The Effect of Lipid Emulsion on Pharmacokinetics and Tissue Distribution of Bupivacaine in Rats

Kejian Shi, MD,* Yun Xia, MD, PhD,† Quanguang Wang, MD,* Yiquan Wu, MD,* Xiaoxi Dong, MD,‡ Chanjuan Chen, BS,* Wan Tang, BS,* Yujian Zhang, MD,* Mengxu Luo, BS,* Xianqin Wang, PhD,‖ Thomas J. Papadimos, MD, MPH,† and Xuzhong Xu, MD*

BACKGROUND: While lipid emulsion may reverse the systemic toxicity of bupivacaine, the pharmacokinetics and tissue distribution of bupivacaine after lipid emulsion infusion are not clear. In this study, we assessed the influence of lipid emulsion administration on the pharmacokinetics and tissue distribution of bupivacaine.

METHODS: Rats in the lipid group were administered IV bupivacaine at the rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$ for 4 minutes, and then were treated with an infusion of 30% lipid emulsion at the rate of 3 $mL \cdot kg^{-1} \cdot min^{-1}$ for 5 minutes; saline was substituted in the control group ($n = 6$ for pharmacokinetics). We then randomly assigned 100 rats into the lipid group and control group ($n = 50$ for distribution). The toxicity model and treatment were the same as the pharmacokinetic portion. Plasma and tissues including brain, heart, liver, spleen, lung, kidney, omentum, and muscle were collected. The plasma concentration and tissue content of bupivacaine were measured by a liquid chromatography-tandem mass spectrometric method. A 2-compartmental analysis was performed to calculate the pharmacokinetics of bupivacaine.

RESULTS: All data are shown as mean ± SD. After treatment with the lipid emulsion, t1/2β of bupivacaine in the lipid group was significantly shorter (110 ± 25 minutes vs 199 ± 38 minutes, $P = 0.001$), the clearance was higher (14 ± 4 $mL \cdot mg^{-1} \cdot kg^{-1}$ vs 9 ± 4 $mL \cdot mg^{-1} \cdot kg^{-1}$, $P = 0.038$), and the t1/2α was longer than that of the control group (4 ± 1 minutes vs 2 ± 1 minutes, $P = 0.014$); the K12 in the lipid group was less than that of the control group (0.13 ± 0.04 vs 0.32 ± 0.13, $P = 0.011$). In the lipid group, the bupivacaine content in heart, brain, lung, kidney, and spleen was lower than that in the control group, but higher in the liver at 20, 30, and 45 minutes.

CONCLUSION: The lipid sink phenomenon was observed in this study. The use of a lipid emulsion accelerated the elimination of bupivacaine. (Anesth Analg 2013;116:804–9)

Accidental intravascular injection of bupivacaine can cause serious cardiac and/or central nervous system toxicity. Weinberg et al.[1] reported that infusion of a lipid emulsion played a significant role in reducing the cardiac toxicity of bupivacaine, which led to the postulation of the lipid sink theory. Subsequently, many animal studies[2–6] and case reports[7,8] have indicated that lipid emulsions are an effective treatment to reverse local anesthetic toxicity.

The toxicity of bupivacaine is closely associated with plasma concentration and tissue content. The lipid sink theory supports the premise that the lipid emulsion creates an expanded lipid phase that binds bupivacaine and decreases its free concentration. Litz et al.[9] followed local anesthetic levels after infusion of a lipid emulsion during the successful resuscitation of a cardiac arrest induced by mepivacaine and prilocaine.[9] Their report indicated a more rapid decline of local anesthetic than in prior reports.[10,11] Mazoit et al.[12] had that lipid emulsions showed a strong affinity for bupivacaine which binds it rapidly and completely. Long-chain fatty acids, which are the main components of a lipid emulsion, are easily captured by liver.[13] Jang et al.[14] showed that 2-(allylthio) pyrazine in lipid emulsion had faster clearance (CL) and a higher affinity for the liver, compared with that in solution. Drugs with a lipid carrier usually have good liver targeting.[15,16] We made the assumption that an infusion of a lipid emulsion tends to deliver bupivacaine to the liver.

