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Direct Effects of Amide-Type Local Anesthetics on Isolated Rat Ventricular Papillary Muscles

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=Abstract= The direct effects of 2 amide-type local anesthetics, lidocaine and bupivacaine, on myocardial contractility were studied in isolated rat heart muscles. Three different clinically equipotent doses of each agent were tested. In Tpd, +dp/dtmax, and −dp/dtmax, the cardiodepressive action of lidocaine seemed to be slightly more than that of bupivacaine, but bupivacaine showed a more depressive action on myocardial contractility from the results of Tr and RT90%. We might say that lidocaine exhibit significant cardiodepressive activity, which is at least similar with bupivacaine.

Key Words: Amide, Local Anesthetic, Lidocaine, Bupivacaine, Cardiodepression.

INTRODUCTION

The systemic toxicity of local anesthetics mainly involves the central nervous system and the cardiovascular system. In general, the cardiovascular system (CVS) is believed to be relatively resistant to the toxic effects of local anesthetics in comparison to the central nervous system (CNS). Even though the cardiovascular actions of local anesthetics were studied extensively, the exact mechanism by which local anesthetics depress myocardial contractility is not precisely known. It has been known that all local anesthetics exert a dose-dependent negative inotropic action by primarily acting at the sodium channel but have little effect on the slow inward calcium currents. The highly lipid soluble local anesthetics like bupivacaine or etidocaine, which may affect the storage or release of cytoplasmic calcium to some extent, show major cardiovascular toxicity.

Albright (1979) drew attention to a small series of anecdotal reports of cardiac arrest associated with regional anesthesia and the highly lipid-soluble and protein-bound local anesthetic agents bupivacaine and etidocaine. This report has lead to a considerable amount of experimentation in an effort to clarify the mechanisms by which local anesthetics may cause cardiodepression, ventricular arrhythmias, cardiac arrest and death, which are only partly associated with their well described CNS toxicity. Once cardiac arrest has occurred, resuscitation may be or difficult or unsuccessful (Davis and De Jong, 1982; Mallampatic et al., 1984).

When we compare lidocaine with bupivacaine, almost all of the investigators have reported that cardiovascular toxicity of bupivacaine is either comparable to its anesthetic potency or greater than lidocaine (Liu et al., 1982; Nath et al., 1986; Leone et al., 1988; Rutten et al., 1989; Buffington, 1989), whereas de Jong et al. (1980) observed that bupivacaine is less toxic than lidocaine in mice when given intraperitoneally.

This study was aimed specifically at identifying and comparing the direct effects of the two different amide local anesthetics which are most frequently used in modern anesthesia practice, namely, lidocaine and bupivacaine.
MATERIALS AND METHODS

Isolated columns of papillary muscle were prepared from left ventricles of rats. The rats were 2-3 months old. Each preparation was placed in an oxygenated (oxygen 95%, carbon dioxide 5%) 80 ml capacity muscle bath containing modified Krebs-bicarbonate solution. The temperature of the bath solution was held constant at 35°C by a thermoregulator (Precision Scientific Co.), and the pH was stabilized at 7.40. One end of the muscle was fixed, and the other was connected to a force displacement transducer (Grass FT03C) and its output recorded on one channel, while another output was connected to the differentiator (Optical Electronics Inc., model 9009) and recorded on another channel of the recorder (Gould Brush Recorder 2400). Each muscle was stimulated (Grass SD9 Stimulator) with 2x8 mm platinum plate electrodes, placed about 10 mm apart parallel to the muscle, at a frequency of 0.25 Hz with a square wave pulse of 6.0 ms duration and voltages 10% above threshold. The length-tension curve of each preparation was determined after 30 minutes of isometric contractions. Changes in muscle length measured with a micrometer transformer could be detected to 0.01 mm. The maximum muscle length-tension (the length at the peak of the length-tension curve) was 5.34 ± 1.57 mm. The muscle was held at the peak of the length-tension curve for 30 min for stabilization, and then peak developed tension (Tpd), resting tension (Tr), maximum rate of tension development (+dp/dtmax) and relaxation (−dp/dtmax), time to peak tension (TPT), and relaxation time (RT50%) were recorded at a paper speed of 100 mm per second.

