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THERMOREGULATION AFTER ATROPINE AND PRALIDOXINE  
ADMINISTRATION(U) ARMY RESEARCH INST OF ENVIRONMENTAL  
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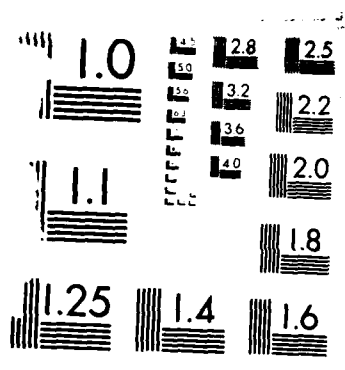
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1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Thermoregulation After Atropine and Pralidoxime Administration		5. TYPE OF REPORT & PERIOD COVERED
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Margaret A. Kolka, Lou A. Stephenson, Stephen P. Bruttig, Bruce S. Cadarette, Richard R. Gonzalez		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Research Institute of Environmental Medicine Natick, MA 01760-5007		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 3M263765D995 WU 141
11. CONTROLLING OFFICE NAME AND ADDRESS Same as 9. above		12. REPORT DATE March 1986
		13. NUMBER OF PAGES 11
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) UNCLASSIFIED
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution is unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Temperature regulation; Sweating; Anticholinergics		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The effects of intramuscular saline (control), atropine (2 mg), pralidoxime (600 mg) or a combination of the two drugs on heat exchange was evaluated in four healthy males during moderately intense seated, cycle exercise (55% VO <sub>2</sub> peak) in a temperate environment (T <sub>a</sub> = 30.3°C, P <sub>w</sub> = 1.0 kPa). Esophageal, rectal, and mean skin temperatures, and chest and forearm sweating were continuously measured. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. Whole body sweating was calculated from weight changes. The expected result of atropine injection,		

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decreased eccrine sweating (-60%, P 0.05) with ensuing elevated esophageal (+0.4°C, P<0.05) and skin temperatures (+2.1°C, P<0.05) was observed relative to control. Heart rate (+28 b/min) and FBF (+9 ml/100cc) were higher after atropine. Pralidoxime, in general, did not affect the core and skin temperature responses to the exercise differently from control; however, a slightly elevated FBF (+3ml/100cc~~min~~, 33%) compensated for the reduction in whole body sweating (-45%, P<0.05) that we observed. The combination of the drugs resulted in significantly higher esophageal (0.4°C) and skin (0.9°C) temperatures than atropine alone, as has been previously shown. The thermoregulatory disadvantage of inhibited sweating by atropine was partially compensated for by enhanced skin blood flow in this environment where  $T_a > \bar{T}_{sk}$ . Pralidoxime was shown to decrease whole body sweating, by a mechanism as yet unexplained. *→ possible: Anticholinergic.*

Thermoregulation After Atropine and Pralidoxime Administration

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## ABSTRACT

The effects of intramuscular saline (control), atropine (2 mg), pralidoxime (600 mg) or a combination of the two drugs on heat exchange was evaluated in four healthy males during moderately intense seated, cycle exercise ( $55\% \dot{V}O_2$  peak) in a temperate environment ( $T_a = 30.3^\circ\text{C}$ ,  $P_w = 1.0$  kPa). Esophageal, rectal, and mean skin temperatures, and chest and forearm sweating were continuously measured. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. Whole body sweating was calculated from weight changes. The expected result of atropine injection, decreased eccrine sweating ( $-60\%$ ,  $p < 0.05$ ) with ensuing elevated esophageal ( $+0.4^\circ\text{C}$ ,  $p < 0.05$ ) and skin temperatures ( $+2.1^\circ\text{C}$ ,  $p < 0.05$ ) was observed relative to control. Heart rate ( $+28$   $\text{b}\cdot\text{min}^{-1}$ ) and FBF ( $+9$   $\text{ml}\cdot 100\text{cc}^{-1}\cdot\text{min}^{-1}$ ) were higher after atropine. Pralidoxime, in general, did not affect the core and skin temperature responses to the exercise differently from control; however, a slightly elevated FBF ( $+3$   $\text{ml}\cdot 100\text{cc}^{-1}\cdot\text{min}^{-1}$ ,  $33\%$ ) compensated for the reduction in whole body sweating ( $-45\%$ ,  $p < 0.05$ ) that we observed. The combination of the drugs resulted in significantly higher esophageal ( $0.4^\circ\text{C}$ ) and skin ( $0.9^\circ\text{C}$ ) temperatures than atropine alone, as has been previously shown. The thermoregulatory disadvantage of inhibited sweating by atropine was partially compensated for by enhanced skin blood flow in this environment where  $T_a > \bar{T}_{sk}$ . Pralidoxime was shown to decrease whole body sweating, by a mechanism as yet unexplained.