Therefore, it can be hypothesized that lipid emulsion plays an important therapeutic role, through the lipid sink effect, in the early stages of bupivacaine toxicity. This effect will cause the bupivacaine concentration of plasma and the tissue content of organs to increase, except for the liver, thereby accelerating its elimination. Accordingly, we designed a rat model using lipid emulsion for the treatment of bupivacaine toxicity to determine the effect of the lipid emulsion on the pharmacokinetics and distribution of bupivacaine.

METHODS

Animal Preparation

All work was approved by Wenzhou Medical College's Animal Care and Use Committee (Wenzhou, Zhejiang, China). Healthy male Sprague–Dawley rats weighing 300 to 350 g were purchased from the animal center of the Chinese Academy of Sciences (Shanghai, China). All rats were fasted overnight for 12 hours, but were allowed to drink water. On the day of the experiment, the rats were anesthetized with

From the *Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical College, Zhejiang, China; † Department of Anesthesiology, The Ohio State University Medical Center, Columbus, Ohio; ‡Department of Anesthesiology, Ruian People's Hospital; and ‖ Analysis and Testing Center, Wenzhou Medical College, Zhejiang, China.

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Address correspondence to Xuzhong Xu, MD, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical College, 2 Fuxue Road, Wenzhou City, Zhejiang Province 325000, China. Address e-mail to xuzhong@263.net.

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an intraperitoneal injection of chloral hydrate (350 mg·kg^{-1}). Tracheal intubation was performed via tracheotomy, and the rats' lungs were mechanically ventilated with 1% to 2% sevoflurane in 100% oxygen using a rodent volume-controlled ventilator (tidal volume = 8 mL·kg^{-1}, rate = 75–80 breaths·min^{-1}, inspiratory/expiratory ratio = 2:3, HX-300, TME Technology Co, Ltd, Chengdu, China). Body temperature was maintained at 38°C to 39°C with a heating lamp. The left carotid artery was cannulated for arterial blood pressure monitoring and blood sample collection. The left internal jugular vein was cannulated for the infusion of bupivacaine, and the right internal jugular was cannulated for the infusion of the lipid emulsion or saline. Electrocardiography was performed using 3 subcutaneous needle electrodes, and the information was recorded. Hemodynamics and electrocardiographic data were recorded by a MedLab data archiving and retrieval system using U/4C051 (Nanjing Medease Science and Technology Co., Ltd, Nanjing, China). On completion of the invasive procedures, all animals were allowed to stabilize physiologically for 15 minutes.

Pharmacokinetics

Twelve male Sprague–Dawley rats were randomly divided into a lipid group and a control group (n = 6). At the end of the stabilization period (baseline time, designated Tb), bupivacaine hydrochloride (Sigma-Aldrich Co., St. Louis, MO) was infused at the rate of 2 mg·kg^{-1}·min^{-1} for 4 minutes in the left internal jugular vein. Once the infusion of bupivacaine was completed (designated 0 minutes), all rats were infused with either 30% Intralipid (Huarui Pharmaceuticals Co. Ltd., Wuxi, China) or saline at the rate of 3 mL·kg^{-1}·min^{-1} for 5 minutes through the right internal jugular vein. Blood samples of 0.5 mL were collected at time 0, 5, 10, 20, 30, 45, 60, 90, 120, 240, and 360 minutes, and the rats were then supplemented with an equal volume of saline (after blood collection). Plasma was separated from blood by centrifugation (4000 rpm, 10 minutes), and stored at −80°C for determination of bupivacaine concentrations.