At the maximum muscle length of the length-tension curve of each preparation, 20 muscles were evenly divided into 2 groups, and each group was exposed to 3 different concentrations of one local anesthetic in random order after a wash-out with the same physiologic solution and 30 minutes' stabilization, so to speak: the lidocaine group to 10, 20, and 40 µg/ml of lidocaine and the bupivacaine group to 2.5, 5, and 10 µg/ml of bupivacaine which are clinically equipotent doses with of lidocaine. For convenience, among the 3 concentrations for each group, we will call the lowest concentration as low concentration, the middle dose as medium concentration, and the highest concentration as high concentration.

The percent changes from the control values of each parameter in each group were obtained. Data for the groups and their concentrations were compared with multiple comparison with a Duncun test after analysis of variances. We accepted the value of p < 0.05 as statistically significant.

RESULTS

Fig. 1 shows a typical tracing for the effects of low concentration of local anesthetics on Tpd in isometric contraction. Bupivacaine showed early stimulation in this figure, which occurred only 2 times out of ten in the low concentration of bupivacaine throughout the experiment.

![Fig. 1. Typical tracing for the effects of low concentration of local anesthetics on isometric contraction](image-url)
Table 1. Effects of amide-type local anesthetics on isometric contraction of isolated rat left ventricular papillary muscles

<table>
<thead>
<tr>
<th></th>
<th>Tpd</th>
<th>Tr</th>
<th>+dp/dtmax</th>
<th>-dp/dtmax</th>
<th>TPT</th>
<th>RT90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lido-</td>
<td>10 -22.78 ± 11.75</td>
<td>-3.87 ± 2.43</td>
<td>-21.49 ± 5.99</td>
<td>-23.63 ± 8.17</td>
<td>-2.65 ± 5.55</td>
<td>-2.00 ± 5.85</td>
</tr>
<tr>
<td></td>
<td>40 -35.16 ± 9.05</td>
<td>-0.22 ± 2.58</td>
<td>-31.79 ± 7.52</td>
<td>-35.19 ± 8.21</td>
<td>0.60 ± 7.99</td>
<td>-0.99 ± 12.285</td>
</tr>
<tr>
<td>vacaine</td>
<td>5.0 -24.82 ± 14.25</td>
<td>-1.99 ± 5.09</td>
<td>-23.90 ± 7.91</td>
<td>-23.31 ± 7.97</td>
<td>1.48 ± 7.45</td>
<td>7.31 ± 5.88</td>
</tr>
<tr>
<td>(μg/ml)</td>
<td>10 -28.49 ± 8.11</td>
<td>2.92 ± 2.88</td>
<td>-29.25 ± 10.56</td>
<td>-28.38 ± 9.98</td>
<td>3.07 ± 5.82</td>
<td>8.30 ± 7.49</td>
</tr>
</tbody>
</table>

Data are % changes of control (mean ± S.D.) measured at the time of stabilization after additions of local anesthetics. All were statistically non-significant when we compared lidocaine treated group with bupivacaine treated group in each equipotent concentration.

Fig. 2. Percent changes of peak developed tension (Tpd) from control. Data (mean ± S.D.) were collected at the time of stabilization after additions of local anesthetics. # : p < 0.05 comparing with low concentration treated group. ∗: p < 0.05 comparing with medium concentration treated group.

Fig. 3. Percent changes of maximum rate of tension development (+dp/dtmax) from control. Data (mean ± S.D.) were collected at the time of stabilization after additions of local anesthetics. # : p < 0.05 comparing with low concentration treated group. ∗: p < 0.05 comparing with medium concentration treated group.

and -dp/dtmax, the differences between lidocaine 10 μg/ml and 40 μg/ml and the differences between lidocaine 20 μg/ml and 40 μg/ml (Fig. 2, Fig. 4), and in +dp/dtmax, the difference between lidocaine 10 μg/ml and 40 μg/ml (Fig. 3) were statistically significant, while the bupivacaine-treated group showed no significance between any two concentrations (Fig. 2, Fig 3, Fig. 4). We did not show the result of the statistical comparison between noncorresponding concentrations of two local anesthetics either in the table or the figures, but the differences between lidocaine 40 μg/ml and bupivacaine 2.5 μg/ml, and the differences between lidocaine 40 μg/ml and bupivacaine 5 μg/ml were also statistically significant.

