COMPARISON OF THE CHRONOTROPIC RESPONSES TO LOCAL ANESTHETICS (PROCAINE, LIDOCAINE, PRILOCAINE, MEPIVACAINE AND BUPIVACAINE) OF THE CANINE SINUS NODE IN SITU

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Abstract—Effects of local anesthetics (procaine, lidocaine, prilocaine, mepivacaine and bupivacaine) on the sinus node of the nerve-intact dog heart were studied in situ by means of selective perfusion of the sinus node through the sinus node artery. The agents caused a dose-dependent decrease in heart rate and the order of their potency in decreasing the heart rate was as follows, bupivacaine > lidocaine = mepivacaine = prilocaine > procaine. The decrease in heart rate produced by these local anesthetics was not affected by prior administration of atropine. With procaine and prilocaine, the decrease in heart rate was followed by an increase which was inhibited by propranolol given into the sinus node artery or was suppressed in reserpine-pretreated dogs. Tetrodotoxin also prevented the positive chronotropic effect of procaine. From these results the following conclusion can be drawn: the negative chronotropic effects of these agents are induced mainly by a direct inhibitory action on the sinus node, and partly by blockade of sympathetic tone, and the interaction with the postganglionic adrenergic nerves plays an important role in the induction of the positive chronotropic responses to procaine and prilocaine.

Although it is well known that lidocaine and other similar local anesthetic agents cause a degree of cardiovascular depression (1), procaine has been reported by several investigators (2–4) to have excitatory effects. Therefore, there appears to exist qualitative differences among local anesthetic agents in their actions on the cardiovascular system. When the cardiovascular responses to local anesthetics are considered as the sum of effects on the heart, blood vessels, and the peripheral and central nervous systems, an evaluation of effects of local anesthetics on the heart has to be made. For this purpose I perfused selectively the sinus node through the sinus node artery of the dog heart and examined the effects of 5 local anesthetics on the heart rate. These drugs were lidocaine and procaine, the most commonly used, and the newly synthetized agents with longer action, prilocaine, mepivacaine and bupivacaine.

MATERIALS AND METHODS

Fifty-three dogs of either sex, weighing 7 to 10 kg, were anesthetized with 30 mg/kg of sodium pentobarbital i.v. and ventilated artificially through a tracheal tube with room air (Respirator Aika R-60). The chest was opened through the right fourth intercostal
space and the heart was cradled in the pericardial sac. The dorsal right atrial artery (sinus node artery) was then dissected free from the atrial wall and after proximal ligation, it was cannulated with a non-slip catheter with an outer diameter of about 0.5 mm at its tip (5-7). Prior to cannulation, heparin was given i.v. in a single dose of 500 U/kg. The arterial blood drawn from the femoral artery was driven by a peristaltic pump (Mitsumi ST-1200) to the catheter. Perfusion flow was set at 20–30 ml/min and the excess blood was returned to the femoral vein by a channel prepared for shunting it through a pneumatic resistance of 100 mmHg. The autonomic nerve supply to the heart was left intact. Blood pressure was measured from the cannulated femoral artery with a pressure transducer (San-ei 1206B). Heart rate was measured with a cardiachometer (San-ei 2130) triggered by R waves of lead II ECG, which was also recorded with an ECG (San-ei N-1100).

In the reserpine-pretreated dogs, 0.2 to 0.3 mg/kg of reserpine (Daiichi Pharmaceutical Co.) was given i.m. 24 hr before the experiments. The other drugs used in this study were procaine hydrochloride (Daiichi), lidocaine hydrochloride and prilocaine hydrochloride (Fujisawa), mepivacaine hydrochloride and bupivacaine hydrochloride (Yoshitomi), acetylcholine chloride, (±)-norepinephrine hydrochloride and tyramine hydrochloride (Nakarai), atropine sulfate (Tanabe), tetrodotoxin (Sigma) and (±)-propranolol hydrochloride (Sumitomo). These drugs were dissolved in 0.9% saline. Doses refer to their bases.

