Acute Toxicity of Etidocaine Following Various Routes of Administration in the Dog

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Received September 25, 1975; accepted February 17, 1976

Acute Toxicity of Etidocaine Following Various Routes of Administration in the Dog. EICHOLZER, A. W., AND FELDMAN, H. S. (1976). Toxicol. Appl. Pharmacol. 37, 13-21. When plasma concentrations of etidocaine of 2.7 µg/ml were achieved in the dog following iv administration, signs of CNS toxicity such as mydriasis, nystagmus, and head tremor were observed. Convulsions occurred at plasma concentrations of about 5.0 µg/ml. Cardiovascular effects were minimal at these concentrations or could be related to the convulsive state of the animal. Toxicity observed after repeated peridural administration is related to the spread of etidocaine in the peridural space and the resultant plasma concentrations. Etidocaine has less of a tendency to spread up the spinal column than lidocaine, which results in fewer instances of Horner's syndrome and respiratory depression.

Etidocaine [(±)-2-(N-ethylpropylamino-2'-butyroxylidide) hydrochloride, Duranest] is a new local anesthetic agent with chemical properties that are significantly different from those of lidocaine (Lund et al., 1973). Adams et al. (1972) reported that etidocaine exhibits excellent frequency of block, rapid onset, and a long duration of action. They predicted it would be a clinically useful agent in, for example, peripheral nerve blocks and in peridural anesthesia. Recent clinical studies have shown that etidocaine is a long-acting agent with a rapid onset and an excellent margin of safety (Bridenbaugh et al., 1974; Bridenbaugh et al., 1973).

The present experiments are part of the continuing pharmacological and toxicological evaluation of etidocaine and were designed primarily to evaluate the acute toxic effects of etidocaine in the dog following intravenous, subcutaneous, and peridural administrations.

METHODS

Intravenous administration. Four adult mongrel dogs (one female and three males) were used for these experiments. Etidocaine HCl was administered iv over a 2-min period in serial doses of 0.1, 0.3, 1.0, 3.0, and 10 mg/kg with a 30-min interval between doses. Drug solutions (2%) were prepared with isotonic saline. Venous blood samples were drawn at 2, 5, 10, and 28 min following dosing.

Subcutaneous administration. Four adult mongrel dogs (two females and two males) were used. Solutions of etidocaine HCl were administered sc, at sites 2–3 in. apart,

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in volumes up to 5 ml. Two concentrations were prepared, 0.75 and 7.5%. Serial doses of 10, 30, and 100 mg/kg were injected at 90-min intervals. Blood samples were drawn at 15, 30, 45, 60, and 90 min following dosing.

**Peridural administration.** Five male adult beagle dogs were used for these experiments. A 1% solution of etidocaine HCl was injected into the epidural space via an implanted catheter. Implantation of the catheter and assessment of the patterns of anesthesia conform to the method described by Lebeaux (1973). Four doses of 5 ml each with a dose interval of 60 min was the schedule used. The average dose of etidocaine at each administration for these five dogs was 4.2 mg/kg. Venous blood samples were drawn at 5, 15, and 45 min following dosing. Gross necropsies were performed on all dogs to confirm the location of the tip of the catheter in the epidural space and to determine if a tracer dye, injected at the end of the experiment, indicated leakage into the surrounding tissues.

On the day before the experiments the dogs were anesthetized with sodium pentobarbital, and polyethylene catheters for monitoring pressures were introduced into the abdominal aorta and inferior vena cava through the femoral vessels. A catheter for drug injections was also implanted in a cephalic vein (Duce et al., 1972). The next day the unanesthetized dogs were secured in a standing position in a canvas sling and the femoral catheters were attached to appropriate Statham physiological pressure transducers (P32AA or P32BB). Subdermal ECG electrodes were applied to the legs and a chest pneumograph was attached to a Grass PT-5A volumetric pressure transducer. The blood pressures, ECG and respiration were recorded simultaneously on a Grass Model 7 polygraph. Rectal temperature was monitored via a thermoprobe fed into a Tri-R electronic recorder. Cardiac output was determined in these experiments by a dye dilution technique (Hamilton et al., 1948) utilizing a Beckman Cardiodensitometer. Any signs of overt toxicity were noted at the time of occurrence. All animals were given sodium heparin, 4 mg/kg, iv.

