supine position on a cradle in the PET camera such that the entire heart could be viewed, an injection of a low dose of ^{11}C palmitate was made. This substance has a high utilization as an energy substrate in myocardial tissue and provides an exact localization of the

myocardium on the PET display screen. The delineation of the heart muscle was made at this time for future reference in other portions of the study. Approximately 1 h after the injection of ^{11}C-palmitate, one of the radiolabeled local anesthetic agents was rapidly injected (2–4 s) as a 5·0 mL bolus into the jugular vein, and followed immediately by a rapid saline flush. Three pigs received two or three local anesthetic agents with at least 2 h between each drug injection. The other pigs received only one agent. The blood and tissue radioactivities measured just prior to injection indicated insignificant residuals. Venous blood samples (5·0 mL) were drawn from the vena cava for the measurement of radioactivity in a well counter at 1, 2, 3, 5, 10, 20, 30, and 40 min after injection of ^{11}C-local anesthetics.

Positron emission tomography

The positron emission tomography (PC 384-3B, Scanditronix, Uppsala, Sweden) was equipped with two detector rings which allowed for simultaneous measurement of the radioactive distribution in three transaxial slices interspaced with 13 mm. The tomograph has a spatial resolution in the plane of 8 mm. The caudal transection included the apex of the heart, the mid-transection consisted of a section through the center of the heart, and the cranial transection included the base of the heart and possibly the atria. Only the left ventricular free wall was utilized for quantitative determinations, generally found on the mid-transection. The other areas of interest were the lung and skeletal muscle of the back. Images were initially collected for ten 12 s periods followed by 12–15 40 s periods and finally be eight 300 s after the injection of ^{11}C-labeled local anesthetics. The variation in collection times was to compensate for the declining available radioactivity.

Calculations

After reconstruction of images, radioactivity measured by PET was corrected for the physical decay for the radionuclide to the time of injection. The calculation of the uptake was performed using the following formula:

$$\text{uptake} = \frac{\text{measured radioactivity (nanocuries per cubic centimeter)}}{\text{administered dose of radioactivity (nanocuries) per gram body weight)}}$$

Thus an uptake of 1·0 corresponds to a homogeneous distribution of radioactivity in the entire body, assuming that $1\,\text{cm}^3 = 1\,\text{g}$. Total radioactivity of weighed blood samples were measured in a well counter. This measured radioactivity was also corrected for physical decay and also expressed as uptake. Values of uptake from the mid-transection or caudal transection were used for the determination of tissue uptakes.

Partition coefficients of drug between tissues and blood were calculated by dividing tissue radioactivity by blood radioactivity using values obtained 10–40 min after injection. The half life ($t_{1/2z}$) for drug in blood, lung, myocardium (left ventricular free wall), and muscle were determined using linear regression calculations, termed the elimination half life. Elimination half lives were calculated from data obtained between 5 and 40 min post-injection.

Statistics

Although the number of animals utilized in this study is small, multiple measurements strengthen the data analysis. Additionally, the small variance in the data between animals implies a reasonable consistency in the experiments. Uptake values for blood, myocardium, lung, or muscle were compared between drugs for each sample time. Additional comparisons were made for uptake values between tissues within a drug group. The same comparisons were performed for the partition coefficients and elimination half lives. Analysis of variance and Tukey test were used. Significance was attained at the $p \leqslant 0{\cdot}05$ level. Data presented are mean $\pm$ standard deviation of the mean unless otherwise noted.

RESULTS

Heart rate, and systolic, diastolic, and mean arterial blood pressure remained stable in all animals throughout the experimental period. No abnormalities in the electrocardiogram were observed during any portion of the study.

Blood kinetics of ^{11}C-local anesthetics

The rapid iv bolus injection of ^{11}C-local anesthetic agents resulted in peak blood activities occurring within seconds of ending the injection. Blood radioactivities of ^{11}C-bupivacaine and ropivacaine (Figure 1) demonstrated a rapid decline during the first 5–10 min after the injection. The lidocaine curve did not clearly show this, perhaps because the rapidly declining portion of the curve occurred prior to the first blood sample measurement at 1 min. This rapid initial distribution was followed by a more gradual decline for the remainder of the experiment. Blood radioactivities corrected for decay at each sample time for ropivacaine and bupivacaine were not significantly different from each other. However, these data for both drugs were significantly higher than those of lidocaine (Figure 1). Mean blood elimination half life ($t_{1/2z}$) ranged from 43·4 min for ropivacaine to 80·2 min for lidocaine; these values were significantly different from each other (Table 1).