Values are mean±SE. The significance of difference between mean values was analyzed by the Student’s t-test and the data were considered to be significant when p values were less than 0.05.

RESULTS

Effect of procaine on the sinus node: Ten µg to 1 mg of procaine was given into the sinus node artery. The basal heart rate of thirty-eight dogs, in which the autonomic nerve supply to the heart was left intact, was 117±1 beats/min. The response of the sinus node was characterized by a biphasic pattern with an initial decrease in heart rate lasting 15 to 20 sec followed by an increase with a gradual onset and a 3 to 5 min duration (Fig. 1). The threshold dose of procaine for producing the positive chronotropic response was 10 µg and that for the negative chronotropic response was 100 µg. As shown in Fig. 2, the negative chronotropic response to procaine was dose-dependent; decreases in heart rate ranged from 12.4% to 47.0% of the basal rate with doses from 100 µg to 1 mg. The incidence of pacemaker shift also increased with doses over 100 µg (Table 1). Pacemaker shift was defined as the change of shape of the P waves and the inversion

![Fig. 1. Effect on heart rate (HR) of procaine 100 µg injected into the sinus node artery. The response was characterized by an initial decrease in heart rate followed by a prolonged positive chronotropic phase, but there was no significant effect on systemic blood pressure (SBP) (upper panel). In the ECG, wondering P wave was not observed (lower panel).](image-url)
or the disappearance (AV nodal rhythm) of the P waves in the electrocardiogram. At a dose of 1 mg, the sinus rhythm was replaced by AV nodal rhythm following sinus bradycardia in all experiments. In order to examine whether the chronotropic effects of procaine were partly mediated by the autonomic nervous system, influences of autonomic drugs were examined on the negative and positive chronotropic effects of procaine. The negative chronotropic response to 100 μg of procaine were unaffected by 10 μg of atropine given into the sinus node artery, this dose completely blocking the action of 0.1 μg of acetylcholine. The negative response to procaine was 10±2% decrease (n=8) and became 11±4% after atropine. In three dogs, bilateral vagotomy did not alter the negative response to procaine. Five μg of propranolol and 3 μg of tetrodotoxin changed the negative responses from 19±7% to 18±4% (n=5) and from 16±1% to 15±2% (n=8), respectively. Procaine also had a negative chronotropic effect in reserpine-pretreated dogs. The positive chronotropic response to procaine.

**Fig. 2.** Dose-response curves for decrease in heart rate to local anesthetics injected into the sinus node artery of the dog heart. Decreases in heart rate are expressed by a percentage of the basal rate. The vertical bars represent ±SE of the mean.

**Fig. 3.** Increases in heart rate produced by various intraarterial doses of procaine and prilocaine. Each point refers to a peak increase. Increases are expressed by a percentage of the basal rate. The vertical bars represent ±SE of the mean.

<table>
<thead>
<tr>
<th>Table 1. Incidence of pacemaker shift</th>
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<tr>
<td>Dose</td>
</tr>
<tr>
<td>Procaine</td>
</tr>
<tr>
<td>Lidocaine</td>
</tr>
<tr>
<td>Prilocaine</td>
</tr>
<tr>
<td>Mepivacaine</td>
</tr>
<tr>
<td>Bupivacaine</td>
</tr>
</tbody>
</table>

*This represents the number of occurrences of pacemaker shift/the number of experiments. The mean of basal rates was 117±1 beats/min.
is summarized in Fig. 3. In contrast to the negative chronotropic response, the positive chronotropic response was not proportional to doses of procaine.