**Experimental procedure.** On the experimental day each dog was allowed 30 min to acclimate. Then three control recordings, 5 min apart, were made including the cardiovascular status, respiration, rectal temperature, and pupil size. Solution administrations were begun, and the above recordings were made again at 1, 2, 5, 10, 15, 30, 45, 60, or 90 min depending upon the dosing interval and method of administration. Maximum percentage changes in these various parameters noted to have occurred after each injection are displayed in the appropriate tables.

Venous blood samples were analyzed for etidocaine content by a gas chromatographic procedure (Scott et al., 1973). Statistical analysis used was the Student's t test (Lindquist, 1953).

**RESULTS**

**Intravenous toxicity.** Table 1 details the cardiovascular and respiratory changes and Figure 1 the corresponding plasma concentrations. Respiratory movements increased significantly \((p < 0.05)\) with a 226% increase following the 0.3-mg/kg dose. After 1.0 mg/kg one dog vomited and three of four dogs showed a transient mydriasis plus nystagmus and head tremor. Immediately after the 3.0-mg/kg dose, mydriasis with no pupillary response to light plus nystagmus occurred in all four dogs. Tonic-clonic convulsions with salivation and urination occurred in all four dogs. Increases in heart...
<table>
<thead>
<tr>
<th>Etidocaine HCl dose (mg/kg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Central venous pressure (cm H$_2$O)</th>
<th>Cardiac output (liters/min)</th>
<th>Respiration (per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>After drug (% change)</td>
<td>Control</td>
<td>After drug (% change)</td>
<td>Control</td>
</tr>
<tr>
<td>0.1</td>
<td>131 ± 14</td>
<td>−3.0</td>
<td>124 ± 54</td>
<td>+3.2</td>
<td>13 ± 8</td>
</tr>
<tr>
<td>0.3</td>
<td>129 ± 15</td>
<td>+4.6</td>
<td>133 ± 55</td>
<td>+6.8</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>1.0</td>
<td>134 ± 12</td>
<td>+4.5</td>
<td>122 ± 76</td>
<td>−9.0</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>3.0</td>
<td>135 ± 15</td>
<td>+27.4c</td>
<td>111 ± 50</td>
<td>+53c</td>
<td>13 ± 8</td>
</tr>
<tr>
<td>10.0d</td>
<td>134 ± 22</td>
<td>−47.8</td>
<td>130 ± 63</td>
<td>+3.0</td>
<td>13 ± 8</td>
</tr>
</tbody>
</table>

* Doses were injected over periods of 2 min at 30-min intervals.
* Values are the maximum percentage change that occurred within 10 min following each dose. Means ± SD for four dogs.
* Significantly different (p < 0.05) from control values by unpaired Student’s t test.
* Three animals moribund at this dose; death occurring within 5 min.
rate and blood pressure accompanied these seizures. After the 10-mg/kg dose three dogs died within 3 min. One dog survived and appeared fully recovered the following day. Respiratory arrest followed by a sharp fall in blood pressure were noted in all three animals at the time of death. The heart continued to beat following respiratory arrest and ventricular fibrillation was observed in one animal at this time.

**Fig. 1.** Plasma concentrations (µg/ml) of etidocaine following iv, sc, and peridural administrations. Time interval between administration of doses: sc, 90 min; iv, 30 min; peridural, 60 min. Values are means ± SE.

*Subcutaneous toxicity.* The cardiovascular and respiratory changes are shown in Table 2. Figure 1 is a graph of the corresponding blood concentrations. Fifteen to twenty minutes after the 30-mg/kg dose, all four dogs vomited and two had head tremors which lasted 5 to 30 min. Following the 100-mg/kg dose mydriasis, nystagmus, salivation, urination, and defecation occurred in three of four dogs. Convulsions were observed in all four dogs which persisted until the death of all animals 7–25 min after dosing. Plasma concentrations of etidocaine at the time of respiratory arrest were 5.7, 7.5, 12.1, and 15.9 µg/ml, respectively, for the four dogs involved. Ventricular extrasystoles were observed in three of four dogs concomitant with respiratory arrest and a rapid fall in blood pressure. Ventricular fibrillation occurred in one dog following respiratory arrest.
<table>
<thead>
<tr>
<th>Etidocaine HCl dose (mg/kg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Central venous pressure (cm H_{2}O)</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>After drug (% change)</td>
<td>Control</td>
<td>After drug (% change)</td>
<td>Control</td>
</tr>
<tr>
<td>10</td>
<td>114 ± 11</td>
<td>−6.1</td>
<td>89 ± 10</td>
<td>+13.5</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>30</td>
<td>108 ± 24</td>
<td>+11.1</td>
<td>87 ± 16</td>
<td>+14.9</td>
<td>12 ± 9</td>
</tr>
<tr>
<td>100( ^{c} )</td>
<td>115 ± 16</td>
<td>−</td>
<td>104 ± 26</td>
<td>−</td>
<td>12 ± 8</td>
</tr>
</tbody>
</table>