Eccrine sweat gland activity is depressed by systemic atropine administration (1,9), primarily by competitive inhibition of receptors which are sensitive to cholinergic nerve stimulation (14). A cutaneous "atropine flush" accompanies these inhibitory effects on the sweat gland (4). Whether the "flush" is an active mode of heat exchange has not been elucidated. We (5) and others (3) have implicated increased cutaneous blood flow after atropine by calculating enhanced dry heat loss. However, an analysis of cutaneous blood flow after whole body atropine administration has not been undertaken.

Pralidoxime chloride (2PAM) is currently used as an antidote to organophosphate poisoning. The action of 2PAM centers around the reactivation of bound acetylcholinesterase for the ensuing hydrolysis of acetylcholine to enable synapses to function normally (6). When given in therapeutic doses (600 mg, i.m), 2PAM caused no changes in core temperature, skin temperature, heart rate or whole body sweating rate in resting men at 40.5°C, 1.5 kPa (13). After oral 2PAM administration (2), there were no changes in core or skin temperature during low intensity exercise at 19, 29, 38 or 46°C. Whole body sweating was reduced an average of 10% in these studies. However, transient hypertension occurs following 2PAM treatment (6). In the presence of a higher sympathetic drive (exercise or combat), sudden and dramatic increases in precapillary vascular resistance (therefore blood pressure) may occur in individuals treated with pralidoxime chloride with ensuing changes in peripheral blood flow and heat dissipation. Additionally, whole body investigations of 2PAM and atropine point to an augmentation of the atropine induced rise in body temperature in the presence of 2PAM (2).

In the present study we were interested in ascertaining the effects of the individual and combined effects of atropine and pralidoxime on the

thermoregulatory effectors in healthy males during moderate intensity exercise in a temperate environment.

## METHODS

Subjects. Four fit males ( $\dot{V}O_2$  peak  $46 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; translates to  $\approx 55 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  on treadmill (11)) volunteered for the study following consent procedures passed by our local Human Use Committee. They had an average ( $\pm$  SD) age of  $21 \pm 2$  yrs, height of  $182 \pm 9.1$  cm, weight of  $81.3 \pm 9.8$  kg, DuBois surface area of  $2.03 \pm .16\text{m}^2$ , percentage of body fat (hydrostatic weighing) of  $18.7 \pm 4.4\%$  and a lean body mass of  $66.1 \pm 3.6$  kg.

Protocol. Testing occurred during November 1985. All subjects were familiarized with all testing and measurement procedures before data collection began. Subjects were tested on four days in an ambient temperature of  $30^\circ\text{C}$  with an ambient water vapor pressure ( $P_w$ ) = 1.0 kPa; after the intramuscular injection of 1 ml of sterile saline, after 2 mg of atropine sulfate (Elkin-Sinn, Cherry Hill, NJ), after 600 mg pralidoxime chloride (Protopam chloride, Ayerst, NY, NY) or following 2 mg atropine plus 600 mg pralidoxime chloride administration. Test days were separated by 48 hours, and the order of drug presentation was counterbalanced. Experiments were conducted between 0700 and 1000h, with any one subject tested at the same time each day to control for circadian variation in heat loss responses (15). Subjects had not eaten the previous 12 hours before testing.