**Effect of lidocaine on the sinus node:** An injection of 10 μg to 1 mg of lidocaine into the sinus node artery produced only a negative chronotropic response which increased in a dose-dependent manner (Figs. 2 and 4). The threshold dose for inducing a significant negative chronotropic response was 30 μg and the amount of decrease in heart rate was 1.9 times as large as that of procaine at 100 μg. Pacemaker shift was observed more frequently with lidocaine than procaine in comparable doses. Pacemaker shift was seen in 4 of 14 experiments even at the dose of 30 μg and the replacement of sinus rhythm by AV nodal rhythm was a constant finding at 1 mg (Table 1). Administration of 10 μg of atropine did not modify the response to 100 μg of lidocaine (n=3).

**Effect of prilocaine on the sinus node:** Prilocaine given into the sinus node artery produced a biphasic chronotropic response similar to that induced by procaine (Fig. 4). The threshold dose for the negative response was 30 μg which decreased the heart rate by 9.4% of the basal rate. One hundred μg of prilocaine produced a sinus depression which was 1.6 times larger than that with procaine (Fig. 2). The incidence of prilocaine-induced pacemaker shift was about the same as that seen with procaine, and AV nodal rhythm was recorded in 3 of 4 experiments at 1 mg (Table 1). Atropine (10 μg) treatment had no effect on the response of the sinus node to 100 μg of prilocaine (n=5). The positive chronotropic response to prilocaine was not proportional to the doses and ranged from a half to two-thirds of the procaine-induced response (Fig. 3).

**Effect of mepivacaine on the sinus node:** Thirty μg to 1 mg of mepivacaine induced a dose-dependent chronotropic response of the sinus node (Figs. 2 and 4). The threshold dose for inducing a significant sinus depression was 10 μg. The decrease in heart rate was 1.9 times that of procaine at

Fig. 4. Chronotropic responses to 100 μg of lidocaine, prilocaine and mepivacaine injected into the sinus node artery of the dog heart. Lidocaine and mepivacaine produced only negative chronotropic effects, but like procaine, prilocaine did produce a biphasic chronotropic effect.

**Fig. 5.** A chronotropic response to 100 μg of bupivacaine injected into the sinus node artery. Bupivacaine produced a larger and longer-lasting decrease in heart rate than other local anesthetics, in comparable doses. In the lower panel, a: normal P waves, b: the inverse P waves, c: process of the recovery to the initial P waves.
100 μg. The incidences of pacemaker shift were 38%, 63% and 100% at 100 μg, 300 μg and 1 mg respectively (Table 1). The response to 100 μg of mepivacaine was not affected by 10 μg of atropine in any experiments (n=3).

Effect of bupivacaine on the sinus node: Bupivacaine in doses of 10 μg to 1 mg caused a dose-dependent depression of the sinus nodal activity (Fig. 2). A significant change in heart rate was seen with a dose of 10 μg. The amount of decrease increased proportionally to the dose of bupivacaine up to 1 mg and was 2.5 times that of procaine at 100 μg. In a given dose, the sinus depression produced by bupivacaine was longer lasting than that induced by other local anesthetics. Figure 5 shows a typical experiment with bupivacaine in which the inverse P waves were observed in lead II and the P waves recovered to initial P waves at Point c. Pacemaker shift which occurred even at the dose of 30 μg in 4 of 7 experiments was seen most frequently among the five agents and the incidence of pacemaker shift exceeded 80% in doses higher than 100 μg (Table 1). The response was also unaffected by atropine treatment (n=3).

Effect of propranolol on the positive chronotropic responses to procaine and prilocaine: The effect of propranolol on the positive chronotropic responses to procaine and prilocaine was studied in 5 dogs. Typical results are shown in Fig. 6. With an injection of 5 μg of propranolol, the heart rate decreased from 114±4 beats/min to 76±1 beats/min (n=5), and positive chronotropic response to 0.1 μg of norepinephrine was abolished. Under these circumstances procaine and prilocaine produced only prolonged monophasic negative chronotropic responses with very slow recovery to the basal rates.

Effect of tetrodotoxin on the positive chronotropic responses to procaine and prilocaine: Tetrodotoxin is a potent inhibitor of the sodium channels. It was found to block the positive chronotropic responses to procaine and prilocaine (Fig. 6). Table 2 summarizes the effects of tetrodotoxin on the positive chronotropic responses to procaine and prilocaine.

