

The effect of hydroxyethylstarch infusion on bupivacaine pharmacokinetics in rats

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Abstract. Background : Bupivacaine is the agent most often used for labor analgesia. However, the risk of accidental intravascular injection of this drug and consequent acute systemic toxicity is ever-present. Although hydroxyethylstarch (HES) is preferred over crystalloid for prevention of hypotension during regional anesthesia, the pharmacokinetics of bupivacaine during fluid preloading has not been studied.

Methods : Twenty-four awake Sprague-Dawley rats were randomly allocated to receive the continuous intravenous infusion of HES 70K, 200K or 400K, or normal saline (NS). After 1 hour of prehydration all animals received bupivacaine, 1mg kg⁻¹, bolus, followed by a continuous infusion, 0.4mg kg⁻¹ min⁻¹ for 15 minutes. After the completion of bupivacaine infusion serial arterial blood samples to determine the plasma bupivacaine concentration were obtained. The plasma concentration-time profile of bupivacaine was fitted to a two-compartment open model, and the estimated intercepts and slopes were used for calculation of standard pharmacokinetic parameters.

Results : The mean peak bupivacaine concentration during HES 400K infusion was significantly lower than during NS infusion (1488 ± 302 ng ml⁻¹ vs 2388 ± 582 ng ml⁻¹). Mean volume of distribution in each of the three HES groups was greater than in NS group. Mean area under curves (AUC) during HES 200K and HES 400K infusions were significantly lower than during NS infusion (32534 ± 4180 and 29619 ± 4431 min ng ml⁻¹, respectively, vs 39802 ± 6268 min ng ml⁻¹). Mean total clearance of bupivacaine during HES 200K and HES 400K infusions was significantly higher than during NS infusion (115 ± 14 and 132 ± 15 ml min⁻¹ kg⁻¹, respectively, vs 92 ± 14 ml min⁻¹ kg⁻¹).

Conclusion : Our results suggest that the increased volume of distribution during HES infusion could be counterbalanced by the increased total clearance, resulting in unchanged half-life or elimination rate constant of bupivacaine.

Key words : Hydroxyethylstarch, local anesthetics ; bupivacaine, pharmacokinetics, rodent.

Bupivacaine is the agent most often used for pain relief in obstetric patients. It possesses motor-sparing properties and has a low trans-placental

transfer rate. However, its systemic toxicity is greater than that of other local anesthetics (e.g., lidocaine). It has been speculated that in pregnancy the pharmacokinetics of local anesthetic including bupivacaine may be affected by changes in volume and composition of body fluid (1) as well and pregnancy-induced changes in hemodynamics.

The aim of maternal volume preloading with either crystalloids or colloids is to reduce the incidence of hypotension following induction of regional (e.g., spinal or epidural) anesthesia. Recent studies have shown that preloading effects of hydroxyethylstarch (HES) may be superior to crystalloid solutions for prevention of hypotension and maintenance of uterine blood flow (UBF) during regional anesthesia in the obstetric population (2-5). However, not much is known about the effects of HES infusion on the pharmacokinetics of bupivacaine and its systemic toxicity. One study in patients undergoing lumbar epidural anesthesia with bupivacaine demonstrated that isovolemic hemodilution with HES leads to lower plasma total bupivacaine concentration after induction of anesthesia, compared with control group of patients

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who did not receive isovolemic hemodilution (6). The purpose of this study was to elucidate the effect of HES infusion on pharmacokinetics of bupivacaine in the awake rats.

METHODS

The experimental study protocol was approved by the Kitasato University Animal Experimental and Ethics Committee. Twenty four adult nonpregnant female Sprague-Dawley rats weighing 220~260 g were obtained from a commercial breeder. They were housed in a temperature-controlled room on a 12-h light-dark cycle, and were given food and water ad libitum. A day prior to the experiment the carotid artery, and jugular and femoral veins of each animal were catheterized under intraperitoneal anesthesia with pentobarbital (33 mg kg⁻¹) and ketamine (17 mg kg⁻¹). The animal was then allowed at least 24 hours to recover from the anesthesia and surgery.