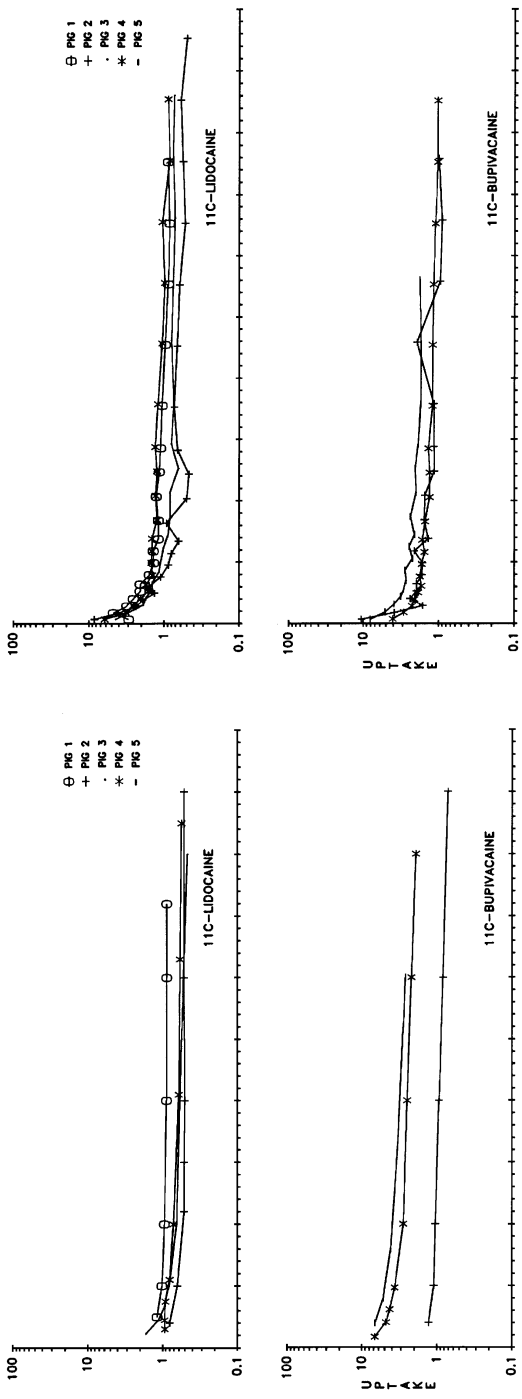

Figure 1. Blood uptake: individual animal blood uptake values for ^{11}C-lidocaine, ^{11}C-bupivacaine, and ^{11}C-ropivacaine. Data are derived from weighed blood samples analyzed in a well counter

Figure 2. Myocardial uptake: individual animal data for uptake ^{11}C-lidocaine, ^{11}C-bupivacaine, and ^{11}C-ropivacaine by the left ventricular free wall as measured by PET

