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INSTITUTE REPORT NO. 233

# EFFECTS OF ATROPINE, 2-PAM, OR PYRIDOSTIGMINE IN EUVOLEMIC OR HEMORRHAGIC CONSCIOUS SWINE

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LETTERMAN ARMY INSTITUTE OF RESEARCH PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129 Effects of atropine, 2-PAM, or pyridostigmine in euvolemic or hemorrhagic conscious swine--Wade et al.

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moderate hemorrhage in conscious swine.

## Abstract

We investigated the effects of atropine, pralidoxime chloride (2-PAM), or pyridostigmine on the physiological and metabolic responses to hemorrhagic hypotension in conscious swine. All treatments were evaluated in euvolemic and hemorrhaged animals (36 ml of blood/kg/over one hour). Hemorrhage reduced blood pressure by 58 mmHg and decreased plasma acetylcholinesterase (AChE) activity by 18% in the control animals (n=6). Atropine injection increased heart rate similarly in hemorrhaged (n=6) and euvolemic (n=6) animals. Blood pressure was also transiently elevated following atropine administration. Injection of 2-PAM acutely elevated the levels of plasma lactate and plasma AChE, but values were similar to those in the untreated animals within 15 min in both euvolemic (n=7) and hemorrhaged (n=7) animals. Treatment with pyridostigmine for 3 days reduced plasma AChE by 37% and red blood cell AChE by 35% (n=12). Pretreatment with pyridostigmine had no effect on any of the responses to hemorrhage. Posthemorrhage treatment with atropine or 2-PAM or pretreatment with pyridostigmine had no detrimental effects on the physiological or metabolic responses to moderate hemorrhage in conscious swine. Keywords ; woonds and injuries ; Trauma +

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## INTRODUCTION

Military personnel are to be issued a nerve agent antidote kit (NAAK), which consists of atropine and pralidoxime chloride (2-PAM) (1,2), for treatment of nerve agent poisoning. Pretreatment with pyridostigmine to be taken in anticipation of nerve agent attack may also be used (2,3). It is assumed that individuals pretreated with pyridostigmine may incur conventional battlefield injuries (4) and that casualties will receive postexposure therapies (5). The effects of these pharmacological pretreatments and antidotes on the care and outcome of the casualty with conventional injuries are unknown. Of concern are the nerve agent antidote's pharmacological effects on the physiological and metabolic responses to injury, interference with the triage of casualties, interaction with analgesics and anesthetics, and patient variability in the response to and recovery from surgery. The present studies were undertaken to investigate the effects of atropine, 2-PAM, or pyridostigmine administration on the physiological and metabolic responses to hemorrhagic hypotension in conscious swine.

#### METHODS

Immature (2- to 3-month-old) Yorkshire swine (gilts and barrows) weighing 20 to 25 kg 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) and allowed water ad lib.

After fasting overnight, each animal was 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 and jugular vein were catheterized using sterile procedures (6). The catheters were tunneled under the skin; the arterial catheter exited on the dorsal surface of the back, and the venous catheter via the neck. The animal was observed until fully recovered and returned to a holding cage. Catheter patency was maintained by flushing at 3- to 4-day intervals with heparin (1000 u/ml) in normal saline.

After five to seven days of postoperative recovery, the animals were fasted overnight. The following morning

the animals were transported to the laboratory in a portable holding cage. The pigs remained in the holding cage throughout the experiment. The animals were connected to a 12-inch pressure-monitoring injection line 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, Model 24005, Cleveland, OH). Following a 30-minute equilibration period, the animals remained euvolemic or were bled at a rate of 36 ml/kg over a 60-minute period for an estimated 50% loss of blood volume. The one-hour bleeding period was selected arbitrarily to simulate a hemorrhage that might be seen in a combat casualty. The rate of blood loss was based again arbitrarily on an exponential scale such that 10% increments of the total estimated blood volume were removed uniformly over successive intervals of 9, 10, 11.5, 13.5, and 16 minutes. Upon completion of the hemorrhage the animals were studied for an additional three hours. Hemodynamic measurements and blood samples (20 ml) were obtained throughout the 60-min hemorrhage period and for three hours during recovery (see Fig. 1 for sample times). Animals underwent one of the following treatments:

1. Saline Control: Upon completion of the hemorrhage period, animals (n=6) were injected intraarterially with 0.1 ml/kg of normal saline (0.9% NaCl). This infusion volume was selected because it was similar to the carrier volume infused in previous studies.

2. Atropine: Animals were injected intra-arterially with atropine sulfate 0.08 mg/kg (Sigma Chemical Co., St Louis, MO) taken up in 0.1 ml/kg of normal saline just after the 60-min sample was taken at the end of the hemorrhage period. Euvolemic animals (n=6) and hypovolemic animals (n=6) were evaluated. The dose of atropine selected is the total dose recommended for treating exposure to nerve agents, i.e., three Mark II autoinjectors (1).

3. 2-PAM: After the blood samples were taken during the 60-min hemorrhage, the animals were injected intraarterially with 20 mg/kg of pralidoxime methochloride (2-PAM) (Aldrich Chemical Co., Milwaukee, WI) taken up in a 0.1 ml/kg of normal saline. Euvolemic (n=7) and hemorrhaged (n=7) animals were injected with 2-PAM after 60 minutes, at the completion of the hemorrhage. The dose

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(20 mg/kg) is similar by weight to the recommended total dose, i.e. 3 Mark II autoinjectors (1).