On the day of experiment, each rat was enclosed in a semi-dark observation box. An arterial catheter was connected to a disposable transducer (Baxter®, Tokyo, Japan), which was connected to a computerized chart recorder and analyzing system (Powerlab/16s, AD Instruments Pty Ltd, Castle Hill, NSW, Australia) with Apple computer 6100/60 in order to continuously monitor the arterial blood pressure (BP) and heart rate (HR). Each animal remained in a stable environment for at least 30 min prior to the experiment.

Rats were randomly divided into four groups ; in each study group, the animals were pre-treated with a continuous intravenous (IV) infusion of either HES 70K (mean molecular weight : 70 kD with degree of substitution : 0.55), 200K (mean molecular weight : 200 kD with degree of substitution : 0.62) or 400 K (mean molecular weight : 400 kD with degree of substitution : 0.70), or normal saline (NS). The infusion rate remained at 15 mL kg⁻¹ h⁻¹ until the end of the study. The electrolyte concentrations of all study solutions were identical ; 154 mEq L⁻¹ of sodium ion and 154 mEq L⁻¹ of chloride ion. HES or NS was continuously infused with an application of an infusion pump (Perfusion syringe pump Model STC-525, TERUMO Co., Tokyo, Japan). After 1h of infusion with either HES or NS, all animals were concomitantly administered intravenous solution of bupivacaine hydrochloride, 1 mg kg⁻¹, bolus, followed by a continuous infusion rate of 0.4 mg kg⁻¹ min⁻¹ over a period of 15 min using a micro infusion pump

(Model SP 100i syringe pump, World Precision Instruments, Inc. Sarasota, FL, U.S.A.).

Serial arterial blood samples (< 0.5 mL each for one determination) to determine the plasma drug concentrations were drawn at 0, 4, 8, 12, 20, 30, 60 and 90 min after the completion of the infusion of bupivacaine. Each blood sample was replaced by the same volume of normal saline. Another blood sample, to determine blood gas analysis, hemoglobin concentration, hematocrit and oxygen content, was drawn at 90 min after the completion of bupivacaine infusion. Then, the animal was sacrificed with lethal concentration of isoflurane. Brain, liver and heart samples were obtained to measure tissue bupivacaine concentration. These tissue samples were immediately frozen at -70°C, and remained frozen until analyzed. The blood samples were centrifuged to separate plasma, and were stored in the freezer at -70°C until analyzed. Plasma total concentrations of bupivacaine and its metabolites 3'-hydroxybupivacaine (3'-OH Bup), 4'-hydroxybupivacaine (4'-OH Bup) and 2', 6'-pipercoloxylidine (PPX) were analyzed by liquid chromatography with spectrophotometric (Ultraviolet) detection method as reported by KASTRISSIOS *et al.* (7) with modifications. The detection limit for bupivacaine and its metabolites was 5 ng ml⁻¹. The linearity between the detection peak height and concentration was confirmed between 5-5000 ng ml⁻¹. The coefficient of variation (CV) % for 3'-OH Bup, 4'-OH Bup and PPX were 3.4%, 4.4% and 6.0%, respectively.

Data were compared using repeated measurements, analysis of variance among group differences and for changes in arterial pressure, heart rate over time. The plasma concentration-time profile during and after intravenous bupivacaine administration were fitted to a two-compartment open model as previously reported (1) with the pharmacokinetic computer program, ADAPT II (8). The estimated intercepts and slopes were used for calculation of standard pharmacokinetic parameters. All pharmacokinetic data were analyzed using Turkey test. Values are expressed as mean ± SD, and a p-value of 0.05 was considered significant.