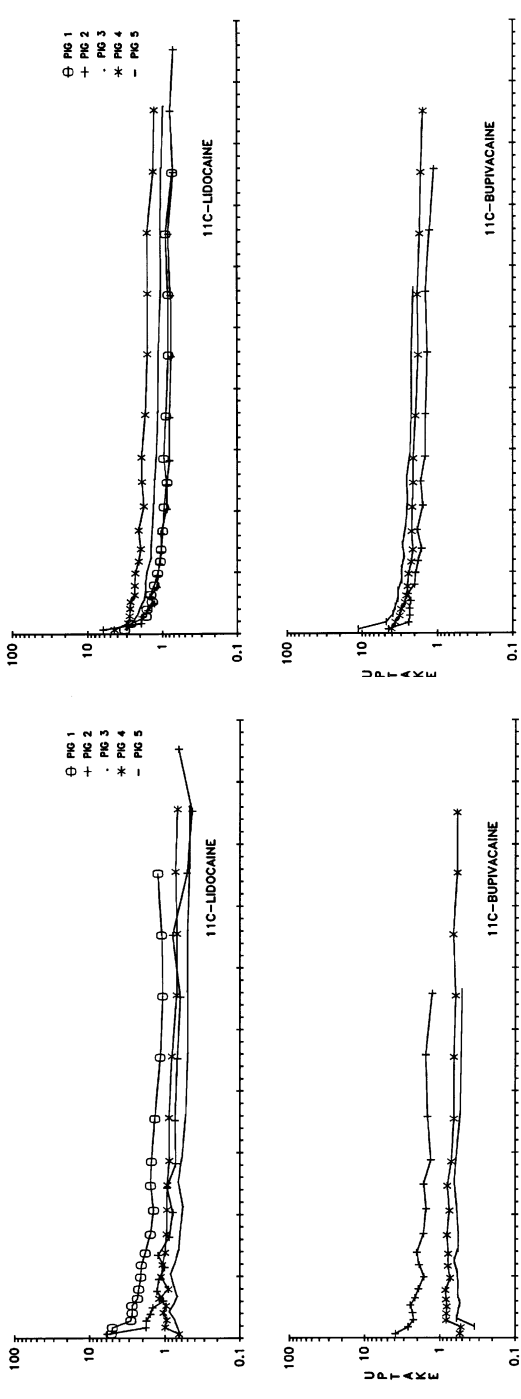

Figure 3. Skeletal muscle uptake: individual animal data for uptake of ^{11}C-lidocaine, ^{11}C-bupivacaine, and ^{11}C-ropivacaine by skeletal muscle as measured by PET

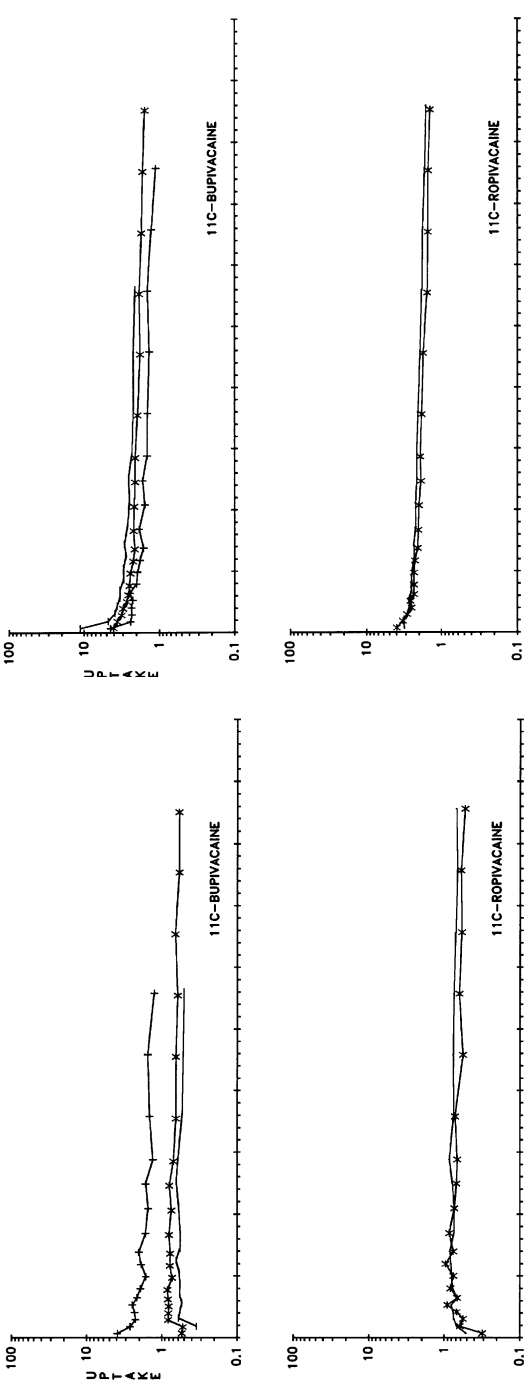

Figure 4. Lung uptake: individual animal data for uptake of ^{11}C-lidocaine, ^{11}C-bupivacaine, and ^{11}C-ropivacaine by lung as measured by PET

Table 1. Elimination half life (min) determined from the linear regression calculation of the terminal phase of the blood and tissue curves. Parenthetical values are mean ± SD

	Blood	Myocardium	Skeletal muscle	Lung
Lidocaine	86·6	40·1	43·3	61
	99	49·8	38·1	67·2
	63	81	53·3	70·7
	72	51·7	56·8	59·2
	(80 ± 16)	(56 ± 18)	(48 ± 9)[a]	(65 ± 5)
Ropivacaine	45·9	54·6	94·9	63·8
	40·8	56·8	78·5	57·6
	(43)*	(56)	(87)[ab]*	(61)
Bupivacaine	62·4	69·3	77	58·2
	53·3	63	88·8	69·8
	39·2	53·3	80	50·9
	(52 ± 12)	(62 ± 8)	(82 ± 6)[a]*	(60 ± 10)

*$p < 0{\cdot}05$: significantly different from lidocaine.
[a]$p < 0{\cdot}05$: significantly different from blood.
[b]$p < 0{\cdot}05$: significantly different from myocardium.