![Fig. 6. Effect of propranolol on the positive chronotropic responses to procaine and prilocaine. After administration of 5 μg of propranolol, the positive chronotropic responses were blocked completely.](image)

**Table 2. Effects of tetrodotoxin on procaine- and prilocaine-induced positive chronotropic responses**

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Basal HR (beats/min)</th>
<th>Increase in HR (%)</th>
<th>Basal HR (beats/min)</th>
<th>Increase in HR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine 100 μg</td>
<td>8</td>
<td>120±6</td>
<td>17±2</td>
<td>104±9</td>
<td>4±1 (1)</td>
</tr>
<tr>
<td>Prilocaine 100 μg</td>
<td>5</td>
<td>106±11</td>
<td>7±4</td>
<td>89±6</td>
<td>1±1 (2)</td>
</tr>
</tbody>
</table>

Values are mean±SE, when compared with respective control values: (1)p<0.001, (2)p<0.3.
Fig. 7. Effect of 3 μg of tetrodotoxin (TTX) on the positive chronotropic responses of the sinus node to procaine and prilocaine. Procaine-induced positive chronotropic response was abolished by TTX which blocked the effect of electrical stimulation (ES) of right vagus nerve, whereas response to 0.1 μg of norepinephrine (NE) remained unaltered. The positive chronotropic response to prilocaine was also suppressed by TTX.

Table 3. Chronotropic responses to procaine, prilocaine and norepinephrine (NE) in reserpine-pretreated dogs

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Basal HR (beats/min)</th>
<th>Decrease in HR (%)</th>
<th>Increase in HR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine 100 μg</td>
<td>10</td>
<td>87 ± 10</td>
<td>17 ± 2</td>
<td>1 ± 1(1)</td>
</tr>
<tr>
<td>Prilocaine 100 μg</td>
<td>5</td>
<td>88 ± 16</td>
<td>31 ± 2</td>
<td>0(2)</td>
</tr>
<tr>
<td>NE 0.1 μg</td>
<td>5</td>
<td>69 ± 6</td>
<td>0</td>
<td>98 ± 12(3)</td>
</tr>
</tbody>
</table>

Values are mean±SE., when compared with respective control values: (1)p<0.001, (2)p<0.05, (3)p<0.001.

prilocaine: When 3 μg of tetrodotoxin, a dose sufficient to block neural excitation in the dog heart (8), was injected into the sinus node artery, the heart rate decreased by about 20 beats/min (Table 2), and electrical stimulation of the right vagus nerve failed to elicit a sudden fall of heart rate. In such tetrodotoxin-treated preparations, the increase in heart rate in response to 100 μg of procaine was only 4% of the basal rate as against 17% before the treatment. Tetrodotoxin also decreased the positive response to prilocaine, a 7% increase in heart rate before tetrodotoxin to a 1% increase, but the change was not statistically significant (Fig. 7, Table 2).

Effect of reserpine on the positive chronotropic responses to procaine and prilocaine: The basal heart rates of 5 reserpine-pretreated dogs before administration of procaine and prilocaine into the sinus node artery are shown in Table 3. In these dogs, 5 μg of tyramine produced an increase in heart rate only by 4±2% (n=10) of the basal rate as against an increase by 34±6% (n=10) in untreated dogs (p<0.001). In such reserpine-pretreated dogs, the positive chronotropic effects of norepinephrine were not significantly different from those in untreated dogs when this drug was given at the end of experiments. Both procaine and prilocaine failed to produce the positive chronotropic responses, even though the decreases in heart rate were unaffected (Fig. 8, Table 3).

DISCUSSION

The action of local anesthetics which protect the heart from ventricular arrhy-
Fig. 8. Effects of procaine and prilocaine on the sinus node in the reserpine-pretreated dogs. One hundred μg of procaine and prilocaine produced no increase in heart rate, but 0.1 μg of norepinephrine (NE) induced a marked increase.