* Doses injected at 90-min intervals.

\(^{b}\) Values are the maximum percentage occurring within 60-min of each injection. Mean ± SD for four dogs.

\(^{c}\) Animals moribund following 100-mg/kg dose. Plasma concentrations of etidocaine at time of respiratory arrest: 5.7, 7.5, 12.1, and 15.9 µg/ml.
### TABLE 3

**Effects of Repeated Peridural Injections of Etidocaine HCl to Dogs**

<table>
<thead>
<tr>
<th>Etidocaine HCl dose (mg/kg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th></th>
<th>Heart rate (beats/min)</th>
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<th>Central venous pressure (cm H₂O)</th>
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<th>Cardiac output (liters/min)</th>
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<td>Control</td>
<td>After drug (% change)</td>
<td>Control</td>
<td>After drug (% change)</td>
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<td></td>
</tr>
<tr>
<td>4.2</td>
<td>148 ± 19</td>
<td>−33.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>113 ± 36</td>
<td>−17.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7 ± 2</td>
<td>−43.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.85 ± 0.9</td>
<td>−28.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45 ± 11</td>
<td>−35.5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4.2</td>
<td>101 ± 10</td>
<td>−6.0</td>
<td>110 ± 30</td>
<td>−15.4</td>
<td>3 ± 1</td>
<td>−17.6</td>
<td>2.47 ± 0.6</td>
<td>−20.0</td>
<td>37 ± 20</td>
<td>−45.9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4.2</td>
<td>105 ± 16</td>
<td>−12.4</td>
<td>99 ± 30</td>
<td>−11.0</td>
<td>3 ± 2</td>
<td>N.C.</td>
<td>2.09 ± 0.6</td>
<td>−19.2</td>
<td>20 ± 5</td>
<td>−10.0</td>
</tr>
<tr>
<td>4.2</td>
<td>91 ± 17</td>
<td>−14.3</td>
<td>89 ± 38</td>
<td>−23.6</td>
<td>3 ± 2</td>
<td>N.C.</td>
<td>1.55 ± 0.3</td>
<td>−18.8</td>
<td>19 ± 3</td>
<td>−10.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Dose: 5 ml, over 5 min, 1% etidocaine HCl; mg/kg average for the five dogs.
<sup>b</sup> Values are maximum percentage change occurring within 10 min of each injection. Means ± SD for five dogs.
<sup>c</sup> Significantly different changes from control (p < 0.05).
Peridural administration. The cardiovascular and respiratory changes are given in Table 3. The corresponding plasma concentrations obtained are shown in Figure 1. The pattern of peridural anesthesia seen in all five dogs following the first dose (5 ml, 1%) include the block of scrotal pain, digital pain (rear legs), and an inability to support the weight of the hindquarters. Horner's syndrome seen as ptosis and relaxed nictitans occurred unilaterally in two dogs while a bilateral syndrome was observed in one dog following the initial dose. Decreases in heart rate, blood pressure, cardiac output, and respiratory movements were seen following this dose as a consequence of the induced anesthesia. Generally these parameters continued to show a decline throughout the dosing sequence. The dog with the bilateral Horner's syndrome succumbed during the injection of the second dose due to respiratory arrest. The remaining four animals, following the second dose, were sedated, with two animals having pronounced abdominal breathing movements. Horner's syndrome intensified and involved both eyes; also, all four dogs had abdominal breathing movements. The fourth dose was lethal to three of four remaining animals when respiratory arrest occurred with one animal surviving four repeated doses. Convulsions were not observed at any time during the dosing schedule. Autopsies revealed that the injection of a tracer dye through the catheter was confined to the peridural space of all animals and that the catheter tips were not projecting more than 0.5 mm into the peridural space.