Table 2. Mean ± SD peak uptake values. Parenthetical values are times to peak uptake in minutes

	Myocardium	Lung	Skeletal muscle
Lidocaine $N = 4$	5·95 ± 1·8	4·2 ± 1·5	3·3 ± 2·6
	(0·48 ± 0·26)	(0·35 ± 0·01)	(1·5 ± 1·4)
Ropivacaine $N = 2$	3·7[a]	3·6[a]	0·86
	(0·36)[a]	(0·65)[a]	(2·7)
Bupivacaine $N = 3$	7·6 ± 3·3	6·6 ± 4·1	1·2 ± 1·8
	(0·35 ± 0·02)	(0·35 ± 0·2)	(1·1 ± 0·7)

[a]$p < 0{\cdot}05$: significantly different from ropivacaine skeletal muscle.

Table 3. Mean ± SD partition coefficients of myocardium–blood, skeletal muscle–blood and lung–blood

	n	Myocardium	Skeletal muscle	Lung
Lidocaine	14	1·40 ± 0·30[a]	1·26 ± 0·21[a]	2·04 ± 0·39[abc]
Ropivacaine	8	0·49 ± 0·05[b]	0·30 ± 0·05	0·78 ± 0·09[bc]
Bupivacaine	7	0·55 ± 0·07[b]	0·23 ± 0·06	0·75 ± 0·07[bc]

n, number of uptake values utilized.
[a]$p < 0{\cdot}05$: significantly different from ropivacaine and bupivacaine.
[b]$p < 0{\cdot}05$: significantly different from muscle.
[c]$p < 0{\cdot}05$: significantly different from myocardium.

Tissue distribution and kinetics of ^{11}C-local anesthetics

Radioactivities from the ^{11}C-local anesthetics in the left ventricular free wall (myocardium) peaked within seconds after the injection (Table 2). Generally, myocardial kinetics followed a trend similar to that in blood, with a rapid decline over the first 3–5 min, followed by a gradual decline (Figure 2). There were no consistent statistically significant differences between drugs for myocardial uptake at each sample time.

Analysis for differences in peak uptake within a drug group between myocardium, lung, and muscle showed no significant difference in the lidocaine- and bupivacaine-treated pigs. Within the ropivacaine group, the peak uptake in the muscle was significantly lower and occurred later than the myocardium and lung uptake (Figures 2–4).

Lung uptake (Figure 4) values followed a trend similar to that observed in the myocardium. There were no consistent statistically significant differences between drugs for lung uptake at each sample time.

Partition coefficients of ^{11}C-local anesthetics. The mean partition coefficient (Table 3) of myocardium–blood was two and one-half times higher for lidocaine ($1{\cdot}40 \pm 0{\cdot}3$) as compared to bupivacaine ($0{\cdot}55 \pm 0{\cdot}07$) and ropivacaine ($0{\cdot}49 \pm 0{\cdot}05$). Similarly, the skeletal muscle–blood partition coefficient was significantly higher for lidocaine ($1{\cdot}26 \pm 0{\cdot}21$) as compared to ropivacaine ($0{\cdot}30 \pm 0{\cdot}05$) and bupivacaine ($0{\cdot}23 \pm 0{\cdot}06$). Lung partition coefficients for lidocaine was also significantly higher ($2{\cdot}04 \pm 0{\cdot}39$) than for ropivacaine ($0{\cdot}78 \pm 0{\cdot}09$) and bupivacaine ($0{\cdot}75 \pm 0{\cdot}07$). All three drugs had significantly higher partition coefficients for lung than for muscle and myocardium. Ropivacaine and bupivacaine myocardium–blood partition coefficients were also significantly higher than for muscle.