The percent changes from the control values in Tr, TPT, and RT90% did not show remarkable change, but generally, bupivacaine showed a lesser degree of decrease or rather increase than lidocaine (Table 1, Fig. 5, Fig. 6, Fig. 7). In Tr, the difference between bupivacaine 2.5 μg/ml and
Fig. 4. Percent changes of maximum rate of relaxation \(-\frac{dp}{dt_{\text{max}}}\) from control. Data (mean ± S.D.) were collected at the time of stabilization after additions of local anesthetics.

\# : p < 0.05 comparing with low concentration treated group.

\* : p < 0.05 comparing with medium concentration treated group.

Fig. 5. Percent changes of resting tension (Tr) from control. Data (mean ± S.D.) were collected at the time of stabilization after additions of local anesthetics.

\# : p < 0.05 comparing with low concentration treated group.

\* : p < 0.05 comparing with medium concentration treated group.

Fig. 6. Percent changes of time to peak tension (TPT) from control. Data (mean ± S.D.) were collected at the time of stabilization after additions of local anesthetics.

\# : p < 0.05 comparing with low concentration treated group.

\* : p < 0.05 comparing with medium concentration treated group.

Fig. 7. Percent changes of relaxation time (RT_{90\%}) from control. Data (mean ± S.D.) were collected at the time of stabilization after additions of local anesthetics.

\# : p < 0.05 comparing with low concentration treated group.

\* : p < 0.05 comparing with medium concentration treated group.

Bupivacaine 10 μg/ml, and the difference between lidocaine 20 μg/ml and bupivacaine 10 μg/ml showed a statistical significance. Also, in RT_{90\%}, the differences between lidocaine 10 μg/ml and bupivacaine 5 μg/ml, lidocaine 10 μg/ml and bupivacaine 10 μg/ml, lidocaine 20 μg/ml and bupivacaine 5 μg/ml, and the difference between lidocaine 20 μg/ml and bupivacaine 10 μg/ml were statistically significant.

**DISCUSSION**

Both of the two local anesthetic agents showed a significant depression of myocardial contrac-
tility in all concentrations. Numerous in vivo and in vitro studies have examined the etiology of cardiotoxicity of amide-type local anesthetics, especially bupivacaine (Morishima et al., 1983; Tanz et al., 1984; Courtney, 1984). Most recently, Clarkson and Hondeghem (1985) reported that in guinea pig ventricular muscle, both lidocaine and bupivacaine produce direct myocardial depression by blocking cardiac sodium channels. Bupivacaine was found to be a more potent channel blocker, which was attributed to differences in binding affinity and sodium channel association kinetics. The observation that all animals that developed ventricular arrhythmia after lidocaine application reverted spontaneously to normal sinus rhythm whereas approximately 50% of the bupivacaine group did not, suggests that the “fast on-slow off” mechanism to explain differences in the direct myocardial depressant effects of lidocaine and bupivacaine. And this suggestion would appear to concur with the difference in myocardial pharmacokinetics (Reiz et al., 1985). In other words, the difference in in vitro cardiotoxicity between local anesthetic agents seems to be related to their affinity for and duration of binding to the sodium channels. Bupivacaine possibly also blocks calcium channels (Reiz and Nath, 1986).

Other mechanisms proposed for cardiotoxicity focus on the ability of bupivacaine to depress atrioventricular node conduction and/or myocardial contractility (Wojtczak et al., 1984). Whereas isolated heart experiments allow evaluation of direct myocardial effects, in vivo studies involving systemic administration do not allow independent observations of specific isolation into the discrete contributions of CNS and CVS to the observed toxicity. A central mechanism for the negative inotropic and chronotropic actions of lidocaine has been reported (Kao and Jacur, 1959). Because the CNS can exert dromotropic, inotropic, and chronotropic effects on the myocardium, some of the cardiovascular system depressant effects of amino-amide local anesthetics might possibly be mediated through the CNS mechanism (Manning, 1977). Koteldo et al. (1984) observed that equivalent doses of lidocaine or bupivacaine produced similar toxicity when injected rapidly intravenously in conscious sheep. Also, in vivo experiment, the body can exert a homeostatic mechanism which could change the effects of local anesthetics on the heart indirectly. Since this study was performed in vitro conditions, we could eliminate the possibility of the above-mentioned mechanisms which could alter the myocardial actions of local anesthetics.