Physiological variables. The seated exercise level was 55% of a previously determined  $\dot{V}O_2$  peak on a modified cycle ergometer (11). Exposure time was 80 minutes, which included a 5 min control period after instrumentation and



equilibration, the injection of the appropriate drug, 30 minutes of rest, 30 minutes of submaximal exercise and a 15-minute recovery period. We continuously recorded esophageal temperature ( $T_{es}$ ), rectal temperature ( $T_{re}$ ), an eight site mean weighted skin ( $\bar{T}_{sk}$ ) temperature (12), and sweating rate (7) from the chest ( $\dot{m}_{sch}$ ) and forearm ( $\dot{m}_{sa}$ ). Heart rate (ECG) and blood pressure (indirect) were measured each 2.5 min. Skin blood flow (FBF) was measured twice each min by venous occlusion plethysmography (8,16) on the contralateral forearm from which blood pressure was measured. Metabolic heat production was estimated by open circuit spirometry at 15 minutes of rest, 10 minutes of exercise, 25 minutes of exercise and at 5 minutes of recovery. Total body sweating rate ( $g \cdot min^{-1}$ ) was determined by pre-and post-weighings of the nude body.

Statistical Analysis. Analysis of variance routines were used to compare the data at the time of the metabolic heat production measurements. Regression equations of both internal temperature measurements over time were generated to calculate the rate of change in heat content. Tukey's test of critical differences was used where appropriate. All differences are reported at  $P < 0.05$ , unless otherwise noted.

## RESULTS

The time course for  $T_{es}$ ,  $\bar{T}_{sk}$ , FBF and arm  $\dot{m}_s$  is shown in Figure 1 for a representative subject during all four treatments. Noticable is the similar effect on all parameters between control and 2PAM experiments, as well as the potentiation of the atropine effect when 2PAM is given in combination. Mean skin temperature drops at the initiation of exercise as evaporative cooling occurs in control experiments but not in atropine experiments. Table 1 contains mean

( $\pm$  SD) cardiovascular data during rest, 10 minutes of exercise, 25 minutes of exercise and 5 minutes of recovery for the four subjects under the four treatments of the study. There were no differences in any of the resting variables. As expected, atropine elevated heart rates during exercise (22%) and recovery (62%) over those rates seen in control experiments with no effect of pralidoxime on heart rate. The combination of atropine and pralidoxime increased exercise (19%) and recovery (80%) heart rates with a slight elevation ( $p = 0.18$ ) in mean arterial pressure (11% exercise, 23% recovery). There was no effect of any treatment on the metabolic heat production. Mean heat exchange information is presented in Table 2 for the four subjects under all testing conditions. Depressed local and whole body sweating (arm, -64%; chest, -77%; whole body, -58%) occurred with atropine as did the expected rise in both core and mean weighted skin temperatures. FBF was elevated following atropine; 83% during exercise and 170% during recovery. Pralidoxime injection, in general, did not affect rest, exercise, or recovery values for  $T_{re}$ ,  $T_{es}$ , or  $\bar{T}_{sk}$ . However, FBF was slightly elevated ( $+3.0 \text{ ml} \cdot 100\text{cc}^{-1} \cdot \text{min}^{-1}$ ; 33%, NS), and whole body sweating ( $-6.2 \text{ g} \cdot \text{min}^{-1}$ , -47%) and recovery chest sweating ( $-0.48 \text{ mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1}$ ) were reduced. The combination of atropine and pralidoxime resulted in higher  $T_{es}$  ( $0.4^{\circ}\text{C}$ ) and  $\bar{T}_{sk}$  ( $0.7^{\circ}\text{C}$ ) than atropine itself during the 25th minute of exercise. FBF, whole body and local sweating were not different from the atropine treatment.

The rate of increase ( $dT/dt$ ) for esophageal and rectal temperature is shown in Table 3 for all treatments. As expected,  $dT_{es}/dt$  was higher than  $dT_{re}/dt$  in all cases. In addition,  $dT_{es}/dt$  was significantly affected by all treatments, whereas  $dT_{re}/dt$  was affected only by the combination of drugs. A graphic representation of the two temperatures over time is shown in Figure 2 for a single subject during both saline and atropine experiments.