4. Pyridostigmine: Pyridostigmine bromide (Mestinon®, Roche Laboratories, Nutley, NJ) was administered orally at 1500, 2300, and 0700 hours at 60 mg per dose for three days. The pyridostigmine was administered in the liquid form by a syringe from which the animal voluntarily licked the contents. Prior to administration of pyridostigmine a blood sample was obtained on day 0 to measure basal plasma and red blood cell acetylcholinesterase activity. On the day of the experiment, procedures were begun at 0900 hours, two hours after the last dosing. Seven animals underwent hemorrhage, while five animals served as euvolemic controls. The dose of pyridostigmine, approximately 9 mg/kg/day, was selected because it had produced the desired reduction (30% to 50%) in plasma and red blood cell acetylcholinesterase activity (2, 3, 7-10).

Blood pressure and heart rate were measured for one minute during each sampling period from the blood pressure tracing and an average obtained. Blood 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 on a System 1303 (Instrumentation Laboratory, Lexington, MA). Plasma and red blood cell acetylcholinesterase activities (AChE) were measured using a Technicon Auto Analyzer II system with modification of the method of Ellman et al (11), that had been adapted by Levine et al (12) and using acetylthiocholine as the substrate (see Letterman Army Institute of Research standard operating procedure OP-ACH-38, 1982 and update). The method of Groff and Ellin (13) was used to measure the levels of 2-PAM in plasma.

Data were analyzed using a two-way analysis of variance with comparisons made between groups (a hemorrhage control versus hemorrhage drug treatment) and over time. Differences between means were assessed using a Newman-Keuls test. When appropriate, a t-test was used. A probability less than or equal to 0.05 was accepted as being significant. Values in the text are mean plus or minus the standard error of the mean.

RESULTS

Control: Hemorrhage produced a significant fall in mean arterial pressure (MAP) of 58 mm Hg (Figure 1, Table 1). MAP rose over the recovery period, but was still reduced in comparison to initial values. Heart rate was not significantly altered. Arterial Pco, was significantly reduced from 37 mm Hg at time 0 to 28 mm Hg at the end of hemorrhage and returned to basal values, 35 mm Hg, during the recovery period (Fig. 2, Table 2). Plasma glucose and blood lactate levels were increased over the course of hemorrhage and remained elevated throughout the recovery period (Figure 2, Table 3). Plasma acetylcholinesterase activity (AChE) decreased during the hemorrhage by 18% and remained reduced during the 3 hours of recovery (Figure 3, Table 4). Red blood cell AChE activity expressed per unit of packed cell volume was unchanged, but over the course of the experiment hematocrit was reduced from 27 to 21% (Table 3).

Atropine: Atropine administration resulted in a significant increase in heart rate which was similar in hemorrhaged and euvolemic animals (Fig. 4, Table 1). Blood pressure was also acutely elevated following atropine administration in hemorrhaged and euvolemic animals (Fig. 4, Table 1). Arterial Pco, levels of plasma glucose and blood lactate, and plasma and red blood cell AChE were not altered following atropine administration in euvolemic animals and were not significantly different following hemorrhage in comparison to untreated hemorrhaged animals (Tables 3, 4).

2-PAM: The administration of 2-PAM did not significantly alter blood pressure or heart rate in euvolemic animals and did not change the response to hemorrhage (Table 1). Blood glucose levels, red blood cell AChE activity, and arterial Pco, also were not changed (Tables 2, 3, 4). However, in euvolemic animals the administration of 2-PAM caused an acute increase in lactate from 4.5 to 10.1 mg/dl at two minutes but the level returned to basal values within 15 minutes, and a similar trend was noted in plasma AChE activity (0.46 ± 0.05 to 0.50 ± 0.05 u/ml in two minutes) (Tables 2, 4). Following hemorrhage the lactate levels changed from 31.8  $\pm$  3.4 mg/dl to 52.9  $\pm$  3.6 mg/dl and the plasma AChE activity from 0.40 + 0.04 U/ml to 0.47 + 0.04 U/ml at two minutes with both parameters returning to pretreatment levels within 15 minutes. The plasma levels of 2-PAM were not significantly different during the recovery period in

treated euvolemic and hemorrhaged animals (Figure 5). The half-life of 2-PAM, 65 to 75 min, was therefore not altered by this degree of hemorrhage.

Pyridostigmine: Beyond the expected reduction in the AChE activities of red blood cells (to 65 ± 5% of initial values) and of plasma (to 63 ± 4% of initial values) following the three days of treatment, none of the measured variables showed significant changes in euvolemic animals over time or varied in the response to hemorrhage in comparison to untreated animals (Tables 1, 2, 3, and 4). The decrease in plasma AChE activity during hemorrhage, 17%, was similar to that observed in euvolemic animals, 20% (Table 4), following administration of pyridostigmine (Table 4).