RESULTS

Mean (± SD) values of mean arterial blood pressure (MAP) and heart rate (HR) at baseline (prior to the infusion) after 1h of HES or NS infusion, and at the end of study are listed in Table 1. Following HES 400K infusion, MAP increased

Table 1
Hemodynamic data (mean \pm SD)

	Normal saline (N = 6)	HES70K (N = 6)	HES200K (N = 6)	HES400K (N = 6)
Baseline				
MAP (mmHg)	123 \pm 12	118 \pm 4	121 \pm 12	118 \pm 6
HR (beats min ⁻¹)	407 \pm 31	418 \pm 37	416 \pm 24	400 \pm 37
1h-Infusion				
MAP (mmHg)	122 \pm 12	118 \pm 8	123 \pm 10	134 \pm 11*‡
HR (beats min ⁻¹)	395 \pm 26	401 \pm 29	400 \pm 34	399 \pm 44
End of Study				
MAP (mmHg)	114 \pm 13	123 \pm 8	125 \pm 8	128 \pm 10†
HR (beats min ⁻¹)	416 \pm 33	421 \pm 28	394 \pm 36	429 \pm 33

MAP = mean arterial pressure ; HR = heart rate ; * Significantly different from baseline ($p < 0.05$) ; ‡ Significantly different from HES70K group ($p < 0.05$) ; † Significantly different from normal saline group ($p < 0.05$).

significantly from the baseline ($p < 0.05$). The MAP after 1h of infusion was also significantly higher in the HES 400 K group than in the HES 70K group ($p < 0.05$). The HR was comparable between the different groups and throughout the study. Mean (\pm SD) values of hemoglobin in NS, HES 70 K, HES 200K and HES 400 K groups were 12.3 ± 1.0 , 10.9 ± 0.7 , 10.3 ± 1.4 and 9.6 ± 1.3 g dl⁻¹, respectively. The values in the three HES groups were significantly lower than that in the NS group ($p < 0.05$). Mean (\pm SD) values of hematocrit in the four study groups were 31 ± 2 , 27 ± 2 , 23 ± 5 and $25 \pm 2\%$, respectively. The values in HES 200K and HES 400K groups were significantly lower than that in the NS group ($p < 0.05$). Mean (\pm SD) values of oxygen content in the four groups were 16.2 ± 1.2 , 14.4 ± 1.0 , 14.2 ± 1.7 and 12.7 ± 1.6 ml dl⁻¹, respectively. The values in the three HES groups were significantly lower than that in the NS group ($p < 0.05$).

The plasma concentration-time profile during and after intravenous administration of bupivacaine, and standard pharmacokinetic parameters are shown in Figure 1 and Table 2, respectively. The pharmacokinetic profile of bupivacaine in a fitted curve shows that the peak bupivacaine concentrations in HES 400K group were significantly lower than in the NS group ($p < 0.05$). The discrepancy in the peak values of bupivacaine concentrations in Figure 1 and Table 2 is secondary to the differences between the measured values and calculated values on the simulated concentration-time curve using mean pharmacokinetic parameters. Area under curves (AUC) in HES 200K and HES 400K groups were significantly lower than in the NS group ($p < 0.05$). Total clearance in HES 200K and HES 400K groups were significantly higher than in the NS group ($p < 0.05$). The volumes of distribution in the

three HES groups were greater than in the NS group.

Bupivacaine concentrations in the brain tissue in the three HES groups were significantly lower than the value in the saline group ($p < 0.05$) (Table 3). However, bupivacaine concentrations in the liver and the heart samples were not significantly different among the four groups (Table 3).

Bupivacaine metabolites (3'-hydroxybupivacaine (3'-OH Bup), 4'-hydroxybupivacaine (4'-OH Bup) and 2', 6'-pipecoloxylidine (PPX)) in plasma and tissues (brain, liver and heart) were not detected in any of the studied animals.

DISCUSSION

The results of our study indicate that fluid preloading with HES, especially HES 200K or HES 400K increased the volume of distribution and clearance of bupivacaine in a rat model when compared to the control group of animals receiving NS infusion. The concentration of bupivacaine in the brain tissue from female rats receiving HES infusion was significantly lower than that from animals, which received infusion of NS. This is an advantage for less central nervous system (CNS) toxicity. However, these pharmacokinetic data do not imply that total bupivacaine was eliminated more rapidly in rats receiving HES than in those receiving NS. Because the increased volume of distribution could be counterbalanced by the increased total clearance of bupivacaine, resulting in unchanged half-life or elimination rate constant of bupivacaine. The precise mechanism of these pharmacokinetic differences was not determined in our study. We assume that most bupivacaine has been distributed out of the central compartment without undergoing any

Table 2
Pharmacokinetic data (mean \pm SD)