## DISCUSSION

This investigation provides initial evidence that systemic atropine administration alters peripheral heat loss, not only via depressed thermoregulatory sweating, but also through elevated skin blood flow. Additionally, pralidoxime administration results in a depressed whole body sweating response without affecting core and skin temperature regulation in a temperate environment during moderate intensity exercise. The combination of the two drugs, in general, confirms the synergism in impairing heat exchange that has been reported previously (2).

The depression in thermoregulatory sweating seen following atropine was expected (1,9), and was of the same magnitude as previously reported for unacclimated subjects (9). The compensation for reduced evaporative heat loss from the skin, which occurs via skin blood flow has been suggested (3,5) and may in part explain the atropine flush which is usually observed. (4). This elevation in skin blood flow appears to be a result of an enhanced sensitivity to the increasing esophageal temperature drive (10).

The responses of the subjects after the pralidoxime injection were not completely expected. One response which appears equivocal is the depression in whole body sweating (Table 2). Smaller decreases in whole body sweating were demonstrated previously (2), but no record of this level of inhibition is available. Paradoxically, local sweating was not depressed by the pralidoxime treatment, perhaps indicating a differential effect of the inhibition of sweat secretion at different locations. Since  $T_{es}$  and  $\bar{T}_{sk}$  were not different after pralidoxime injection compared to saline treatment (Table 2), the slight enhancement in FBF resulting in further sensible heat loss together with the regulatory sweating observed was sufficient for whole body heat dissipation. In environments where

$T_a \geq \bar{T}_{sk}$ , heat dissipation would be compromised during pralidoxime treatment due to inhibited sensible heat exchange by the environmental gradient as well as by inhibited evaporation. The enhancement in skin blood flow is contrary to what we expected, since transiently increased vascular resistance has been seen after pralidoxime (6), which would result in unchanged or lower skin blood flow.

Atropine given in combination with pralidoxime (separate injections, same time frame) resulted in elevated  $T_{es}$ ,  $\bar{T}_{sk}$ , and impaired sweating. However, these responses were significantly augmented, over those seen with atropine alone, implying a synergism between the drug actions (2). Chest and whole body sweating were slightly lower in the combined experiments, while FBF was not different from atropine treatment, which resulted in the elevated core and surface temperatures observed. Again, if the thermal gradient from the environment to the body surface is reversed, as in the case where  $T_a > \bar{T}_{sk}$ , this potentiation of atropine effects with 2PAM would increase the heat strain on the individual and affect performance.

One technical point can be made of this investigation which is clearly shown by Figure 2. The use of esophageal temperature as a central indicator of thermal input offers a much more accurate and rapid response of core temperature, critical in situations when temperatures are rapidly changing (Figure 1). In fact, the significant changes in  $dT_{es}/dt$  with all drug treatments are not picked up by  $dT_{re}/dt$  until the drugs are combined (Table 3). Therefore, during thermal transients (i.e. the early stages of exercise or recovery), the two temperatures cannot be related by a constant or a delta value. This fact must be considered when interpretations of drug effects are made from calculations of rate of change in core temperature.

We have demonstrated that atropine affects the cutaneous perfusion (arm site) as well as peripherally inhibiting eccrine (cholinergic) sweating. Specifically, FBF is enhanced with atropine and this avenue partially compensates for the sweating inhibition evident in this relatively cool environment. Pralidoxime, on the other hand, appears to also inhibit sweating and increase FBF, albeit to a much lesser extent than atropine, although the regulation of internal core temperature ( $T_{es}$ ) is not radically affected in comparison to control experiments for the dosage and environmental conditions of this study, although the rate of heat loading is enhanced (Table 3). It would be interesting to study and determine if this is the case in an environment where the gradient between ambient temperature and  $\bar{T}_{sk}$ , (e.g.  $T_a - \bar{T}_{sk}$ ) is small or when skin temperature actually exceeds ambient temperature. Finally, the combination of atropine and pralidoxime had a synergistic effect on heat storage, pointing to the possibility of heat injury in more severe environmental conditions.

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## ACKNOWLEDGEMENTS

The authors acknowledge the expertise of M.A. Brody and T.J. Doherty with the data collection; T.J. Doherty and K.P. Perregaux for data analysis, Dr. P.I. Fitzgerald for the hydrostatic weighings, and Dr. J. Dziados for the medical supervision of the study.