### DISCUSSION

In the investigation of atropine, 2-PAM, or pyridostigmine administration on the physiological and metabolic responses to hemorrhage, possible detrimental effects leading to a decrease in survival were of concern. However, the moderate hemorrhage in this study of conscious swine caused no severe adverse effects with any of the therapies investigated.

A change in heart rate was shown with atropine injection in both euvolemic and hypovolemic animals. The increase in heart rate did not attain maximal values for pigs (14). In humans the dose of atropine used in our study produces only a moderate increase in heart rate (15, The slight but significant increase in blood 16). pressure of about 10 mm Hg observed with atropine may be beneficial and may in fact possibly influence survival in severe hemorrhage. In humans, however, a slight decrease in systolic blood pressure has been reported (15, 16). Though no negative effects were found, we are still concerned about the responses to atropine (tachycardia, mydriasis, dizziness, lassitude and increased body temperature in some instances) which would interfere with the triage of the battlefield casualty. This problem has vet to be resolved.

The administration of 2-PAM produced acute increases in blood lactate and plasma AChE activity. The increase in lactate during hemorrhage may be detrimental if adequate buffering capabilities are not available. Plasma lactate concentration is indicative of outcome (survival)

in a variety of traumatic conditions (17, 18, 19). The rise in plasma AChE activity due to 2-PAM may be beneficial by partly rectifying the reduction in activity incurred during hemorrhage. However, both the increases in blood lactate and plasma AChE activity in response to 2-PAM administration were acute, lasting 5 minutes, and would appear to have no influence on the care or outcome of the combat casualty.

The clearance of 2-PAM from the plasma was not altered by hemorrhage in the present study, though a reduction due to a decrease in metabolism and excretion associated with falls in renal and hepatic blood flow during hemorrhage was postulated (20, 21). The observed half life of 2-PAM in pigs is 65 to 75 min, similar to that in man (22).

Although the reduction in AChE activity achieved in the swine chronically administered pyridostigmine was similar to that in man with the pretreatment dose, i.e. 20-40%, a larger dose per kilogram was required. Furthermore, the measured metabolic and physiologic responses to hemorrhage in the swine were not altered by pyridostigmine. It thus appears that pretreatment with fyridostigmine will not be of immediate concern in the outcome of the combat casualty. However, the interaction of pyridostigmine with anesthetics and analgesics, specifically morphine (23, 24), is still of concern.

In untreated animals, plasma AChE activity was reduced with hemorrhage and remained decreased over the course of the experiment. Others have reported a similar fall in total blood AChE activity with hemorrhage and in burn victims (25-29). The 18% reduction in plasma AChE activity in the present study could have been caused primarily by transcapillary refill, which may account for as much as 30% of the plasma volume following this degree of hemorrhage (30, 31). Frawley et al (27) reported that AChE activity may remain at a reduced level for days after a battlefield injury. In the present study, while no change in red blood cell AChE activity per milliliter of packed cell volume was found, there was a reduction in red cell volume due to hemorrhage, resulting in a decrease in total vascular red blood cell AChE activity. The combined reduction of AChE associated with red blood cells and plasma represents a 57% decrease in vascular AChE activity.

A fall in vascular AChE activity does not indicate associated changes in autonomic nervous system function, as changes in plasma levels may not reflect changes in AChE at the synaptic cleft. The decrease in available AChE in the vascular compartment is possibly of little consequence since inhibition of up to 90% of activity is necessary to produce abnormal function, due to AChE being present in most tissues in quantities in excess of that normally required to degrade acetylcholine (32), However, the decrease in AChE due to hemorrhage may explain the findings of Piscevic et al (33) that simultaneous hemorrhage and chemical agent trauma resulted in the death of animals exposed to normally nonlethal doses of the nerve agent sarin. Thus, the reduction in AChE activity that occurs during traumatic hemorrhage may potentiate the responsiveness to acetylcholine (nerve agents).

In conclusion, pharmacological pretreatment with pyridostigmine or the administration of the antidotes atropine or 2-PAM does not appear to affect the physiological and metabolic responses to hemorrhagic hypotension as investigated in conscious swine not exposed to nerve agent poisoning. Of concern still are the possibilities that these agents may interfere with analgesics and anesthetics, and may vary the response to and recovery from surgery. These issues remain to be investigated.

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Figure 1: Heart rate and mean arterial pressure in response to hemorrhage in six conscious swine.



Figure 2: Arterial CO, pressure, blood lactate and blood glucose levels in response to hemorrhage in six conscious swine.





Figure 3: Plasma and red blood cell acetylcholinesterase activity (AChE) in response to hemorrhage in six conscious swine.

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Time (min)

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Figure 5: Plasma 2-PAM levels in response to intraarterial administration in euvolemic ( $\bigcirc$ ) and hypovolemic (O---O) conscious swine.

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Toble 1: Meon acterial pressure, pulse pressure, and hect rate of swine with euvolemeic (E) or hemorrhoge (H) (e-66 min) with tractment of control (C), atropine (A), 2–PAM (2P), or pyridostigatine (P).