	Normal saline (N = 6)	HES70K (N = 6)	HES200K (N = 6)	HES400K (N = 6)
Peak (ng ml ⁻¹)	2388 \pm 582	2088 \pm 697	1790 \pm 362	1488 \pm 302*
Min (ng ml ⁻¹)	148 \pm 45	119 \pm 36	129 \pm 65	110 \pm 13
Cl (ml min ⁻¹ kg ⁻¹)	92 \pm 14	106 \pm 24	115 \pm 14*	132 \pm 15*
Vd (ml kg ⁻¹)	576 \pm 469	1197 \pm 1063§	829 \pm 659‡	1629 \pm 1321†
AUC (min ng ml ⁻¹)	39802 \pm 6268	36505 \pm 8124	32534 \pm 4180*	29619 \pm 4431*

* P < 0.05 ; compared with normal saline group ; § P = 0.67 ; compared with HES 70K group ; ‡ P = 0.97 ; compared with HES 200K group ; † P = 0.24 ; compared with HES 400K group ; Peak = peak value of bupivacaine concentration ; Cl = clearance ; Vd = volume of distribution ; AUC = area under curve.

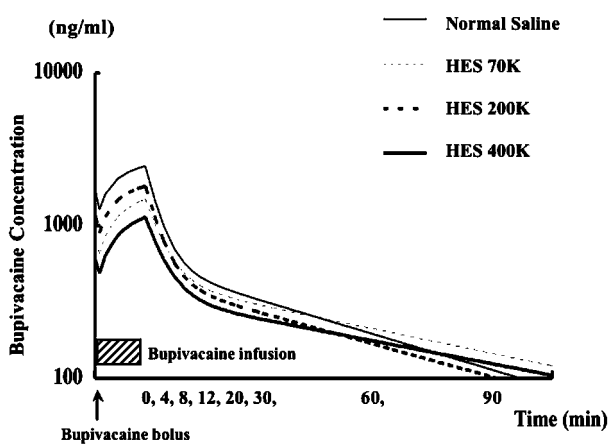


Fig. 1. — The plasma bupivacaine concentration-time curves during and after intravenous bupivacaine administration in rats. The plotting points show the average of each time point. These points are fit to a two-compartment open model in each group.

significant metabolism, as we were unable to detect any metabolites of bupivacaine in plasma in any of the four groups.

UEYAMA *et al.* measured the blood volume (BV) and cardiac output (CO) before and after volume preloading with either lactated Ringer's (LR) solution or HES in 36 parturients scheduled for elective Cesarean section (2). The volume of infused solution remaining in the vascular space after administration of either LR or HES solution over 30 min corresponded to 28% of the LR solution and 100% of the HES infused (2). Furthermore, a significant correlation between the percentage increase in blood volume and that of cardiac output was observed (2). In our study, the peak concentration of bupivacaine in HES 400K group was approximately 62% of the value in the NS group. This is consistent with findings of UYAMA *et al.* (2). We speculate that while most of the HES solution infused over 2 h remained in blood vessels, at the same time only 30% of the

infused saline was intravascular in the control (NS) group. Therefore the difference in peak concentrations of bupivacaine between HES 400K and NS groups could be explained in part by the dilutional effect of the infused solution. Although we did not measure BV, it is likely that HES infusion resulted in an expanded BV and hemodilution. This is further supported by the observed decreases in hematocrit, and haemoglobin concentrations, and a decrease in arterial blood oxygen content (9-11).

We previously reported on the effect of NS and magnesium sulphate (MgSO₄) infusion on the metabolism of bupivacaine (12). The volume of distribution in the NS group of this study was similar to the value in the previous study ; however, clearances in this study were obviously higher than in the previous study. The situation in which elimination from body exceeds liver blood flow includes contribution of renal excretion, and/or change in the volume of distribution of the drug. Since we did not measure the urine output, we could not determine the reason for the discrepancy of the two studies. However, it is unlikely that renal excretion would significantly contribute to the bupivacaine elimination/excretion, and indeed, WIDMAN (13) reported that only a small percentage of unmetabolized bupivacaine is eliminated by the kidneys. Therefore, it is possible that altered bupivacaine pharmacokinetics during HES infusion may result from the changes in the hepatic blood flow. For some drugs (e.g., lidocaine), the effect of increased hepatic blood flow was reported to accelerate the metabolism with high liver extraction ratio ; however, this was not reported with other drugs (e.g., bupivacaine) with low liver extraction ratio (14). A more plausible explanation of our findings is that the increased CO from increased BV increased blood flow to the peripheral tissue, resulting in increased redistribution of bupivacaine. FREYSCHUSS *et al.* (15) and STRATTON *et al.* (16) previously reported that infusions of a low-dose of epinephrine increased both CO and skeletal

