Hypoglycemia Enhances Bupivacaine-induced Cardiotoxicity in the Rat

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The effect of blood glucose concentration on bupivacaine-induced cardiotoxicity was investigated in normoglycemic and hypoglycemic adult rats and compared to that of equipotent doses of lidocaine. The anesthetic agents were injected intraperitoneally into tracheostomized animals anesthetized with ketamine. ECG and direct blood pressure measurements were recorded continuously. Femoral arterial blood was used for determinations of glucose level, potassium concentration and base deficit values. Blood was drawn from the heart at the time of death for local anesthetic levels. In hypoglycemic animals, bupivacaine rapidly produced serious dysrhythmias leading to asystole. In normoglycemic rats, only ST-segment changes followed bupivacaine injection and death ensued from hypoxemia secondary to respiratory failure. With lidocaine, both hypoglycemic and normoglycemic rats died of hypoxemia following respiratory paralysis without antecedent dysrhythmias. Thus, hypoglycemia enhanced the cardiac effects of bupivacaine but not those of lidocaine. (Key words: cardiotoxicity: bupivacaine vs lidocaine, normoglycemia vs hypoglycemia)

(Lu GP, Schwalbe SS, Marx GF, et al.: Hypoglycemia enhances bupivacaine-induced cardiotoxicity in the rat. J Anesth 6: 255–261, 1992)

The clinical impression that the threshold for circulatory collapse consequent to intravascular injection of bupivacaine is lower in pregnant than nonpregnant patients[1] has been confirmed in sheep experiments[2,3]. Pregnancy favors the development of "accelerated starvation" (predisposition to hypoglycemia and ketogenesis) after even short periods of fasting[4]. Dextrose containing intravenous solutions are frequently avoided for hydration prior to regional block to prevent fetal hyperglycemia and consequent neonatal hypoglycemia. Such prehydration, however, is often administered in the absence of a current maternal blood glucose determination. Since low blood glucose levels tend to produce cardiovascular instability[5], we suspected that hypoglycemia might be a contributing factor for the more serious cardiotoxicity noted in obstetric patients.

Rats have been used as a model for diabetes research because their glucose metabolism is comparable to that of man[6]. Rats have also been employed for studies of the effect of local anesthetics on the heart[7]. We therefore chose the rat as a model for an investigation of the influence of blood glucose

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concentration on the cardiovascular effects of bupivacaine and lidocaine.

Methods

Following approval by our Animal Investigation Committee, the cardiac effects of bupivacaine and lidocaine were assessed in normoglycemic and hypoglycemic Wistar rats anesthetized with ketamine. Preliminary studies were undertaken in normoglycemic animals to elicit the appropriate doses of the respective drugs. The lowest dose of ketamine to produce unconsciousness was found to be 80 $mg \cdot kg^{-1}$ body weight (b.w.) and the lowest dose of bupivacaine to universally initiate ECG changes was observed to be 100 $mg \cdot kg^{-1}$ b.w. Ketamine 80 $mg \cdot kg^{-1}$ b.w. was therefore chosen as sleep dose for all rats and bupivacaine 100 $mg \cdot kg^{-1}$ b.w. was selected for all experiments dealing with this agent. Lidocaine, in contrast, was used in three different doses (200, 300, 400 $mg \cdot kg^{-1}$ b.w.) because of diversities in the reported potency ratios between bupivacaine and lidocaine in different species[3,11–13].

After establishment of anesthesia, a tracheostomy was performed in order to ensure a patent airway and to permit suctioning. The left femoral artery was cannulated for continuous blood pressure (BP) recording and intermittent blood gas determinations. Electrocardiographic (ECG) leads were applied for constant recording of cardiac activity. Blood drawn from the arterial line immediately before local anesthetic administration was used for determinations of blood glucose level, potassium concentration and base deficit value (calculated from pH and P_{CO_2}). The local anesthetic was injected into the peritoneal cavity over three minutes using a weight-based dosage.