Distribution of Bupivacaine

We randomly assigned 100 male Sprague–Dawley rats into 20 groups (n = 5): lipid5, lipid10, lipid20, lipid30, lipid45, lipid60, lipid90, lipid120, lipid240, lipid360, control5, control10, control20, control30, control45, control60, control90, control120, control240, and control360. Lipid 5 to 360 were the treatment groups that received lipid emulsion infusion; control 5 to 360 were the control groups that received a saline infusion. The toxicity model and treatment were the same as the pharmacokinetic portion of the study. Rats in the lipid 5 to 360 and control 5 to 360 groups were killed at 5, 10, 20, 30, 45, 60, 90, 120, 240, and 360 minutes, respectively. Tissues including brain, heart, liver, spleen, lung, kidney, omentum, and muscle were collected, frozen in liquid nitrogen, and stored at −80°C.

Measurement of Bupivacaine

A liquid chromatography-tandem mass spectrometric (Bruker Esquire; Bruker Company, Karlsruhe, Germany) method was developed and validated for the detection of bupivacaine. The parameters of liquid chromatography-tandem mass spectrometry were the same as Chen et al.'s[17] report.

Bupivacaine hydrochloride was prepared in a blank plasma or blank tissue homogenate for calibration curves within the range of 0.01 to 40 μg·mL^{-1} (μg·g^{-1} for tissue). The samples for recovery and precision measurements were prepared at 0.02, 10, and 40.0 μg·mL^{-1} (μg·g^{-1} for tissue) (n = 5, repeated for 5 days).

Frozen tissue samples of 0.2 g were homogenized with 2 mL ultrapure water. Plasma 0.2 mL or 2 mL of tissue homogenate was added to 62.5 ng of ropivacaine as an internal standard, 0.05 M KOH for alkalization, and 1 mL N-hexane and 4 mL acetoacetate for extraction of bupivacaine. The preparations were mixed with a vortex generator for 1 minute and centrifuged at 4000 rpm for 10 minutes. The upper organic phase was neutralized and acidified with 0.3 mL 1.5% HCL solution, and then mixed with a vortex generator for 1 minute, followed by centrifugation at 4000 rpm for 10 minutes. An aqueous phase subnatant of 0.25 mL was taken for the determination of bupivacaine levels.

All of the correlation coefficient values (r^2) were >0.995. The lower limit of detection for bupivacaine was 5 ng·mL^{-1}. Recovery of bupivacaine from plasma and the 8 tissues ranged from 91.9% to 112.6%. Intraday and interday relative standard deviations were <6%.

Pharmacokinetic Calculation

Pharmacokinetic parameters were calculated by a 2-compartmental analysis model using DAS Ver2.1.1 (Drug and Statistics, Mathematical Pharmacology Professional Committee of China. Shanghai, China). All the data were obtained from the end of bupivacaine infusion until the last sampling time.

Elimination half-life was designated as t1/2 and was calculated using the equation: t1/2 = 0.693/λz. The area under the blood concentration–time curve (AUC) was determined using the trapezoidal method. Apparent volume (V) of distribution was defined as the volume of body fluid that is accounted for when the drug distribution is equivalent to the drug concentration in plasma and was calculated with Vd = Dose /C. CL was defined as the apparent volume of distribution (Vd) removed from the body per unit time and was calculated by the equation: CL = Dose/AUC. K10 represents a rate constant of drug elimination from the central compartment, K12 as that from central compartment to peripheral compartment, and K21 as that from the peripheral compartment to the central compartment.

Statistical Analysis

The number of animals in each group was determined based on preliminary study (n = 3). Half-life time of bupivacaine in the lipid and control groups was 106 ± 19 minutes and 194 ± 39 minutes. We assumed a type 1 error protection of 0.05 and a power of 0.90. Six rats were required for each group. All data were analyzed using SPSS 13.0 (SPSS Inc, Chicago, IL) for Windows and presented as mean ± SD. Mean arterial blood pressure and heart rate between the 2 groups were analyzed with 2-way repeated measures analysis of variance. Pharmacokinetic parameters and bupivacaine content between the 2 groups were compared by independent-sample t test, and corrected P value was chosen when equal

variances were not assumed. $P < 0.05$ was considered to be of statistical significance. Curve fitting and bar charts were performed by GraphPad Prism v5.0 (GraphPad Software Inc., San Diego, CA).

