EFFECTS OF ACUTE ACETYLCHOLINESTERASE INHIBITION BY PYRIDOSTIGMINE BROMIDE INJECTION IN EUVOLEMIC AND HYPOVOLEMIC CONSCIOUS SWINE

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Effects of acute acetylcholinesterase inhibition by pyridostigmine bromide injection in euvolemic and hypovolemic conscious swine--Wade et al

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In conducting the research described in this report, the investigation adhered to the “Guide for the Care and Use of Laboratory Animals,” as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

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The effects of acute reduction of blood cholinesterase activity, induced by pyridostigmine bromide injection (300 μg/kg intra-arterially), on physiological and biochemical parameters were assessed in conscious swine with and without hemorrhagic hypotension. Pyridostigmine administration reduced red blood cell acetylcholinesterase (AChE) activity by 61% with values returning to basal values within 3 hrs in both euvolemic and hypotensive animals. In hypovolemic animals plasma AChE activity was reduced by 35% compared to 14% in euvolemic animals. The greater reduction with hypovolemia was due to a 14% decrease during hemorrhage. The acute reduction of AChE activity by pyridostigmine injection in euvolemic and hypovolemic conscious swine did not significantly alter a range of biochemical and physiological parameters. Acute transient symptoms of reduced AChE activity were noted in a few of the hemorrhaged animals.
Abstract

The effects of acute reduction of blood cholinesterase activity, induced by pyridostigmine bromide injection (300 μg/kg intra-arterially), on physiological and biochemical parameters were assessed in conscious swine with and without hemorrhagic hypotension. Pyridostigmine administration reduced red blood cell acetylcholinesterase (AChE) activity by 61% with values returning to basal values within 3 hrs in both euvolemic and hypovolemic animals. In hypovolemic animals plasma AChE activity was reduced by 35% compared to 14% in euvolemic animals. The greater reduction with hypovolemia was due to a 14% decrease during hemorrhage. The acute reduction of AChE activity by pyridostigmine injection in euvolemic and hypovolemic conscious swine did not significantly alter a range of biochemical and physiological parameters. Acute transient symptoms of reduced AChE activity were noted in a few of the hemorrhaged animals.
On the conventional battlefield many injuries result in hemorrhage (1). An injury caused by conventional weapons plus chemical agents resulting in hemorrhage will probably expose military personnel to chemical agents due to perforation of protective clothing by the missile producing the injury.

Trauma, such as burns and hemorrhagic hypotension, has been shown to reduce blood cholinesterase activity (2-5). These types of injury also may potentiate the actions of cholinergic drugs (6-8). Piscevic et al (9) found that simultaneous hemorrhage and chemical trauma resulted in the death of animals exposed to normally nonlethal doses of the nerve agent sarin. Hemorrhagic hypotension causes a reduction in blood cholinesterase activity, which may potentiate the lethal effects of nerve agents. Thus, the reduction in blood cholinesterase activity incurred during trauma on the battlefield may lead to an increased susceptibility to poisoning by nerve agents. We therefore investigated the physiological and biochemical effects of acute reduction of blood cholinesterase activity induced by pyridostigmine bromide administration in conscious swine with and without hemorrhagic hypotension.

Methods

Immature (2- to 3-month-old) Duroc swine (both gilts and barrows) were studied. The animals were purchased from a commercial supplier and housed in the Institute for at least ten days prior to surgery. They were fed a commercial ration (Purina, St Louis, MO) and allowed water ad lib.