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£-A	97±3	16645	10716	101+6	1044G			111	484	2824
Į	<b>9274</b>	4514	5245	2745	2444		97111	100±9	96±18	<b>8118</b>
-3e	97±5	8816	8144	1010E			56±2	55±3	11 11 11	66±6
81 ±	10145						9246	9079 8	10018	9628
1				9226	4425	48±7	6 <u>1</u> 84	1105	5414	111
; ]			8 1 1		いたち	8788	182±6	10413	162±5	
			1 1 1	5114	2 2 2	474	97FG	4815		( <sup>0</sup> ) 1 1 1 1
Ine Pressure										
Ĵ										
¥	5327	2917	4518	2442	41474	8464				
Ę.	5612	4144	1				CI 24+	52±12	48514	59219
Ŧ	į						1911	1848	38±5	37±5
-3			2787	C197		<b>J6±3</b>	1975	1997	4127	7484
8. ±				1 1	111	4448	424	42±5	2815	3945
1				6787	555	42±1	5454	43±3	4244	4546
	Ì.	1200	1	5353	5128	5618	46+8	4847		
ł	6119	2013	, , ,	2314	2112	2815	3453	2843		ן יי ו ו ו ו
art Rate										<b>)</b>   
ats/sin)										
	14125	132212	121+10	118+0						
	13427	139124	220424	211426			13211	141±12	162±5	167±11
	132±6	128112	142418			4138/1	172415	151±16	132±10	138±10
	14129	13148	123+7	12146		180214	176±13	168±10	172±10	161213
	3748	1 30+ 3			1581	CI 171	122±4	13128	13018	119±8
	3115	12547	•	012671	C1 2021	131211	136±13	148±17	142214	155±15
	14358	128412	1 <sup>9</sup> 1 1 1 1 1	11111	11226	128 <u>19</u>	125±10 128±14	130±10 134+0	123±10	1 1 1

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<sup>4</sup>velues net ebtained: <sup>\*</sup>Significently different free H-C, P-O,105: <sup>\*</sup>Significently different free 60 min for eurotenic enimale.