RESULTS

Hemodynamics

Mean arterial blood pressure and heart rate in both groups are shown in Figure 1. There was no statistical significance between the 2 groups ($P = 0.444$ for mean blood pressure, $P = 0.209$ for heart rate).

Pharmacokinetics Parameters

The concentration–time curve between the 2 groups is presented in Figure 2. The comparison of pharmacokinetic parameters between the 2 groups is shown in Table 1. Compared with the control group, the lipid group had an increased t1/2α (4 ± 1 minutes vs 2 ± 1 minutes, $P = 0.014$) and bupivacaine elimination CL (14 ± 4 mL·mg^{-1}·kg^{-1} vs 9 ± 4 mL·mg^{-1}·kg^{-1}, $P = 0.038$), while exhibiting a reduced t1/2 β (110 ± 25 minutes vs 199 ± 38 minutes, $P = 0.001$) and K12 (0.13 ± 0.04 vs 0.32 ± 0.13, $P = 0.011$). The comparison of the apparent Vd, AUC (0–t), AUC (0–∞), K10, and K21 between groups demonstrated no statistical significance.

The Tissue Bupivacaine Content

Treatment with lipid emulsion decreased the bupivacaine content in the heart, brain, spleen, muscle, and lung. However, the initial bupivacaine content in the liver was increased and was then followed by a reduction in content after 2 hours. The comparison of bupivacaine content between the lipid and control groups, in 8 different organ tissues, is presented in Figure 3.

DISCUSSION

Our investigation demonstrated that after infusion of lipid emulsion, bupivacaine elimination half-life and K12 decreased, the CL rate increased, distribution half-life was prolonged, and the content in brain, myocardium, lung, kidney, spleen, and muscle was reduced. However, the bupivacaine content in the liver was increased at the time points of 20, 30, and 45 minutes.

In this study, we chose a model of bupivacaine toxicity without cardiac arrest. We resolved that using a cardiac arrest model would lead to a scenario of prolonged duration of recovery and a variability in hemodynamics,[18] especially in the face of the infusion of lipid emulsion for resuscitation whereby the determination of bupivacaine metabolism and distribution, i.e., the pharmacokinetics,

Table 1. Comparison of Pharmacokinetics Between the Lipid and Control Groups

Parameter	Lipid group	Control group	*P* value
t1/2α (min)	4 ± 1	2 ± 1	0.014
t1/2β (min)	110 ± 25	199 ± 38	0.001
Vd (L·kg^{-1})	0.26 ± 0.05	0.24 ± 0.05	0.456
CL (mL·min^{-1}·kg^{-1})	14 ± 4	9 ± 4	0.038
AUC (0–t) (mg·L^{-1}·min^{-1})	588 ± 170	800 ± 371	0.233
AUC (0–∞) (mg·L^{-1}·min^{-1})	640 ± 199	1123 ± 620	0.099
K10 (1/min)	0.05 ± 0.02	0.04 ± 0.01	0.111
K12 (1/min)	0.13 ± 0.04	0.32 ± 0.13	0.011
K21 (1/min)	0.02 ± 0.01	0.04 ± 0.03	0.170

All data are presented as mean ± SD. For each group, $n = 6$.

t1/2 = elimination half-life; Vd = volume of distribution; CL = clearance; AUC = area under the blood concentration–time curve; K10 = rate constant of drug elimination from the central compartment; K12 = rate constant of drug elimination from central compartment to peripheral compartment; K21 = rate constant of drug elimination from the peripheral compartment to the central compartment.