Elimination half life ($t_{1/2z}$) of ^{11}C-local anesthetics. Mean elimination half life ($t_{1/2z}$) for myocardium and lung ranged from 56 and 65 (lidocaine) to 62 and 60 min (bupivacaine). In muscle, the $t_{1/2z}$ for bupivacaine and ropivacaine were similar at 82 and 87 min respectively while significantly different from lidocaine at only 48 min. Muscle $t_{1/2z}$ for ropivacaine and bupivacaine were also significantly longer than in blood. Within the lidocaine group, no differences were found between tissues (Table 1).

DISCUSSION

High ^{11}C-radioactivities were seen in the heart, a highly perfused organ, very rapidly after the injection. Myocardial uptake values were similar between drugs, indicating that no increase or differential affinity for the myocardial tissue existed among these drugs. A similar trend was found for lung uptake.

Initial peak muscle uptake values for the three local anesthetics occurred later than those in the myocardium, reaching significance only in the ropivacaine group. Although with lidocaine and bupivacaine initial uptake time is skeletal muscle did not attain significance, these values were three to four times longer than those observed in myocardium and lung. These differences in time to peak uptake between tissues may be related to differences in tissue blood flow and tissue binding. Highly perfused organs such as the heart and lung receive more drug per unit time than tissue of lower perfusion such as skeletal muscle (at rest). Our findings of similar trends in the slow-decay portion of the radioactivity in blood and myocardium have also been noted in rats given lidocaine.[24]

Theoretical concepts of pharmacokinetics dictate that ultimately the plasma concentration and the tissue concentration of drug will decline in parallel, thus exhibiting identical $t_{1/2z}$ values. However, the rapid radioactive decay of ^{11}C ($\approx$20 min), the goals of our experiments to study the acute regional distribution of local anesthetic after an iv bolus injection, and the testing of a previously published physiologic pharmacokinetic model for lidocaine mandated the essential study design which was employed. Therefore, the $t_{1/2z}$ data should be viewed as an apparent half life of drug over the experimental time of these studies. While estimates of these parameters are not rigorous in the pharmacokinetic context, they are of potential value in understanding the comparative acute cardiotoxicity of these drugs. Hence, they represent a relevant point of discussion.

Electrophysiological studies in isolated cardiac cells have shown that bupivacaine and ropivacaine have longer washout times as compared to lidocaine.[15,25] Reports of difficult and prolonged resuscitations after bupivacaine overdosage may be related to the differences in myocardial washout times for these agents. However, in the current study, no statistical differences were found between drugs for myocardial $t_{1/2z}$ or for lung $t_{1/2z}$.

Muscle $t_{1/2z}$ for bupivacaine and ropivacaine were significantly longer than that of lidocaine. The octanol–water partition coefficients of bupivacaine and ropivacaine are higher than that of lidocaine. These properties may give a higher affinity to tissue lipids for the highly lipophilic agents.

Corrected blood radioactivities for bupivacaine and ropivacaine were significantly higher than those of lidocaine at any given time during the experiment. This may be explained by a larger volume of distribution and higher total body clearance of lidocaine as compared to bupivacaine or ropivacaine.

In dogs receiving a 15 min iv infusion of local anesthetic, the total body clearance for lidocaine was 56 mL min^{-1} kg^{-1}, greater than that of bupivacaine, which was 32 mL min^{-1} kg^{-1}, and that of ropivacaine, which was 41 mL min^{-1} kg^{-1}.[26,27] Similar relationships for clearance of lidocaine and bupivacaine have also been reported in the rabbit.[28] Mean volume of distribution in the dog of lidocaine (2.3 L kg^{-1}) was found to be two times higher than that of either bupivacaine or ropivacaine (1.2 and 1.1 L kg^{-1}

respectively).[26,27] Based on the data from the current study, it appears that the kinetics of the three local anesthetics studied have a similar relationship to that reported in the dog.[26,27]

Myocardial–blood coefficients of 1·75 for lidocaine have been reported for sheep by Morishima *et al.*,[29] and a bupivacaine myocardial–blood coefficient of 0·75 has been reported by Goehl and co-workers in the monkey.[30] These are similar to those in the current study in pigs. However, in general, tissue–blood partition coefficients from the current study are different from those reported previously in other animal species. Myocardium–blood partition coefficients for lidocaine in the rat, 5·0;[31] rabbit, 5·4;[32] dog, 2·6;[33] sheep, 2·7;[34] and man, 3·5;[35] average two to four times higher than seen in the current study in the pig, 1·40. Similarly, partition coefficients for bupivacaine in rabbits, 1·8 and 8·5,[36,32] and sheep, 3·5 and 4·2,[29,34] were three to eight times higher than seen in the pig, 0·55. This variability may not be unexpected, given the great differences in pharmacokinetics between the various animal species[37] and methodological differences. PET data include radioactivity in the myocardial cells as well as in extracellular space and blood within the tissue.