Distance of

Wade et al--17

**De le felle de la contracte de** 

01         044         1245         11255         11215		•		5	ų	ļ	2				
01         0000         11245         10216         11245         10216         11226         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         10216         102171         10217         10											240
0000         12000         00000         11225         00000         1225         00000         1225         00000         1225         00000         1225         00000         1225         00000         1225         00000         1225         00000         1225         00000         1225         00000         1225         000000         000000         000000 </td <td>j s</td> <td>-</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	j s	-									
0013         0013 <th< td=""><td>Ŧ</td><td>~</td><td>12425</td><td>10015</td><td>86<u>1</u>2</td><td>112±5</td><td>167±10</td><td>11746</td><td>100+6</td><td>1804.6</td><td>3114</td></th<>	Ŧ	~	12425	10015	86 <u>1</u> 2	112±5	167±10	11746	100+6	1804.6	3114
0022         10024         0024         0024         10024         0025         <	6-A	6 <del>1</del> 66	86±3	8713	9412	86±2.2	92±10	8519	2.17	2112	C+C8
PP:0         Deta         Deta <thdeta< th="">         Deta         Deta         <thd< td=""><td>Ŧ</td><td>8812</td><td>10916</td><td>10727</td><td>9914</td><td>11423</td><td>103±6</td><td>112118</td><td>116+7</td><td>10145</td><td></td></thd<></thdeta<>	Ŧ	8812	10916	10727	9914	11423	103±6	112118	116+7	10145	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	42 - 3	Ĩ	8413	8014	8311	88+1.5	86+2	A444	111	6770	07001
823.1         823.1 <th< td=""><td>8 ±</td><td>-</td><td>946</td><td></td><td>100+2</td><td>187+7</td><td>182+9</td><td>102+5</td><td>14147</td><td>1718</td><td></td></th<>	8 ±	-	946		100+2	187+7	182+9	102+5	14147	1718	
04.3         116.2          111.21         103.2          105.2         1	Ĵ	9213.3	6214	•	0	8.3+4	6744		2+7K	1+54	
37.421.2       27.481.3       31.231.4       31.231.4       32.231.5       33.621.7       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.6       33.621.7       34.621.6       33.621.1       33.621.7       34.621.6       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       33.621.1       34.721.2       36.61.1       37.221.2       36.61.1       37.221.2       36.61.1       37.221.2       36.61.1       37.221.2       36.61.1       37.221.2       36.61.1       37.221.2       36.61.1       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.6       37.221.2       36.41.2       37.221.2       36.41.2       37.222.2       37.222.2	1	94±3	11622			11123	10312	1 <b>°</b> 3 1 1 1 1 1 1	106±2	10412	1 <sup>9</sup> 1 1 1 1 1
Y4:1.2       Z'.0:1.7       31.31.9       Ma.21.6       31.21.4       32.21.5       33.61.1       34.61.1	Pco <sub>2</sub> (m	( <sup>0</sup> ,									
36.8E1.6       37.8E1.6       37.8E1.6 <td< td=""><td>ł</td><td>37.4±1.2</td><td>27.811.7</td><td>31.321.9</td><td>36.221.6</td><td>31.221.4</td><td>32.221.5</td><td>33.011.8</td><td>35.641.0</td><td>35.441.4</td><td>5 147 GE</td></td<>	ł	37.4±1.2	27.811.7	31.321.9	36.221.6	31.221.4	32.221.5	33.011.8	35.641.0	35.441.4	5 147 GE
39.250.0       31.81.1       35.650.5       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.651.6       35.751.5       35.651.6       35.251.7       35.251.7       35.251.7       35.251.7       35.251.6       35.251.6       35.251.6       35.251.6       35.251.6       35.251.6       35.251.6       35.251.6       35.651.6       37.651.6       37.651.6       37.651.6       37.651.6       37.651.6       37.651.6       37.651.6       37.652.601       37.642.606       7.642.606       7.642.606       7.642.606       7.642.606       7.642.606       7.642.606       7.642.606	E-A	36.6±1.8	39.921.0	37.3±2.6	37.913.6	37.8±1.5	39.621.7	40.912.7	41.412.6	39.612.3	A 141 A4
37.351.6       39.121.4       3421.5       30.321.2       30.421.6       37.221.2       30.421.6       37.221.2       30.421.6       37.221.2       30.421.6       37.221.2       30.421.6       37.221.2       30.421.6       37.221.2       30.421.6       37.221.2       30.421.6       37.441.6       37.441.6       3	¥¥	39.9±0.9	31.8±1.3	35.6±0.5	35.818.65	35.6±1.0	35.910.6	36.8±8.5	36.410.9	38.6±1.6	37.711.6