The investigation was carried out in two phases on adult nongravid female rats of similar age (60–70 days). The first phase was conducted on sets of three animals: One rat (control) was fed until approximately one half hour prior to the study, when food was removed from the cage. The second animal was fasted for one and a half days with unrestricted access to water and a third was fed but injected with regular insulin (1 $unit \cdot kg^{-1}$) one half hour before the experiment. Bupivacaine 100 $mg \cdot kg^{-1}$ was used in 7 sets; lidocaine was administered in 9 sets as follows: 200 $mg \cdot kg^{-1}$ in four, 300 $mg \cdot kg^{-1}$ in three, and 400 $mg \cdot kg^{-1}$ in two sets. At the moment of cardiac asystole, blood was drawn from the heart for determination of local anesthetic concentration in 4 of the sets of rats receiving bupivacaine and 3 of the sets receiving lidocaine 200 $mg \cdot kg^{-1}$. The samples were drawn into heparinized tubes which were immediately placed on ice. The plasma was removed by centrifugation and frozen until assayed by chromatography/spectrometry for the two local anesthetics and their metabolites: 2,6-pipecolylxylidine (PPX) for bupivacaine and monoethylglycinexylidine (MEGX) for lidocaine[8,9].

The second phase was undertaken to determine blood bupivacaine levels in normoglycemic rats corresponding to the time of death of the hypoglycemic animals. Three fed rats were sacrificed by an overdose of pentobarbital 5 min after a 100 $mg \cdot kg^{-1}$ bupivacaine injection and blood was immediately obtained from their heart.

The data are expressed as the mean $\pm$ the standard error of the mean. Analysis of variance (ANOVA) and the linear coefficient of correlation were used for the statistical analyses. Differences were considered statistically significant if the calculated P value was less than 0.05.

Results

All rats were of similar weight (216

Table 1. Details of the ECG changes in the bupivacaine-injected rats

Note that the interval between injection of bupivacaine and onset of ECG changes is expressed in seconds in the hypoglycemic animals and in minutes in the controls.

Group of rats																	
Starved						Insulin						Control					
	ECG 1		ECG 2		ASYST		ECG 1		ECG 2		ASYST		ECG 1		ECG 2		RR ϕ	ASYST
#	Dx	sec	Dx	sec	sec	#	Dx	sec	Dx	sec	sec	#	Dx	min	Dx	min	min	min
1	ST↓	185	bigem	240	330	1	HR↓	240	HR↓↓	350	375	1	HR↓	6	ST↓	10	13	14
2	PVC↑	210	PVC↑↑	235	305	2	HR↓	185	HR↓↓	245	300	2	HR↓	7	ST↓	9	$13\frac{1}{2}$	15
3	QRS>	175	PVC↑	245	295	3	QRS>	170	PVC↑↑	210	310	3	HR↓	7	HR↓↓	10	$11\frac{1}{2}$	13
4	HR↓	180	HR↓↓	250	315	4	ST↓	180	bigem	205	295	4	HR↓	6	ST↓	8	13	14
5	ST↓	240	bigem	265	345	5	HR↓	210	HR↓↓	275	380	5	HR↓	$4\frac{1}{2}$	ST↓	$7\frac{1}{2}$	12	13
6	PVC↑	180	PVC↑↑	230	320	6	PVC↑	230	PVC↑↑	260	310	6	HR↓	5	ST↓	9	$13\frac{1}{2}$	15
7	QRS>	175	bigem	255	350	7	bigem	240	bigem	260	285	7	HR↓	7	ST↓	7	12	13
8	HR↓	190	HR↓↓	240	310	8	ST↓	190	bigem	305	315	8	HR↓	$6\frac{1}{2}$	ST↓	8	$11\frac{1}{2}$	13
9	QRS>	235	PVC↑↑	335	390	9	PVC↑	215	PVC↑↑	265	330	9	HR↓	5	ST↓	9	13	14

ECG 1 = initial ECG changes
ECG 2 = subsequent ECG changes
Dx = diagnosis
RR ϕ = respiratory arrest
ASYST = asystole
bigem = bigeminy
HR↓ = mild bradycardia
HR↓↓ = severe bradycardia
ST↓ = ST segment depression
QRS> = widening QRS compelx
PVC↑ = occasional premature ventricular contractions
PVC↑↑ = frequent premature ventricular contractions

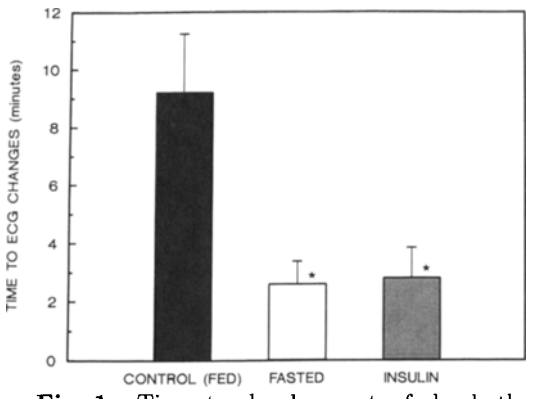

Fig. 1. Time to development of dysrhythmias consequent to bupivacaine injection.