DISCUSSION

Munson et al. (1975) recently presented data indicating that etidocaine shows CNS toxic effects before depressing either ventilation or circulation. The data obtained in our studies further substantiate this statement for etidocaine.

At plasma concentrations of etidocaine at which signs of CNS toxicity were evident, such as nystagmus and head tremors, cardiovascular changes were minimal. This is also consistent with the data reported by Constantino et al. (1968) which showed that lidocaine produced only minor and transient changes in cardiovascular functions in the dog. Jordfeldt et al. (1968) presented data for mepivacaine, bupivacaine, and lidocaine which revealed that they did not have any depressive effects on vital cardiopulmonary functions, whether given in subconvulsive doses in man or in convulsive doses in the dog.

Respiratory changes following etidocaine, iv were quite marked even at low doses in the dog. This must be due to a direct effect on the CNS; however, subsequent increases in ventilation result from the metabolic acidosis which is a consequence of the increased muscular activity induced by the convulsions seen at higher doses of etidocaine. Respiratory arrest is considered to be the primary cause of death (Telivuo and Katz, 1970) although ventricular fibrillation may be a contributing factor in some instances.

Ptosis and relaxed nictitans, characteristics of Horner's syndrome appeared after the first peridural administration of etidocaine in 3/5 dogs. The unilateral or bilateral expression of these characteristics are indications that the anesthetic has spread up the vertebral column to thoracic segments T-1-2-3. Lebeaux (1973) found that lidocaine (2%, 5 ml) caused Horner's syndrome in all dogs injected while bupivacaine (0.5%, 5 ml) produced Horner's syndrome in 8/12 peridural dogs. Etidocaine, therefore, like
bupivacaine appears to spread less than lidocaine. Exaggerated cephalad spread occurred in one animal following the first injection which resulted in the bilateral expression of Horner's syndrome and this animal died during the second administration of etidocaine. Bromage (1962) described the complex interaction of such factors as age, patient condition, posture, and concentration of anesthetic, which in man were shown to affect spread of the analgesic solution in the peridural space. In the dogs in which the drug was administered via the peridural route, the factors influencing spread are thought to be catheter position, quantity of fat in the peridural space, channeling of the solution in this fat as well as concentration of the solution, injection time, and volume of solution injected. Additionally, as one dog survived four successive injections, leakage of anesthetic solution from the peridural space through the various nerve root canals may also play a role in determining the spread of the anesthetic.

The reductions in blood pressure, heart rate, and also a fall in cardiac output, seen in the dogs after peridural administration, may be a consequence of the induction of a block above vertebral segment T-1. Similar reductions of about 19% in cardiac output have been recorded in surgical patients following induction of a block above T-1 (McLean et al., 1967); however, Bonica et al., (1970) did not find a reduction in cardiac output in healthy volunteers after a block above T-1.

The change in respiration seen to occur after the second administration of etidocaine indicates that breathing has become almost exclusively diaphragmatic due to anesthesia of spinal segments up through T-2 and paralysis of the intercostal muscles. Convulsions were not observed in any of these dogs but manifestations of systemic toxicity in the form of shivering and sedation were present when the plasma concentrations of etidocaine approached 4.7 μg/ml. Comparable experiments with lidocaine (100 mg, 5 ml) administered via the peridural route to similar sized dogs produced a plasma concentration of about 3.0 μg/ml 5 min after the injection (Lebeaux, 1973). Etidocaine (50 mg, 5 ml) also produced blood concentrations of 3.0 μg/ml at 5 min indicating that etidocaine reaches the systemic circulation in greater quantities than lidocaine. One explanation for this is that etidocaine has been shown to be a more potent dilator of blood vessels than lidocaine (data to be published).

Death after repeated peridural administration results from the eventual cephalad spread of the drug which involves the vertebral segments C:4–5 and blockade of the roots of the phrenic nerve controlling diaphragmatic respiration.

Thus, in these studies we have shown that etidocaine produces patterns of toxicity similar to those reported for other local anesthetics in the dog and that CNS toxicity occurs before cardiovascular depression can be observed.

REFERENCES


ETIDOCAINE IN THE DOG


CONSTANTINO, R. T., CROCKETT, S. E., AND VASKO, J. S. (1968). Cardiac and peripheral effects of lidocaine. Amer. J. Cardiol. 21, 94.