36.250.6       30.521.2       35.240.7       30.421.6       34.521.5       34.140.5       30.421.8       30.421.6         30.350.6       30.421.3        40.211.3       37.321.1       37.321.1       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       30.421.8       31.221.101       31.221.011       31.2	E20	37.6±1.6	39.1±1.4	36±1.5	36.3±6.9	38.7±1.5	38.7±1.2	30.811.5	38.111.0	37.2±1.2	36.611.0
30.326.4       40.61.1        40.21.3       37.21.5        30.41.6       30.41.6       30.41.6       30.41.6       30.41.6       30.41.6       30.41.6       30.41.6       30.41.6       30.41.7       30.41.7       30.41.6 <t< td=""><td>å Ŧ</td><td>36.510.6</td><td>30.512.2</td><td>36.220.7</td><td>21.221.6</td><td>34.8<u>1</u>8.8</td><td>34.721.5</td><td>34.110.5</td><td>36.011.2</td><td>36.111.0</td><td>37, 310.5</td></t<>	å Ŧ	36.510.6	30.512.2	36.220.7	21.221.6	34.8 <u>1</u> 8.8	34.721.5	34.110.5	36.011.2	36.111.0	37, 310.5
35.556.6       26.421.3	2	38.328.4	40.6±1.9	• 1 1 1	0 ( 1 1 1	40.2±1.3	37.941.5	•       	38.411.8	39.4±0.9	0
7.422.010       7.4582.011       7.4122.017       7.4122.014       7.4082.005       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4122.012       7.4412.010       7.4222.012       7.4412.012 <td>1</td> <td>36.510.8</td> <td>26.411.3</td> <td>• • •</td> <td>• • •</td> <td>38.4±1.8</td> <td>32.312.2</td> <td>• • • •</td> <td>32.3±2.1</td> <td>33.241.7</td> <td></td>	1	36.510.8	26.411.3	• • •	• • •	38.4±1.8	32.312.2	• • • •	32.3±2.1	33.241.7	
7.422.010       7.432.012       7.4312.013       7.4312.013       7.432.013       7.432.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012       7.4411.012	Ŧ										
7.4381.013       7.4391.003       7.4311.023       7.4311.023       7.4311.023       7.4321.003       7.4321.003       7.4321.003       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4321.000       7.4421.000       7.4321.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4421.000       7.4402.010       7.4421.000 <td>¥</td> <td>7.429±.010</td> <td>7.458±.622</td> <td>7.4214.017</td> <td>7.4174.014</td> <td>7.4001.009</td> <td>7.4185.015</td> <td>7.4254.014</td> <td>7 4104 012</td> <td>7 4114 818</td> <td>010 TOOT 1</td>	¥	7.429±.010	7.458±.622	7.4214.017	7.4174.014	7.4001.009	7.4185.015	7.4254.014	7 4104 012	7 4114 818	010 TOOT 1
7.422.010       7.432.000       7.402.000	E-A	7.4381.013	7 4394 600		7 4474 813	7 4114 000	7 4744 617				118-Tao+'/
7.442.018 7.402.013 7.432.013 7.432.013 7.432.013 7.432.013 7.432.013 7.432.013 7.442.013 7.472.018 7.402.015 7.402.013 7.442.010 7.4132.011 7.432.013 7.432.013 7.432.013 7.442.013 7.4922.014 7.432.016 7.402.013 7.4142.010 7.4132.011 7.432.014 7.452.015 7.452.015 7.4922.016 7.402.015 7.432.016 7.432.011 7.405.019 7.432.015 7.432.014 7.4922.016 7.402.015 7.432.015 7.432.014 7.452.015 7.432.014 7.452.015 7.4922.016 7.402.015 7.432.015 7.432.014 7.452.015 7.432.015 7.432.014 7.4922.016 7.402.015 7.432.015 7.432.014 7.452.015 7.432.014 7.452.015 7.432.014 7.4922.015 7.5042.015 7.4012 7.4312.026 7.4202.019 2.1.4014 7.452.016 7.4312.001 7.4922.015 7.5042.015 7.432.016 7.4312.016 7.4312.014 7.452.016 7.4512.014 7.4312.015 7.5042.015 7.4312.016 7.4322.016 7.4512.01 7.4732.014 20.220.0 20.620.0 20.620.1 19.620.4 19.820.6 2120.6 21.4014 27.520.0 23.521.0 27.421.0 27.421.0 27.421.0 27.421.0 27.521.0 28.521.0 27.521.0 28.521.0 27.521.0 28.521.0 27.521.0 28.521.0 27.521.0 28.521.0 27.521.0 28.521.0 27.521.0 28.521.0 27.520.0 28.551.2 28.521.0 28.521.0 28.520.0 28.551.2 28.520.3 28.521.0 28.520.0 28.551.3 28.521.0 28.520.0 28.551.3 28.521.0 28.520.0 28.551.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.0 28.551.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.521.3 28.520.0 28.550.0 28.550.0 28.550.0 28.550.0 28.550.0 28.550.0 28.550.0 28.550.0 28.550.0 28.520.0 28.520.0 28.520.0 28.550.0 28.550.0 28.550.0 28.520.0 28.550.0 2	¥	7.4272.010	7.4574.022	7 3964 906	7.4801.812	7 4814 818	ACA HART 7	170'TICL'/	879 T074 1	120.124.7	1.0.4804.7
7.472.010       7.402.010       7.412.010       7.432.014       7.454.020       7.452.015       7.451.005	<i>6</i> 2−3	7.4441.814	7.4344.818	7 4444	7 4344 612	7 4244 412	7 4974 F		100.1011.1	000 767474	/.44/I.B.