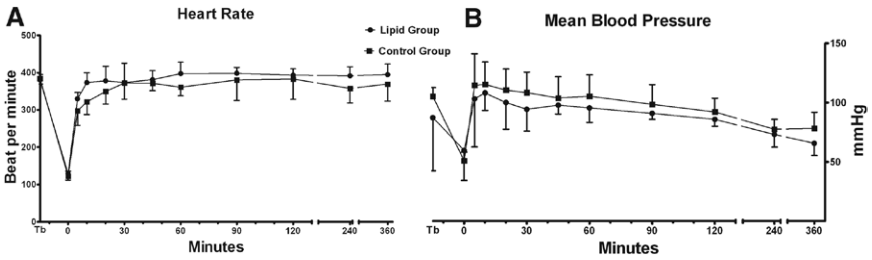

Figure 1 . Mean and 95% confidence intervals of heart rate and mean arterial blood pressure of the lipid and control groups are shown during Tb to 360 minutes, $n = 6$. There is no statistically significant difference of heart and blood pressure between the groups.

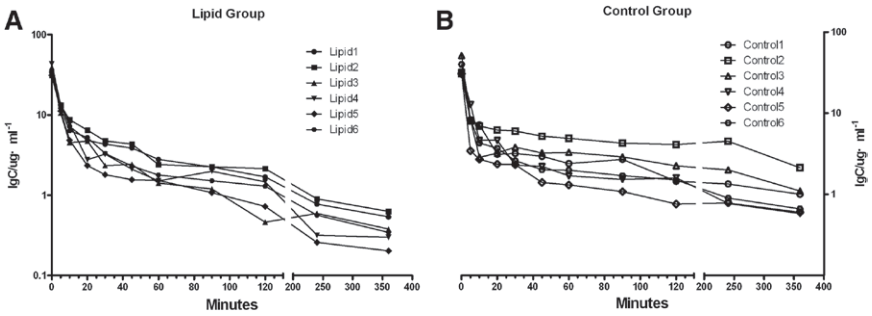

Figure 2. A, Individual plasma concentration–time profile in 6 rats in the lipid group. B, Individual plasma concentration–time profile in 6 rats in the control group. All curves are on semilogarithmic coordinates. The value in Y axis is the logarithm of value of plasma concentration.