Bupivacaine has a high protein binding ratio. Even in pH 7.4, the ratio between bupivacaine and lidocaine is about 80% : 65% (Sage et al., 1984). Therefore we could easily guess that an equipotent dose of bupivacaine may show more cardiodepressive activity than lidocaine in this kind of experimental model because there is no protein at all in the physiologic solution. Besides, if the bupivacaine concentration is above 4-5 μg/ml, this high blood concentration would tend to saturate binding sites of albumin and alpha 1-acid glycoprotein and thus lead to a relatively high fraction of the unbound drug. Lee et al. (1990) reported that 5 μg/ml of bupivacaine brought the arrest of twitch in 4 out of 10 cases in an experimental model same as this study, whereas a clinically equipotent dose of lidocaine brought none.

But in this experiment, lidocaine showed a more cardiodepressive tendency than bupivacaine, even though a great portion of the results was statistically insignificant. In Tpd, +dp/dt\text{max}, and −dp/dt\text{max}, it was statistically significant between high dose of lidocaine and low and medium doses of bupivacaine. And lidocaine also showed definite differences in myocardial depression among its three doses, while bupivacaine did not. We might say that lidocaine has more cardiodepressive activity, particularly at high concentration which is 4 times the usual clinically attainable plasma concentration. This finding is different from the mainstream of other reports.

This difference may result from several factors. There is a possibility that bupivacaine concentrations we studied are near the top of the slope in the dose-response curve, whereas lidocaine concentrations belong to the steep portion of the slope. The myocardial depressions in our experiment for low concentrations were almost same for each drug, but there was a tendency for greater depression in high concentrations of lidocaine.
We might speculate that "fast in - fast out" mode of action by lidocaine could be altered by the concentration we used, even though Clarkson and Hondeghem (1985) reported that high concentration of lidocaine blocked sodium channels in "fast in - fast out" manner. Lee et al. (1990) observed 6 out of 10 cases of early stimulation (10-20% higher than control values) at 2.5 μg/ml of bupivacaine. He proposed the possibility of a biphasic action of bupivacaine on myocardium at clinical concentration. We observed two cases of early stimulation in this experiment (Fig. 1). Vornanen (1986) suggested that procaine eliminates aftercontractions, which are probably synchronized miniature calcium fluctuations, thereby allow more uniform loading of the sarcoplasmic reticulum with calcium and greater amount of release during the next twitch. In addition, procaine may also cause small sensitization of contractile proteins to calcium. A similar action might occur in the early phase when we administer bupivacaine.

Moller and Covino (1988) reported that at least 60 minutes is required to washout bupivacaine from isolated rabbit Purkinje fiber-ventricular muscle model. In our experiment, we washed the papillary muscles with cold physiologic solution and waited for stabilization at most 30 minutes in every procedure like some other studies. Possibly, the short waiting time and coolness of the solution might not be enough for the muscle to recover from the previous experimental procedure, especially for lidocaine. It has been known that bupivacaine has the higher lipid solubility than lidocaine. Therefore after a large proportion of the receptor-attached bupivacaine could remain at the heart muscle due to its high affinity, the next dose of bupivacaine could not effectively occupy the receptor sites more than lidocaine because the previously administered dose might bring a change of sodium channel kinetics, if washout and stabilization time was not enough.

Another possibility is that it may be attributed to differences in experimental animals. For example, Kasten and Martin (1986) demonstrated that sheep are more sensitive to bupivacaine than dogs. We used rats, which was different from several other studies in which guinea pigs were used. In addition, bupivacaine is less toxic to heart than lidocaine in mice when given intraperitoneally.