The opinions and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy or decision unless so distinguished by other official documentation.

Human subjects participated in these studies after giving their informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers on Research.

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**FIGURE LEGENDS**

Figure 1. The time course for esophageal, mean skin temperature, skin blood flow and arm sweating for a given subject after saline, atropine, 2PAM and atropine plus 2PAM. The drug is injected at 5 min, exercise begins at 35 min and recovery begins at 65 min.

Figure 2. The time course for both esophageal and rectal temperature for one subject after saline (upper panel) and atropine (lower panel).

Table 1. Mean ( $\pm$ SD) cardiovascular variables for rest, exercise and recovery during the four treatments.

	Heart Rate (b $\cdot$ min $^{-1}$ )	Mean Arterial Pressure (Torr)	$\dot{V}O_2$ (l $\cdot$ min $^{-1}$ )
<u>Saline</u>			
Rest	67 (8)	92 (11)	0.29 (.10)
Exercise 1	127 (4)	93 (13)	2.17 (.28)
Exercise 2	130 (5)	103 (3)	2.21 (.23)
Recovery	87 (10)	95 (8)	0.48 (.20)
<u>Atropine</u>			
Rest	59 (13)	83 (5)	0.23 (.05)
Exercise 1	146 (11)*	105 (12)	2.02 (.22)
Exercise 2	158 (4)*	101 (13)	2.05 (.29)
Recovery	142 (13)*	105 (12)	0.36 (.08)
<u>Pralidoxime</u>			
Rest	66 (12)	95 (5)	0.25 (.02)
Exercise 1	126 (11)	104 (7)	1.91 (.27)
Exercise 2	123 (12)	102 (3)	1.96 (.37)
Recovery	93 (23)	96 (14)	0.37 (.11)
<u>Combination</u>			
Rest	71 (11)	99 (11)	0.20 (.03)
Exercise 1	139 (6)*	107 (10)	1.97 (.21)
Exercise 2	155 (2)*	114 (13)	2.05 (.11)
Recovery	157 (14)*	116 (11)	0.36 (.11)

\*Different from saline ( $p > 0.05$ )

Rest = 20 minutes of rest, 15 minutes after drug injection

Ex1 = 10 minutes of exercise, 40 minutes after drug injection

Ex2 = 25 minutes of exercise, 55 minutes after drug injection

Recovery = 5 minutes after exercise, 65 minutes after drug injection

Table 2. Mean (+SD) temperature parameters for the four subjects during the four treatments at rest and recovery.