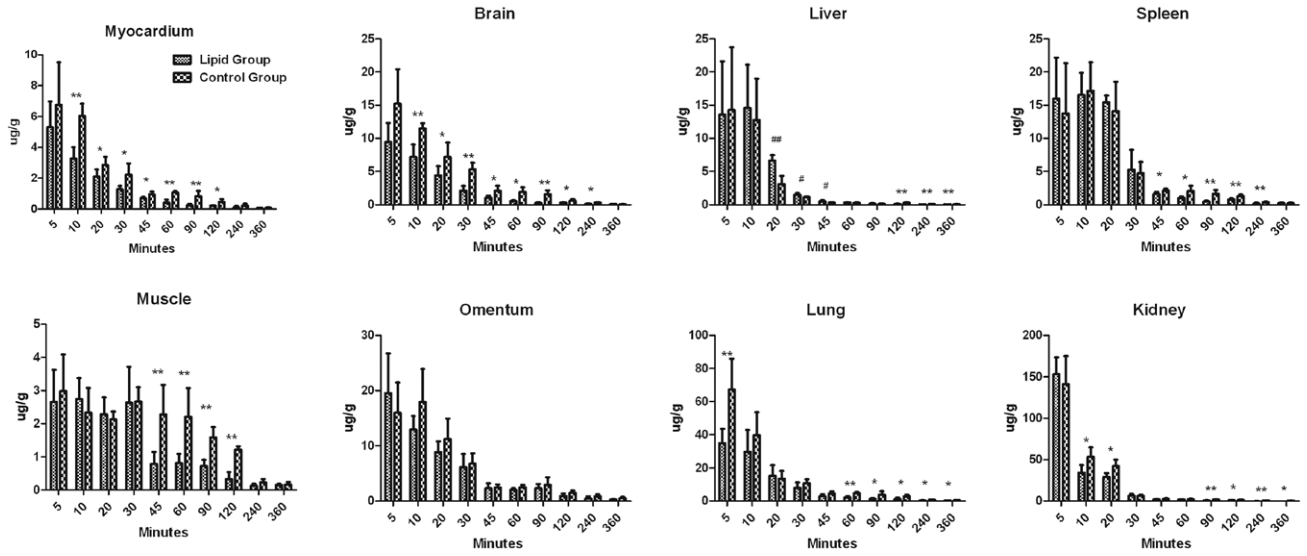

Figure 3. Concentration of bupivacaine in myocardium, brain, liver, spleen, muscle, omentum, lung, and kidney. Data are expressed as the mean ± SD. **P* < 0.05, ***P* < 0.01, content of bupivacaine was lower compared with the control group. #*P* < 0.05, ##*P* < 0.01, content of bupivacaine was higher compared with the control group. *P* value between 2 groups at 5, 10, 20, 30, 45, 60, 90, 120, 240, and 360 minutes as follows: myocardium: 0.334, <0.001, 0.045, 0.036, 0.025, <0.001, 0.005, 0.027, 0.120, 0.114; brain: 0.060, 0.002, 0.039, <0.001, 0.039, 0.011, 0.002, 0.029, 0.044, 0.645; liver: 0.895, 0.660, 0.001, 0.027, 0.016, 0.242, 0.481, 0.004, 0.002, 0.001; spleen: 0.624, 0.810, 0.537, 0.719, 0.024, 0.046, 0.004, 0.003, 0.008, 0.698; muscle: 0.636, 0.378, 0.552, 0.953, 0.009, 0.009, 0.001, <0.001, 0.116, 0.626; omentum: 0.403, 0.121, 0.232, 0.634, 0.713, 0.053, 0.430, 0.059, 0.118, 0.068; lung: 0.008, 0.284, 0.654, 0.162, 0.088, <0.001, 0.020, 0.028, 0.020, 0.039; kidney: 0.520, 0.019, 0.011, 0.988, 0.155, 0.199, 0.003, 0.027, 0.002, 0.017.

would become exceedingly complicated. Although cardiovascular complications such as arrhythmia or hypotension may manifest when bupivacaine is infused at the rate of 2 $mg \cdot kg^{-1} \cdot min^{-1}$ for 4 minutes (in our study model), recovery can occur promptly when such an infusion is discontinued, or when an infusion of lipid (or saline) is initiated.

In the early stage of the end of lipid emulsion infusion, the bupivacaine concentration of plasma increased and the t1/2α became prolonged, this implies that there were increased levels of bupivacaine in plasma. Additionally, the value of K12 demonstrated that lipid emulsion limited the migration of bupivacaine from the central compartment to the peripheral compartment, which confirmed the effectivity of the lipid sink theory. It would seem intuitive that the Vd should be reduced, but, in fact, the Vd of the lipid group was not reduced compared with the control group. This may be attributed to the complex change of plasma concentration. Although the plasma concentration was increased by the lipid sink effect in the early stages, the liver content and elimination of bupivacaine were increased in regard to the hepatic pharmacologic trends of lipid emulsion. This led to a rapid decrease in plasma concentration, which offset the effect of the early increase in plasma concentration on Vd. Long-chain triglycerides, the main components of lipid emulsion, have an affinity for the liver.[13] Bupivacaine is a liposoluble drug, binding tightly to a lipid emulsion.[12] After lipid emulsion infusion, the contents of bupivacaine in the liver at 20, 30, 45 minutes were higher than the control group, suggesting that the liver may be facile in its uptake of bupivacaine because of its long-chain triglyceride (cytochrome P450 is the primary catabolic enzyme of bupivacaine).[19] This increase of bupivacaine in the liver may have caused an acceleration of metabolism and may be the explanation as to why the elimination half-life of the lipid group was shorter, as well as the reason for its increased CL.