Heavener (1986) provided evidence that the CNS effects of bupivacaine, but not of lidocaine, induced ventricular arrhythmia in cats when injected into the cerebral ventricle. Thomas et al. (1986) observed more profound effects related to its potency and physicochemical properties of bupivacaine than lidocaine when they injected both local anesthetics into the vasomotor and cardioactive areas in the rat medulla. Without the influence from CNS, bupivacaine may show less toxicity than lidocaine to heart.

But in Tr, bupivacaine showed a progressive increase greater than lidocaine. And in RT50%, bupivacaine showed more of an increase than lidocaine in medium and high concentrations. These results are similar with others. We might say that bupivacaine makes the heart muscle more rigid because it showed the prolongation of recovery time from the effects of local anesthetics and the elevation of resting tension.

Cronau et al. (1988) reported that bupivacaine and lidocaine showed indistinguishable effects on glucose utilization, lactate production, and tissue glycogen. Neither of the local anesthetics had any influence on energy charge or creatine phosphate content after 15 minutes' exposure to both local anesthetics in the isolated perfused working rat heart preparation. But Kashimoto et al. (1990) speculated that high doses of local anesthetics may depress cardiac contractility and thereby reduce the myocardial content of ATP. Therefore we could not rule out the possibility that lidocaine and bupivacaine may act differently on energy utilization and thereby on myocardial contractility.

In summary, the cardiodepressive action of lidocaine is somewhat greater than bupivacaine in view of Tpd, +dp/dtmax, and −dp/dtmax, as the concentration increases. But we could not say that lidocaine is more cardiotoxic than bupivacaine because Tr and RT50% showed different results from Tpd, +dp/dtmax, and −dp/dtmax. More studies are needed to clarify this important issue. We might say that lidocaine also showed the significant cardiodepressive activity, at least similar with bupivacaine at equipotent concentrations. Therefore
we have to pay special attention to those patients who are going to receive lidocaine or bupivacaine, especially those whose myocardial function has already been compromised.

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= 국문 초록 =

Lidocaine과 bupivacaine이 쥐의 좌심유두근에 미치는
직접적 효과에 관한 비교연구

서울대학교 의과대학 마취과학교실

이상철

국소마취제는 심혈관계와 중추신경계에 독성을 지녔으며 이중 심혈관계는 중추신경계
보다 더 높은 농도의 국소마취제 투여로 그 독성이 발현되는 것으로 알려져 있다. 이 심
혈관계에 대한 작용은 ester계 국소마취제의 경우 대체로 미약한 것으로 알려져 있으나
amide계 국소마취제에서는 강한 심근수축 억제력을 지닌것으로 보고되어 왔다.
본 연구는 amide계의 국소마취제 중 음상에서 가장 흔히 사용되는 lidocaine과 bupiva-
caine이 심근수축력에 미치는 직접적인 영향을 비교검토하기 위하여 쥐의 좌심실에서 분
리한 유두근을 이용하여 isometric contraction에 미치는 효과를 관찰하였다. 음상적으로 같은
정도의 효력을 나타낼 수 있는 lidocaine과 bupivacaine의 비용인(등효농도) 4:1을 사용
하여 각군에서 음상에서 사용시 흔히 얻을 수 있는 혈장농도인 lidocaine 10 μg/ml 및 bupiva-
caine 25 μg/ml와 이의 2배, 4배의 3가지 농도의 효과를 무순으로 비교관찰하였다.
Tpdm, + dp/dtmax, − dp/dtmax에서는 lidocaine이 농도가 높음수록 더 큰 역제작용을 나타
내는 듯이 보이나 등효농도에서 양국소마취제간에 통계적 유의성은 없었다. 그러나 bupiva-
caine과는 달리 lidocaine의 농도에서 lidocaine의 낮은 농도 및 bupivacaine의 낮은
농도에 비하여 유의한 수축력 저하를 나타내었다. Tr, TPT, RT90時間 보면 bupivacaine이
단소 현저한 억제를 보이는 듯이나 역시 통계적 유의성은 없었다.
본 실험의 결과로 미루어 보건대 lidocaine은 적어도 bupivacaine에 상응할 만한 심근
수축력의 억제력을 지녔다고 생각되는 바 특히 심근 기능이 저하된 환자에 사용시 bupiva-
caine과 더불어 각별한 주의가 필요하다고 사료되는 바이다.