Saline	T <sub>es</sub> (°C)	T <sub>re</sub> (°C)	T <sub>sk</sub> (°C)	FBF (ml·100cc <sup>-1</sup> ·min <sup>-1</sup> )	Arm ml s <sup>-1</sup> (mg·cm <sup>-2</sup> ·min <sup>-1</sup> )	Chest ml s <sup>-1</sup> (mg·cm <sup>-2</sup> ·min <sup>-1</sup> )	M <sub>2</sub> (g·min <sup>-1</sup> )
Rest	36.67 (.15)	37.17 (.25)	34.04 (.28)	1.84 (.83)	.16 (.06)	.31 (.35)	13.23 (3.68)
Exercise 1	37.15 (.14)	37.27 (.22)	33.32 (.59)	6.09 (.87)	.97 (.17)	1.43 (.31)	
Exercise 2	37.37 (.15)	37.64 (.15)	33.62 (.51)	9.21 (.42)	1.08 (.30)	1.78 (.61)	
Recovery	37.01 (.36)	37.76 (.16)	33.64 (.50)	5.55 (1.76)	.74 (.38)	1.78 (.87)	
<u>Atropine</u>							
Rest	36.61 (.20)	37.06 (.20)	34.06 (.30)	1.84 (.45)	.15 (.04)	.23 (.28)	5.53 (1.37)
Exercise 1	37.08 (.18)	37.13 (.15)	34.92 (.48)*	11.04 (3.08)*	.35 (.20)*	.33 (.34)*	
Exercise 2	37.78 (.18)*	37.62 (.14)*	35.72 (.49)*	17.08 (5.78)*	.43 (.14)*	.61 (.28)*	
Recovery	37.80 (.22)*	37.97 (.11)*	36.03 (.35)*	15.04 (8.01)*	.45 (.17)*	.67 (.36)*	
<u>Pralidoxime</u>							
Rest	36.48 (.30)	36.92 (.28)	33.97 (.54)	1.93 (.94)	.12 (.01)	.12 (.02)	7.03 (2.16)
Exercise 1	37.00 (.29)	37.14 (.25)	33.76 (.54)*#	9.13 (4.13)	1.14 (.32)	1.47 (.33)	
Exercise 2	37.16 (.25)#	37.56 (.22)	33.95 (.80)#	12.26 (4.20)#	1.41 (.21)*	1.67 (.39)	
Recovery	36.98 (.21)#	37.66 (.19)	33.80 (.73)#	5.34 (1.82)#	.72 (.43)	1.44 (.80)*	
<u>Combination</u>							
Rest	36.76 (.28)	37.11 (.23)	33.97 (.64)	1.35 (.29)	.16 (.04)	.34 (.30)	5.35 (2.91)
Exercise 1	37.32 (.25)	37.24 (.20)	35.34 (.65)*#†	12.64 (1.74)*	.35 (.24)	.26 (.14)*	
Exercise 2	38.18 (.27)*#†	37.83 (.28)	36.40 (.57)*#†	17.36 (4.63)*†	.45 (.18)	.45 (.16)*	
Recovery	38.28 (.21)*#†	38.29 (.27)	36.71 (.29)*#†	16.31 (2.12)*†	.40 (.21)*	.95 (.30)*	

\* Different from saline (p > 0.05)

# Different from atropine (p > 0.05)

† Different from pralidoxime (> 0.05)

Table 3. Individual and mean ( $\pm$ SD) dT/dt ( $^{\circ}\text{C}\cdot\text{min}^{-1}$ ) for esophageal and rectal temperatures during exercise transients for the four treatments.

<u>Saline</u>	<u>Esophageal</u>	<u>Rectal</u>
S <sub>1</sub>	.08779	.04060
S <sub>2</sub>	.09360	.02349
S <sub>3</sub>	.06259	.02232
S <sub>4</sub>	.06823	.01899
	<u>.0781</u> (.0150)	<u>.0264</u> (.0097)
 <u>Atropine</u>		
S <sub>1</sub>	.07400	.04059
S <sub>2</sub>	.07669	.02273
S <sub>3</sub>	.05310	.02810
S <sub>4</sub>	.0604	.03111
	<u>.0660</u> (.0112)*	<u>.0306</u> (.0075)
 <u>Pralidoxime</u>		
S <sub>1</sub>	.07909	.05701
S <sub>2</sub>	.10814	.03067
S <sub>3</sub>	.08648	.02030
S <sub>4</sub>	.08187	.02423
	<u>.0889</u> (.0132)*#	<u>.0331</u> (.0165)
 <u>Combination</u>		
S <sub>1</sub>	.08605	.04387
S <sub>2</sub>	.06235	.04336
S <sub>3</sub>	.05352	.03851
S <sub>4</sub>	.05195	.03707
	<u>.0635</u> (.0157)*†	<u>.0407</u> (.0034)*#†

S<sub>1</sub> through S<sub>4</sub> are subject numbers.

\* Different from saline ( $p > 0.05$ )

# Different from atropine ( $p > 0.05$ )

† Different from pralidoxime ( $p > 0.05$ )