Lidocaine myocardium, lung, and muscle $t_{1/2z}$ were similar to each other. Blood lidocaine $t_{1/2z}$ was about 40% longer. The longer calculated $t_{1/2z}$ for lidocaine in blood may be related to the production of a radioactive metabolite. Additionally, lidocaine is more rapidly metabolized by liver enzymes than bupivacaine or ropivacaine, and the production of lidocaine metabolites would be expected to occur earlier than for the other two drugs, especially during the relatively short experimental time of this study. It is therefore feasible that the production of a radioactive metabolite caused the measured radioactivities to remain high, thus resulting in a falsely prolonged blood $t_{1/2z}$. Monoethylglycinexylidide (MEGX) is a major metabolite of lidocaine and is less lipid soluble than lidocaine. Therefore, it may not penetrate the tissue as easily, explaining why the $t_{1/2z}$ in muscle, lung, and myocardium were not prolonged, as was the case in blood. On the other hand, it is difficult to determine whether the radioactive label remained on the MEGX or on the cleaved alkyl group.

Some mention of the role of the lung should be made with regard to the cardiotoxicity of local anesthetic agents. It has been demonstrated in pigs and man that a large fraction of lidocaine in the blood is rapidly taken up by the lungs.[38] This rapid, initial uptake after iv injection may play a role in buffering the exposure of the brain and heart to large concentrations of local anesthetic after intravenous administration. However, the rapid uptake by the lung is also accompanied by a rapid release of drug back into the circulation, such that the lung's initial buffering effect is completed by 10–15 s after the injection is made.[38] These findings are similar to those seen in the radioactivities of the lung in the current study (Figure 4). Peak lung radioactivities occurred immediately after the injections. The first PET recording made over a 12 s period following the injection showed lung radioactivities beginning to decline. This rapid declining trend continued for several minutes.

Drug distribution and clearance are affected by organ blood flow, which can be altered by changes in cardiac output or vascular resistance. Based on previously reported results in the dog, the assumption was made that the dose of parent local anesthetic was so small that no drug-induced changes in cardiovascular status would result.[8,11,14] Indeed, although the animals were anesthetized, basal cardiac and blood pressure conditions were similar in each animal and remained constant for the duration of the experiment.

Several caveats must be noted with regard to this study. The studies were designed to examine the regional pharmacokinetics associated with the rapidly occurring phenomenon of acute cardiovascular toxicity of intravenously administered local anesthetics. The study is based on the measurement of *in vivo* uptake of radiolabeled pharmaceutics. Care must, therefore, be exercised in interpreting the results based solely on the measurement of radioactivities. In this study, however, there are support data from previously published work which employed more classical pharmacokinetic techniques.

It is possible that the distribution of metabolites of lidocaine may be different than those of the analogous drugs bupivacaine and ropivacaine. Although it was not possible to evaluate this in the current study, this possibility would make the comparison of tissue uptakes between drugs difficult. However, in the clinical setting and in animal studies the acute cardiovascular toxicity of these agents occur rapidly, prior to the point at which metabolites would play an important role.

In summary, we have demonstrated the usefulness of positron emission tomography for the evaluation of relative tissue distribution and kinetics associated with rapidly occurring phenomena such as acute systemic toxicity. The results indicate that lidocaine, bupivacaine, and ropivacaine enter the myocardium and lung very rapidly after an in bolus injection, and the muscle lags slightly in its uptake of these drugs. These findings support previously published simulations of distribution.[1] No evidence was found to indicate that any of these agents enters the myocardium in a disproportionately greater amount than the others, or diffuses back into the blood compartment at measurably different rates. These results are in agreement with previously reported results in sheep.[39] The current study indicates that the increased cardiotoxicity and arrhythmogenic potential of bupivacaine compared to ropivacaine and lidocaine are not related to an unusually high quantitative myocardial distribution, but are more likely related to distinctly different effects upon the electrophysiology of the myocardial cell or to a combination of direct myocardial effects and other related pharmacologic effects.

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