Table 3
Bupivacaine concentrations in tissues (brain, liver and heart) ($\mu\text{g wet g}^{-1}$)

	Normal saline	HES70K	HES200K	HES400K
Brain	0.23 \pm 0.09 (n = 5)	0.14 \pm 0.05*	0.13 \pm 0.04*	0.13 \pm 0.07*
Liver	0.11 \pm 0.06 (n = 2)	0.14 (n = 1)	0.13 (n = 1)	ND (n = 0)
Heart	0.23 \pm 0.07 (n = 6)	0.25 \pm 0.09 (n = 4)	0.20 \pm 0.05 (n = 6)	0.16 \pm 0.05 (n = 6)

* $P < 0.05$; compared with normal saline group ; ND = not detected.

muscle blood flow in humans. In another study SHARROCK *et al.* (17) evaluated the effects of intravenous low-dose epinephrine and phenylephrine infusions on plasma concentrations of bupivacaine after lumbar epidural anesthesia in humans. Peak arterial plasma concentrations of bupivacaine were observed 10 min after epidural anesthesia and were significantly lower in patients receiving epinephrine infusions. Cardiac output was significantly greater in patients receiving epinephrine infusion (17). The authors postulated that the smaller circulating concentrations of bupivacaine observed in patients receiving epinephrine were caused by increased CO and a greater volume of distribution than in patients receiving phenylephrine. We therefore postulate that the reduced peak plasma total concentration of bupivacaine during HES infusion in our study was caused by first, the plasma dilution effect and, second, the increased CO.

SANTOS *et al.* (1) studied the comparative pharmacokinetics of ropivacaine and bupivacaine in nonpregnant and pregnant ewes, and found the highest total serum drug concentrations at the end of infusion. For both drugs, pregnancy was associated with lower volumes of distribution during the terminal phase of drug elimination, as well as with a lower total body clearance (1). Based on this study, it is reasonable to anticipate that an accidental intravascular injection of bupivacaine might be more toxic in pregnant than in nonpregnant patients (1). ARTHUR *et al.* (18) studied the alterations in the pharmacokinetic properties of local anesthetics following local anesthetic-induced seizures, and concluded that the total body clearance decreased significantly when the concentration of bupivacaine reached toxic/seizure-inducing levels (18). These studies may provide further evidence that HES, especially high molecular weight HES such as 200 kD or 400 kD, preloading for the prevention of regional anesthesia-induced hypotension might be of an additional advantage in minimizing, or preventing CNS toxicity from an acci-

idental intravenous injection of bupivacaine in the obstetric patient. However, a limitation of the present study was that we could not measure free bupivacaine concentration, which was responsible for systemic toxicity. Furthermore, our data shows that HES preloading results in an increased volume of distribution and an increased clearance of bupivacaine. It is possible that the changes of these parameters have less impact of the half-life or elimination rate constant of bupivacaine, resulting in offset of the advantage with low peak concentration of bupivacaine in plasma or brain.

These findings might be of a great significance in the practice of obstetric anesthesia for at least three reasons ; first, bupivacaine is still the most commonly used local anesthetic for labor analgesia, second, it has a potential for both cardiovascular and CNS toxicity following accidental intravascular injection, and third, pregnancy might be associated with lower volumes of distribution during the terminal phase of drug elimination, and lower total body clearance.

In conclusion, the increased volume of distribution during HES infusion could be counterbalanced by the increased total clearance, resulting in unchanged half-life or elimination rate constant of bupivacaine. There is no obvious advantage of HES infusion for bupivacaine-induced systemic toxicity.

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