After fasting overnight the animals were given a preanesthetic intramuscular injection of 0.08 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl and 2.2 mg/kg xylazine. Halothane anesthesia was induced using a face mask and maintained with an endotracheal tube. The posterior aorta was catheterized using sterile procedures (10). The catheter was tunneled under the skin and exited on the dorsal surface of the neck. The animals were observed until fully recovered and returned to holding cages. Catheter patency was maintained by flushing at 3- to 4-day intervals with heparin (1000 u/ml) in normal saline.
After 5 to 7 days of postoperative recovery each animal was fasted overnight. The following morning the animals were transported to the laboratory in a portable holding cage, and they remained in the holding cage. The animals were then connected to a 12-inch pressure-monitoring injection line that had been fitted with a three-way stopcock and filled with heparinized saline. The system was then flushed with heparinized saline and connected to a pressure transducer and monitoring system (Gould, 22405). Following a 30 minute equilibration period, the animals were hemorrhaged at 36 ml/kg, 50% of the estimated blood volume, in a logarithmic fashion (11, 12). Between minutes 0 and 60, equal increments of blood were withdrawn at 9, 19, 44, and 60 min. Upon completion of the hemorrhage the animals received an intra-arterial injection of normal saline (0.1 ml/kg, 0.9% NaCl), n=6 [data from these animals have been reported previously (12)] or pyridostigmine bromide (300 µg/kg, Mestinon® 5 mg/ml, Roche Laboratories, Nutley, NJ) n=7. Additionally, nine (n=9) animals which did not undergo hemorrhage were treated with the same dose of pyridostigmine bromide.

Measurements of hemodynamic variables were obtained at 0, 60, 62, 65, 75, 90, 105, 120, 135, 150, 165, 180, 210, and 240 minutes. Arterial blood samples were taken at 0, 60, 62, 65, 75, 90, 105, 120, 180, and 240 minutes. Additional blood samples were obtained during hemorrhage to determine acetylcholinesterase activity (see Fig. 1). Blood pressure, heart rate, and pulse pressure were measured for one minute prior to each sampling period and an average obtained. Plasma lactate (Sigma Chemical Co., St Louis, MO) and glucose (Beckman Instruments, Anaheim, CA) levels were measured by standard assay techniques. Hematocrit was measured by the microcapillary method. Blood gases were measured by a System 1303, (Instrumentation Laboratory, Lexington, MA).

Acetylcholinesterase activities of the plasma and red blood cells were determined with a Technicon Auto Analyzer II system using a modification of the method of Ellman et al (13) adapted by Levine et al (14). Acetylthiocholine was used as the substrate (see Letterman Army Institute of Research Standard Operating Procedure OP-ACH-38, Auto Analyzer II Acetylcholinesterase Assay, 1982).

Data were analyzed using a two-way analysis of variance with comparisons made between groups and over time. Differences between means were assessed using the Newman-Keuls procedure. A significance level of 0.05 was
used on all tests. Values in the text are mean plus or minus the standard error of the mean.

Results

Hemodynamic: Heart rate was not altered during the sampling periods by hemorrhage or the administration of pyridostigmine (Table I). In euvoletic animals blood pressure was not altered by pyridostigmine; however, pulse pressure was significantly decreased by 12 mmHg. Blood pressure was reduced by hemorrhage and was not affected by injection of pyridostigmine.

Arterial Blood Gases: Arterial blood measurements were not altered in euvoletic animals by the injection of pyridostigmine (Table II). There were differences in arterial O₂ pressure and HCO₃ between the two groups of hemorrhaged animals, but these differences were not altered by pyridostigmine administration because a time group interaction was not noted. Thus, pyridostigmine did not change arterial blood gas in euvoletic and hemorrhaged animals.

Lactate/Glucose/Hematocrit: Although blood lactate and glucose levels increased during hemorrhage and hematocrit decreased, no effect from pyridostigmine administration was noted (Table III). Also in euvoletic animals no changes were noted due to this drug dosage.

Acetylcholinesterase Activity: Administration of pyridostigmine caused an immediate reduction in plasma and red blood cell AChE activity in both euvoletic and hemorrhaged animals (Table IV). Red blood cell AChE activity was acutely reduced (more than 50%) and gradually returned to basal levels over the following three hours (Fig. 1). In euvoletic animals given pyridostigmine, a 14% decrease in plasma AChE activity occurred, while in hemorrhaged animals a 35% reduction was noted. This difference was due to a 15% decrement in activity incurred over the course of hemorrhage.

Adverse Effects: Although few of the biochemical and physiological measurements were altered by pyridostigmine administration, side effects were noted. The side effects of pyridostigmine occurred only in the hemorrhaged animals. Upon administration of pyridostigmine following hemorrhage, a pronounced bradycardia was observed in 4 of 7 animals (Fig. 2). This bradycardia was rectified within
two minutes as there was no difference in heart rate or that of hemorrhage-control animals. In two animals hemorrhaged and given pyridostigmine, fasciculation was observed, and in one of these animals a period of labored breathing was noted. No adverse effects were noted in euvolemic animals treated with pyridostigmine.