Litonius et al.[20] showed that IV lipid emulsion reduced the half-life of bupivacaine, and Litz et al.[9] reported that infusion of lipid emulsion accelerated the decline of mepivacaine and prilocaine levels. Our results are consistent with both of these studies. A comparison of pharmacokinetic parameters between the 2 groups in our study indicated that lipid emulsion played a significant role in the reduction of bupivacaine toxicity and the prevention of the recurrence of toxicity after resuscitation.

The content of bupivacaine in tissues of the myocardium and brain affects toxicity.[21] Thus, the key to recovery is to reduce the content of bupivacaine. In this study, there were significant decreases of bupivacaine content in the heart and brain after administration of lipid emulsion. The average content in the myocardium was about half of that in the control group and subsequently was maintained at a low level, which is consistent with previous reports.[3,22,23] Therefore, we can also infer that lipid emulsions reduce central nervous system toxicity because of the decreased content in brain tissue.

Furthermore, the content of bupivacaine in other tissues seems to be related to organ perfusion. The high content found in the lung and kidney is attributed to their abundant blood perfusion. The pulmonary system is the first organ mass that lipid emulsion passes through, so the earliest decrease in bupivacaine content may be demonstrated here.[24] This early decrease in the content of bupivacaine as it passed through the lungs was more evident in the treatment group as compared with the control group, and the concomitant weakening of the influence of the lungs at the end of the infusion was also evident. At 60 minutes, the content of bupivacaine in the lung was lower than that in control

group, again due to accelerated elimination. The variation of bupivacaine in the kidney is similar to that of the lung. Although a decline of bupivacaine in lung and kidney was observed, the lipid sink effect played an important role in the early stages, but accelerated elimination was predominant in the later stages. There was no lipid sink phenomenon observed in the spleen, muscles, and the omentum in the early stage of bupivacaine toxicity. Nevertheless, the accelerated elimination decreased the concentration of bupivacaine in the latter stage, except for the omentum.

A weakness of our study design is that we measured the total concentration of bupivacaine in plasma, but not its free concentration. The model used in this study is quite different from the asystole models used previously, of which the pharmacokinetics and distribution are more complicated because of the diversity of survival rate and hemodynamics after cardiopulmonary resuscitation.[25] This is a study design difference that must be taken into consideration when interpreting our data.

In this study, we have demonstrated that after an infusion of lipid emulsion, the content of bupivacaine in the liver increases, as well as the CL of bupivacaine, and its half-life decreases. The lipid sink effect and accelerated elimination play an important role in the distribution of bupivacaine in rats, both of which are important mechanisms of action of lipid emulsions in the reversal of the systemic toxicity of bupivacaine. ■

DISCLOSURES

Name: Kejian Shi, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Kejian Shi has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yun Xia, MD, PhD.
Contribution: This author helped design the study and write the manuscript.
Attestation: Yun Xia has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Quanguang Wang, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Quanguang Wang has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yiquan Wu, MD.
Contribution: This author helped conduct the study and write the manuscript.
Attestation: Yiquan Wu has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Xiaoxi Dong, MD.
Contribution: This author helped conduct the study and study data collection.
Attestation: Xiaoxi Dong has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Chanjuan Chen, BS.
Contribution: This author helped conduct the study.
Attestation: Chanjuan Chen has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Wan Tang, BS.
Contribution: This author helped conduct the study.
Attestation: Wan Tang has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yujian Zhang, MD.
Contribution: This author helped conduct the study.
Attestation: Yujian Zhang has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Mengxu Luo, BS.
Contribution: This author helped analyze the data and data collection.
Attestation: Mengxu Luo has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Xianqin Wang, PhD.
Contribution: This author helped analyze the data and data collection.
Attestation: Xianqin Wang has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Thomas J. Papadimos, MD, MPH.
Contribution: This author helped write the manuscript and Critical manuscript review, writing and preparation.
Attestation: Thomas J. Papadimos has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Xuzhong Xu, MD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Xuzhong Xu has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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