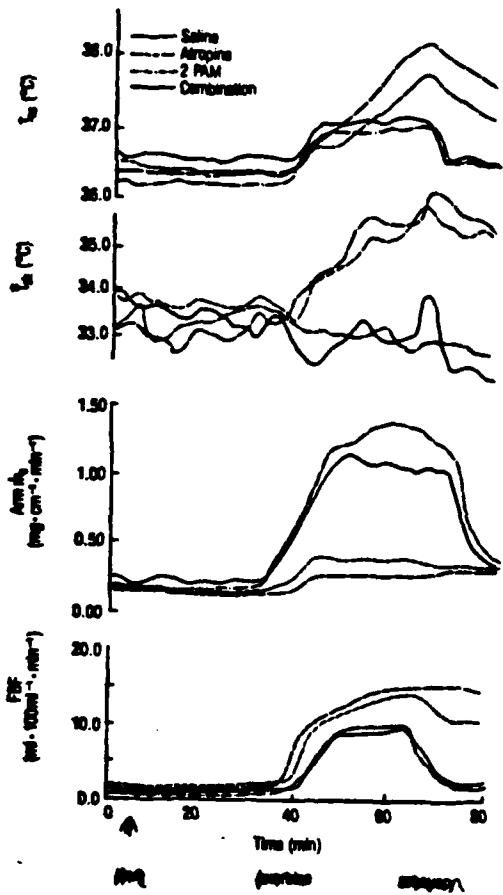


Fig. 1

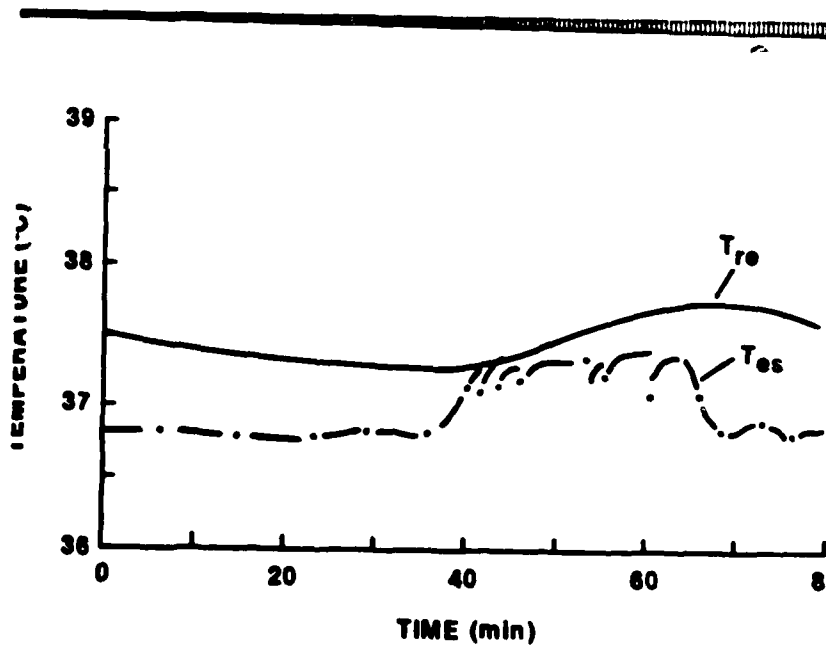
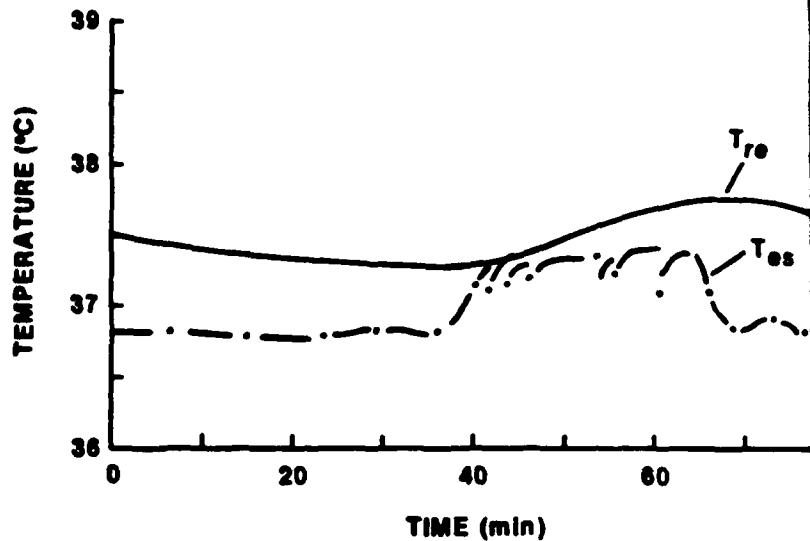


Fig 2.(a,b)

END

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