Thymias by reducing its excitability can also lead to hemodynamic deterioration by depressing the cardiac function in the normal heart (9). The results in the current study showed that selective administration of the 5 local anesthetics into the sinus node artery of the dog heart caused a dose-dependent decrease in heart rate which was associated with pacemaker shift at higher doses. The relative potencies which caused the negative chronotropic responses were approximately proportional to the anesthetic potencies of the agents (10–12). The negative response to procaine was not affected by treatment of the sinus node with atropine which completely blocked the effect of acetylcholine to induce a sinus bradycardia or a sinus arrest. There was also no change in the negative chronotropic response to procaine by bilateral vagotomy. Furthermore, treatments with propranolol, tetrodotoxin and reserpine only slightly diminished the negative chronotropic response to procaine. Similar results were obtained also for prilocaine. Therefore, the negative chronotropic responses to local anesthetics may be mainly due to a direct depression of the sinus node. However, it cannot be ruled out that part of the negative chronotropic response is due to decrease in the sympathetic tone mediated by inhibition of sympathetic nerves by local anesthetics.

The primary electrophysiological effect of local anesthetics on the nerve membrane is believed to be a reduction in permeability of the cell membrane to Na ions. In the presence of local anesthetics, there are marked decreases in the rate of rise of the depolarization phase and the amplitude of the action potential which are associated with little or no change in both the threshold potential and the membrane resting potential (12). Taylor and others (13–16) reported that procaine caused a reduction in the amount and rate of development of the early transient and late steady state currents in the excised voltage clamped squid axon and lobster giant axons. The present study demonstrated that the potency of negative chronotropic responses to local anesthetics was proportional to the local anesthetic activity. The latter activity was proportional to depression of the fast Na conductance. A recent unpublished investigation by the author showed that procaine and lidocaine decreased the rate of rise of phase 4 depolarization and the amplitude of the action potential and prolonged the duration in the
sinus node cell of dog heart. In the sinus node, the resting potential is low, and less negative, compared with that of Purkinje fibers (17-20). This indicates that the slow inward current system may be important in generating sinus node action potential (21, 22). However Hashimoto et al. reported that local anesthetics do not necessarily suppress the Ca channel and the effects on the Ca channel are not related to their Na channel blocking effects in guinea pig atria (23). Therefore, the fast Na current may be of importance in generating the action potential of the sinus node cell. However, the possibility exists that local anesthetics act on the slow inward currents and/or potassium currents in the canine sinus node.

Foldes et al. (2) reported that an intravenous infusion of procaine caused an increase in heart rate in 80% of twelve unanesthetized subjects. Wikinski et al. (3) also found arterial hypertension and sinus tachycardia in a patient who had inadvertently been given 4,000 mg of procaine. The present and our previous results also demonstrated the positive chronotropic response of the sinus node to procaine (24). However, the positive chronotropic effect was not dose-dependent because of the concomitant negative chronotropic response. In similar experiments, Chiba (4) suggested that the positive chronotropic response induced by procaine in the isolated canine atrial preparation might be due to a direct stimulation of beta-receptors. However, in the present study the positive responses to procaine and prilocaine disappeared after treatment with propranolol, or in reserpine-pretreated dogs. Also in the tetrodotoxin-treated preparation, the sinus acceleration was abolished or decreased. These results cannot be explained if these agents are beta-receptor stimulants. Therefore, the author concludes that interaction with the postganglionic nerves is essential for the induction of the positive chronotropic responses of the sinus node to procaine and prilocaine.

Local anesthetics can be classified into two chemical groups. Procaine belongs to the ester-type and lidocaine, prilocaine, mupivacaine and bupivacaine belong to the amide-type. The positive chronotropic responses of the sinus node to local anesthetics do not seem to depend upon the chemical structures.

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