Time (mean ± SE) was significantly shorter for the hypoglycemic rats as compared with the control animals (*$P < 0.005$).

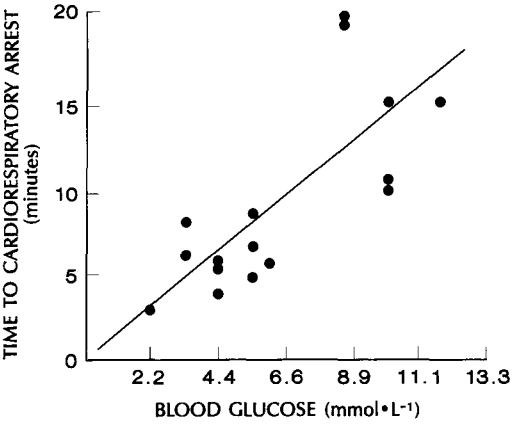

Fig. 2. Time to cardiorespiratory arrest vs. serum glucose level.

The linear coefficient of correlation (r)=0.76.

± 23 gm). Mean blood glucose levels in the fed animals were 9.8 ± 1.1 mmol·l^{-1} (normal 8.5 ± 0.9)[10], in the fasted rats 4.2 ± 1.3 mmol·l^{-1} and in the insulin rats 4.5 ± 1.7 mmol·l^{-1} ($P < 0.001$ between the fed and the hypoglycemic rats). Potassium levels were within normal limits (5.7–6.0 mEq·l^{-1}) in all animals. Mean base deficits were 3.7 ± 0.5 mEq·l^{-1} in the fed rats, 8.2 ± 0.6 mEq·l^{-1} in the fasted rats and 4.5 ± 0.8 mEq·l^{-1} in the rats who received insulin. There were no statistically significant differences between the three groups with respect to initial BP, P_{O_2} or P_{CO_2}.

In the fed animals, the injection of bupivacaine was followed by ST-segment changes after 7–10 min. Asystole secondary to progressive respiratory depression occurred in 13–15 min. In the rats made hypoglycemic by either fasting or insulin administration, bupivacaine produced hypotension, bradycardia, ST-segment changes and serious dysrhythmias such as premature ventricular contractions and bigeminy, within 3–4 min, leading to asystole in 5–7 min (table 1). The cardiac differences in time to onset of ECG changes (fig. 1) and occurrence of asystole between normoglycemic and hypoglycemic animals were statistically significant ($P < 0.005$ for ECG changes and $P < 0.0001$ for death). The lower the blood glucose levels were, the shorter was the time to cardiorespiratory arrest (r=0.76; $P < 0.001$) (fig. 2). With lidocaine, there was no significant difference between the normoglycemic and hypoglycemic rats. All the animals in this group died of respiratory paralysis, preceded by bradycardia without dysrhythmia. With the 300 and 400 mg·kg^{-1} doses, slowing of the heart rate began 5–6 min after injection, with the 200 mg·kg^{-1} dose, 7–9 min after injection; death invariably occurred 3–5 min after the onset of bradycardia. Convulsions were not observed in any of the animals.

Blood bupivacaine concentrations ranged from 7.1 to 14.0 μg·ml^{-1} in the fed rats, from 93.3 to 216.6 μg·ml^{-1} ($P < 0.02$ vs control) in the fasted rats and from 88.8 to 153.9 μg·ml^{-1} ($P < 0.005$ vs control) in the rats receiving insulin (table 2). There was no statistically significant difference in the serum bupivacaine levels obtained between the fasted or insulin groups ($P > 0.25$). These concentrations were inversely related to the time of death (r=−0.73). There was a weak correlation with the plasma glucose levels

Table 2. Concentrations (mean ± SE) of bupivacaine (4 sets of rats) and lidocaine (3 sets of rats) in cardiac blood obtained at the time of death

Group	Concentration ($\mu g \cdot ml^{-1}$)	
	Bupivacaine	Lidocaine
FED (control)	8.8 ± 2.2	186 ± 72
Fasted	138.4 ± 43.1*	152 ± 71
Insulin	96.7 ± 26.2*	182 ± 47

*$P < 0.05$ vs control

(r=0.58).