**Discussion**

Pyridostigmine is a reversible inhibitor of acetylcholinesterase (AChE), the enzyme that degrades the neurotransmitter acetylcholine. In the present study pyridostigmine was used to evaluate the effects of acute reductions of AChE activity in hemorrhaged swine. Hemorrhage and trauma reduce AChE activity (2-5), which may be detrimental to individuals exposed to further reductions in activity, thus potentiating the actions of acetylcholine. In the present study the biochemical and physiological effects of further reductions in AChE activity following hemorrhage were investigated and no pronounced decrements noted. Furthermore, in euvolemic animals the reduction of AChE activity showed no effect.

The absence of changes in cardiovascular and biochemical parameters in the presence of reductions of 33% in plasma and 61% in red blood cell AChE activity may be due to the preponderance of AChE in tissues. In fact, a reduction of over 90% in blood activity is often required to elicit symptoms of acetylcholinesterase poisoning (15, 16).

Symptoms of acetylcholine toxicity (bradycardia, fasciculation, labored breathing) were noted in hemorrhaged animals following reduction of AChE activity induced by pyridostigmine administration. Though the symptoms were acute and inconsistent in this group, they are pronounced in that no adverse responses were noted in either of the other treatment groups, hemorrhage untreated or euvolemic with pyridostigmine. The presence of symptoms following pyridostigmine administration to hypotensive animals in the present study are in conflict with the observations of Piscevic et al (9). In their studies simultaneous hemorrhage and reduction of AChE activity by administration of a nonlethal dose of the nerve agent sarin to rats resulted in death with symptoms not observed or of "insignificant" intensity. Although symptoms were noted in the present study of swine, all animals survived the procedure, and the reduction in AChE
activity by pyridostigmine administration was probably not as pronounced as that induced by sarin.

In conclusion, acute reduction of AChE activity by pyridostigmine administration in euvoletic or hemorrhagic conscious swine failed to significantly alter a range of biochemical and physiological parameters. However, acute transient symptoms of reduced AChE activity were noted in a few of the hemorrhaged animals.

Recommendations

1. Further work is required to study the combined effects of trauma and exposure to nerve agents.

2. Future work should be conducted in an animal model that allows symptomatology as well as physiological and biochemical parameters to be assessed.
References


Fig 1: Red blood cell and plasma acetylcholinesterase activity (AChE), as a percent of initial activity, in hemorrhage-control (▲—▲), (for initial values, see Table IV), hemorrhage-pyridostigmine (○—○), and control-pyridostigmine (●—●) conscious swine.
Fig 2: Blood pressure tracing in three animals prior to and immediately following intra-arterial injection of pyridostigmine (33 µg/kg).
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<td>0.37°10.85</td>
<td>0.38°10.83</td>
<td>0.38°10.83</td>
</tr>
<tr>
<td><strong>Red Blood Cell ACHE (u/ml Hb)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hemorrhage-Saline</td>
<td>4.1120.89</td>
<td>3.4720.79</td>
<td>4.5290.89</td>
<td>4.3020.83</td>
<td>4.4120.84</td>
<td>4.2320.84</td>
<td>4.0120.84</td>
<td>3.8220.84</td>
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<td>Hemorrhage-Pyride</td>
<td>3.5320.88</td>
<td>4.0020.88</td>
<td>1.56°10.10</td>
<td>1.30°10.10</td>
<td>1.56°10.10</td>
<td>1.91°10.10</td>
<td>2.33°10.20</td>
<td>2.14°10.19</td>
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<tr>
<td>Control-Pyride</td>
<td>4.0120.89</td>
<td>4.0220.88</td>
<td>2.14°10.21</td>
<td>2.38°10.33</td>
<td>2.73°10.49</td>
<td>2.05°10.30</td>
<td>2.15°10.29</td>
<td>3.53°10.32</td>
</tr>
</tbody>
</table>

* Significantly different from hemorrhage-saline, P<0.05.

* Significantly different from 60-min value in control-pyride, P<0.05.
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