7.472.014 7.4432.016 7.452.016 7.432.011 7.402.016 7.432.016 7.4312.001 7.4312.001 7.4312.001 7.4312.001 7.4312.001 7.4312.01 7.4311.0 7.441	27 1	7.4774.018	7 4864 828		210-TOUT -	A10 4114 7	110 TOCT - 1	219-1804-1	100-2604-1	210.2044.7	7.4361.808
7.4742.016 7.5042.015 7.4512.020 7.4202.019 7.4012.005 7.4512.017 7.4732.015 05 7.4512.005 7.4505 7.4505 7.4505 7.4505 7.4505 7.4505 7.4505 7.4505 7.4505 7.4505 7.45517 7.7512.005 7.45517 7.7512.005 7.45517 7.7512.005 7.45517 7.4551	9	7 4924 814	7 4514 616		D	410-TC14-1			CIB. 20C+./	*18'Toc+'/	7.4491.012
23.31.2 19.859.8 20.659.7 19.629.4 19.820.6 2120.8 21.929.8 23.4118 24.411.3 28.229.8 27.359.8 27.359.8 27.211.0 28.221.0 27.421.4 27.520.8 27.221.0 28.221.1 23.729.9 23.521.2 28.221.2 28.221.4 22.521.4 22.521.2 28.221.2 28.221.4 27.520.8 27.221.0 27.421.4 27.520.8 27.221.0 27.421.4 27.520.8 27.221.0 27.421.4 27.520.8 27.221.0 28.271.2 27.721.4 27.520.8 27.221.0 28.271.2 27.721.4 27.520.8 27.221.0 28.271.4 27.520.8 27.221.0 27.421.4 27.520.8 27.221.0 27.221.0 27.421.4 27.520.8 27.221.0 27.221.0 27.421.4 27.520.8 27.221.0 28.221.1 22.720.9 25.521.2 28.221.2 28.201.4 22.421.1 22.720.9 23.521.2 28.221.2 28.220.8 28.250.3 28.220.4 28.250.3 27.221.0 28.221.2 28.220.3 27.221.0 28.221.2 28.220.3 27.221.2 27.421.4 27.21.4 27.221.1 22.721.1 22.721.1 22.721.1 22.721.1 22.721.1 22.721.1 22.521.1 22.521.1 22.521.2 28.220.3 28.200.3 28.220.3 28.200.3 28.220.3 28.200.3 28.200.3 28.200.3	; <b>1</b>	7.4741.016	7.5441.033	1 <sup>9</sup> 1 1 1 1 1 1 1	1 <sup>0</sup> 1 1 1 1 1 1 1	7.4311.620	7.426±.019	"         	7.4562.016	7.4512.005 7.4732.014	
23.321.2 19.826.8 20.620.7 19.620.4 19.820.6 2120.6 21.926.6 23.421.6 24.41.3 24.220.8 27.221.0 24.41.3 24.240.8 24.221.0 27.421.4 27.550.8 27.221.0 26.421.2 25.420.8 27.221.0 27.421.4 27.550.8 27.221.0 26.421.2 25.420.8 27.221.0 27.221.	() 8 8										8 9 1
24.229.8 27.319.6 26.613 26.4112 25.49.8 26.21.0 77.414 27.529 27.2119 24.721.2 22.729.9 22.114 22.514 22.421.1 22.314 24.211 23.729 25.5112 24.0112 24.0615 28.596.6 26.129.5 28.129.8 26.329.4 26.429.6 25.129 25.519 27.311.0 23.121.2 22.429 21.92112 23.496.6 23.49.6 25.4118 25.5113 25.6113 27.311.0 23.121.2 22.429 21.92112 23.496.6 23.649.6 25.5213 25.8213 27.311.2 21.121.2 21.419 21.92112 23.496.6 23.649.6 25.5118 25.5113 25.5113 27.311.2 21.121.2 21.419 21.92112 23.496.6 23.649.6 25.5213 25.8213 27.311.2 21.121.2 22.410 21.92112 23.496.6 28.6112 25.6112 25.5113 25.5213 25.8213 27.311.2 21.121.4 20.0000000000000000000000000000000000	¥	29.3±1.2	19.810.8	20.610.7	19.6±9.4	19.8+0.6	2148.8	21 949 R	9 141 10		
26.71.2 22.719.9 22.111.4 22.51.4 22.41.1 22.31.4 24.21.1 23.729.9 25.51.2 26.01.2 26.020.6 26.520.6 26.120.5 26.120.6 26.320.4 26.420.6 25.520.3 27.31.0 22.111.2 22.420.9 21.921.2 23.440.6 22.651.2 24.5118 25.51.3 25.821.3 27.31.1 2.111.6 23.520.3 23.641.6 20.641.6 20.651.6 25.520.3 28.221.2 21.111.6 20.641.6 20.641.7 21.640.6 20.620.8 20.60.9 20.270.6 28.221.2 21.111.6 20.641.7 21.641.7 21.640.6 20.620.8 20.600.8 22.720.6	6-A	26.210.8	27.3±0.6	26.010.3	26.4±1.2	25.4+0.8	26.241.0	27 441 4	37 640		0.022.42
26.0±1.2       26.6±0.6       28.5±0.5       26.1±0.5       26.1±0.5       25.5±0.3         27.3±1.0       23.1±1.2       22.4±0.8       21.9±1.2       23.4±0.6       25.5±0.3       25.5±0.3         27.3±1.0       23.1±1.2       22.4±0.8       23.4±0.6       23.4±0.6       23.5±0.3       25.5±0.3         29.7±0.9       30.6±1.0       -       -       29.6±1.0       28.5±0.6       28.7±0.6         26.2±1.2       21.1±1.4       -       -       29.8±1.0       28.5±0.6       28.5±0.6         28.2±1.2       21.1±1.4       -       -       29.8±1.0       28.5±0.6       28.7±0.6	₹	26.71.2	22.7±0.9	22, 111, 4	22 5+1.4	22 441 1	22 341 4	34 241 1	0.017.10	0.1177./2	A-120-/7
27.341.0 23.141.2 22.440.9 21.941.2 23.440.6 23.621.2 24.541.8 25.541.3 25.841.3 25.841.3 25.841.3 25.841.3 25.841.3 26.241.2 28.840.82 29.840.9 28.740.8 28.2420.82 29.240.9 28.740.8 28.2420.82 29.240.9 28.740.8 28.2420.8 28.2400.8	8-J	26.0±1.2	26.6±0.6	26.6±0.6	26.1±0.5	26.1+0.8	26.3+8.4	26 4+0 F	26 1+0 6	2.120.02	26.221.2
	87 7	27.3±1.0	23.111.2	22.4±8.9	21.911.2	23 448 6	23.641.2	24 541 8	36 641 1		• . DIO . C2
	Ĵ	29.7 <u>19</u> .9	30.611.0	0		29.8+1.8	28.8+0.8	0.170.47	0.040.02	C.110.C2	26.21.0
	1	26.211.2	21.121.4		0       	2 641 7			4.010.47	0.01.01	1 1 1 1