In the three fed animals sacrificed at five minutes after the bupivacaine injection, i.e., at the usual time of death of the hypoglycemic rats, the bupivacaine concentrations were low (10.5 ± 2.0 $\mu g \cdot ml^{-1}$). In contrast to the bupivacaine results, the lidocaine blood concentrations of all three groups were within the same range (table 2). PPX and MEGX concentrations were low in all animals. PPX ranged from 0.02 to 0.08 $\mu g \cdot ml^{-1}$, MEGX ranged from 1.37–2.77 $\mu g \cdot ml^{-1}$.

Discussion

Lidocaine was chosen as the comparative local anesthetic because it has been used for this purpose in many animal experiments[2,7,13]. Furthermore, lidocaine and bupivacaine are the two most commonly employed anesthetic drugs for obstetric extradural block[11,12]. As mentioned earlier, the reported potency ratio between bupivacaine and lidocaine has not been uniform. In humans, bupivacaine is three to four times more potent than lidocaine[10,11], yet in sheep and mice, the potency of bupivacaine is only twice that of lidocaine[2,13]. Although our clinical comparisons of the two local anesthetics were undertaken at three different ratios 1:2, 1:3 and 1:4, the pharmacologic determinations were limited to the 1:2 ratio, the ratio equipotent in mice[13].

Our findings are comparable to those of a study evaluating the cardiac effects of intravenously administered equivalent doses of lidocaine and bupivacaine in unanesthetized sheep[2]. After intravenous lidocaine injection, no animal developed arrhythmias other than minimal ST-T wave changes. After injection of bupivacaine, all animals had ECG changes and/or arrhythmias, most commonly widening of the QRS complex, but also premature ventricular contractions and severe ST-T wave depression.

The presence of hypoglycemia enhanced the cardiac effects of bupivacaine, regardless of whether it was produced by fasting or by insulin administration. One may thus assume that the hypoglycemic state was the primary factor causing a reduced threshold for cardiac toxicity.

Bupivacaine levels in the heart of the normoglycemic rats were low regardless of whether death had occurred by local anesthetic induced cardiac arrest (13–15 min after the bupivacaine injection) or the animals were sacrificed by administration of pentobarbital (5 min after the bupivacaine injection). In the hypoglycemic rats, by contrast, the levels were highest in the animals dying the fastest. There appear to be two possible mechanisms for the increased drug levels. One is a reduction in cardiac output with retention of unmetabolized drug, the other is an alteration of unknown nature in the metabolic degradation of the drug. Whatever the explanation, such high levels may contribute to the difficulty in cardiopulmonary resuscitation following accidental intravascular injection of bupivacaine in healthy patients. The absence of convulsions is explained by the presence of an anesthetic state and/or the use of a local anesthetic large enough to paralyze the central nervous system without excita-

tion.

Bupivacaine has been shown to cause significant changes in cardiac conduction and repolarization[14,15]. Glucose depletion is known to attenuate normal cell repolarization[16]. In addition, an *in vitro* study on mechanisms of bupivacaine-induced depression of myocardial contractility suggested that inhibition of energy metabolism was a major contributor to bupivacaine cardiotoxicity[17]. Although only the role of calcium chloride and adenosine triphosphate was assessed, glucose is an essential provider of energy for aerobic metabolism. Thus, it appears that hypoglycemia may be added to the list of other factors, such as hypoxia, hypercarbia or acidemia, which are known to accentuate the cardiac effects of bupivacaine.

Whether the above findings can be extrapolated to the human remains questionable. However, the study has demonstrated an important difference in the cardiac effects of bupivacaine versus lidocaine.

Supported in part by the Fujimori Fund of the Department of Anesthesiology, Albert Einstein College of Medicine.

Preliminary data presented at the 1986 Annual ASA Meeting (Anesthesiology 65:A191, 1986)

(Received Aug. 28, 1991, accepted for publication Jan. 8, 1992)

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