A A DA DA DA DA DA

<sup>9</sup>Values not obtained.

Table 3: Blood lactate, blood glucose, and hemotocrit values in swine for euvolemia (E) or hemorrhage (H) (G-50 min) with treatment of control (C), atropine (A), 2-PAM (2P), or pyridostigmine (P).

	8	89	23	53	Ę	8	182	128	180	248
Blood Lectate										
(mg/dt)										
¥	뒁	56±15	67±12	66110	61±13	59212	52±11	53±11	2729	2219
E-A	8±1	7±1	611	1123	12±3	6±1	6±1	5±1	6+3	511
¥	1144	4826	4327	48±9	46±7	4846	<b>38</b> ±9	32±9	20±7	1924
E-29	611	441	1021	7110	6±1	5±1	5±1	5±1	511	51
₽2₽	5±1	27 <u>1</u> 5	48±6	3613	2123	26±3	2012	18±3	9±2	1152
<del>٩</del> ۳	14	41	, 1	9     	421	643	7       	6±3	17	' ' '
1	15±2	53±12	• I I I	• r 1 1	67215	66±17	"     	52±13	33±10	1 1 1
Blood Glucose										
(19/8m)										
¥	89±7	145±24	157±16	163229	162±19	159120	138221	151221	129±10	123±8
E-A	75±4	5772	6917	7518	6119	7744	75±3	77±2	71±10	85214
Ŧ	7813	113±7	116±15	128118	118215	10010	165118	100±7	95±16	129±19
E-20	9116	88±7	96±12	97112	92±5	9619	<b>5766</b>	86±5	8816	93±11
82 ±	88±4	128±9	150217	129214	127±13	113411	115±10	109±12	111±8	120110
£	4400	67±5	0 ( 1 1	• • • •	6413	66±3	י י ו ו	64±4	65±6	, <u>1</u>
ł	83±7	124±15	• t • 1 • 1	7 I 1 1	142±2	140±18	, , , ,	127±19	124±18	   
Hematocrit (X)	(2)									
¥	27.221.5	22.6±1.6	22.7±1.4	22.5±1.4	22.5±1.5	22.3±1.5	22.7±1.7	21.7±1.8	21.7±1.7	21.0±1.7
¥-₩	28.5±1.6	27.711.4	27.511.8	26.311.4	26.7±1.5	26.0±1.4	26.211.3	25.5±1.5	25.7±1.4	26.8±1.2
¥	26.8±1.8	22.5±8.9	21.221.1	21.3±0.6	20.2±0.9	28.011.0	19.8±1.0	19.8±0.8	19.5±0.9	20.21.1
ని సి	26.7±9.6	26.7±0.9	26.8±0.7	27.010.5	26.4±0.7	26,1±0,6	26.1±0.7	25.8±0.7	25.8±0.9	25.4±1.8
47 1	26.310.8	23.210.9	23.1±0.9	22.740.7	22.3±0.6	21.9±0.6	21.7±0.5	21.1±0.5	21.1±1.3	21.1±1.0
đ	28.4±1.8	27.2±1.1	0       	0 ( 1 1	27.6±1.5	27.6±1.4	• • • •	27.2±0.8	27.2±1.6	, , , , ,
ł	29.3±8.4	22.610.8	• I I I I	• 1 1 1	22.4±0.8	22.1±1.0	7         	21.7±1.2	20.110.9	1 1 1

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Table 4: Plasma and red blood cell acetylchollnesterase activity (AChE) as a percent of initial value in consciaus swing during evvolmmia (E) or hemorrhoge (H) (8-69 min) with treatment of control (C), atropine (A), 2-PAM (2P), and pyridaetigasine (P).
n conscia 2-PAN (2
i value li ine (A),
f initial C), atrop
percent e control (
hE) as a t <b>ae</b> nt of
ilvity (AC with tree
erose oct -68 min)
chollneat 9e (H) (8
ll acatyl heaorrho
l blood ce lia (E) or (P).
a and red 9 eurolem ostignine
t: Plosa durln pyrid
Table

					(uim) mail	~				
		8	8	3	R	8	281	120	881	248
Please ACM (K) (K) (K) (K-A (K-A (K-A (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K-A) (K) (K) (K) (K) (K) (K) (K) (K) (K) (K	06 18823. 6 188212. J 18821. 1 18821. 1 18821. 1 1882. 5 61218. 6 6324. 5	8623.2 165212.6 8626.3 162216.5 5826.6 5826.6 5824.6	8124.2 8125.15 84213.1 162211 109211 10125.6 10125.6	7914.2 18914.3 8714.3 18318 8218 8218 8228 6 7	7914.2 18712.5 83118.9 18119.8 1718.8 5718.8 5718.8	81±4.8 101±12.6 81±12.1 81±12.1 81±6.6 59±16.6 67±4.6	8244.4 18643.7 7849.5 181411.8 8428.6 8428.6 8428.6 1 - 1 - 1	7946.2 191414.5 81.9411.5 182410.6 8846.9 5948.9 5948.9	78±5.4 184±11.4 79±10.7 181±9.8 87±8.8 56±19.8 56±19.8	8424.6 8429.4 88271.5 88271.5 10229.6 9128.6 9128.6 9128.6
¥ ŭ ¥ ŭ ¥ ŭ ¥	100121 <sup>6</sup> 10018 10018 100117 100128 4814 7817	85119 128222 94115 94222 82218 5228 6728.4 <sup>+</sup>	111122 198419 88412 88112 81115 11429 7	107123 115116 84114 88218 124136 124136 124136	104111 119425 119425 90413 90413 50413 5246 5245	103215 104226 86214 88212 96224 5825 5825 6328	86116 86113 86113 87114 87114 86111 86111	90±12 80±9 82±14 82±16 82±16 82±16	90±16 79±18 89±18 115±16 91±19 55±6 55±6	88±9 101±12 165±16 165±16 101±16 85±18 63±6 51±4

<sup>0</sup>initial values (or plassa (u/si)): H-C = 0.49610.010; E-A = 0.49810.061; H-A = 0.56420.62; E-2P = 0.45710.048; H-2P = 0.44510.038; E-P = 0.49210.064; H-P = 0.44710.067.

b Values not obtained.

1 A. A.

<sup>C</sup>initial values for red blood cell (U/m P ): H-C = 4.11**10.90;** E-A = 4.2010.70; H-A = 4.8220.40; E-2P = 2.4610.31; H-2P = 2.6010.73; E-P = 3.6810.30; H-P = \$.7110.21,

•

<sup>5</sup>ignificantly different from H-C. Pc8.00

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