Table 6.2.3.1 Comparative Summary of Human/Animal Pharmacokinetics and Pharmacodynamics (continued)

Investigator	Number of Subjects, Species, Sex & Design	Route of Administration and Dosage Form	Dose and Frequency	Plasma PB Pharmacokinetic Parameter Estimates	Pharmacodynamic Parameter Estimates RBC AChEI	Location of Ref./Rpt.
Joiner, R. L. & Kluwe, W. M. (1988)	Rhesus monkey N = 12 BC	Gavage solution	Single dose: 0.286 mg/kg	C_{max} 14.1 ± 9.5 ng/ml T_{max} 0.93 ± 0.52 hours AUC 1987-2311 ng•min/ml	I_{max} 30 ± 10.5% $T_{½}$ 2.7 hours T_{max} 1.31 ± 0.35 hours AUC 840 ± 369 ng•min/ml	Vol. 1.42 p. 000022
			0.571 mg/kg	C_{max} 26.6 ± 11.2 ng/ml T_{max} 1.10 ± 0.53 hours AUC 5217-5288 ng•min/ml	I_{max} 43.0 ± 14.7% $T_{½}$ 3.1 hours T_{max} 1.43 ± 0.40 hours AUC 1656 ± 898 ng•min/ml	
			1.14 mg/kg	C_{max} 44.8 ± 22.8 ng/ml T_{max} 1.15 ± 0.62 hours AUC 7656-7671 ng•min/ml	I_{max} 23 ± 10% $T_{½}$ 3.8 hours T_{max} 1.34 ± 0.54 hours AUC 2847 ± 900 ng•min/ml	
			Repeated dose: 1.2 mg/kg q8h for 6 doses	Not determined	I_{max} 22.6 ± 2.4% Trough ≈ 8 hours	
			1.2 mg/kg, 1st dose 1.8 mg/kg,	Not determined	I_{max} 36.8 ± 2.9% Trough ≈ 8 hours	

BA: Balanced
BC: Baseline-controlled
BLS: Balanced 4x4 Latin Square
CO: Crossover
DB: Double-blind
I_{max}: Maximum percent inhibition
Inh: Inhibition at the specified time
OD: Open design
PC: Placebo-controlled
RA: Randomized
RCB AChEI: Red blood cell acetylcholinesterase inhibition
SP: Split
T_{inh}: Time of maximum inhibition
* Voluntarily withdrew from placebo group after 4 days.

Comments to the Medical Reviewer

1. Compared to healthy subjects, in anephric patients pyridostigmine elimination half-life increased (112 vs 379 minutes) and systemic plasma clearance decreased from 8.6 to 2.1 ml/kg/min. Lower pyridostigmine bromide doses or longer dosing intervals may be necessary in renally impaired subjects.

2. There is no direct evidence that acetylcholinesterase inhibition is an appropriate surrogate marker in humans, i.e., protection from the adverse effects of nerve gas is related to the inhibition of acetylcholinesterase in RBC. The assumption that since 20-40% inhibition of acetylcholinesterase protects monkeys from nerve gas, the same may not be true in humans. Furthermore, the 20-40% inhibition of RBC AChE observed in monkeys should be based on multiple dose studies conducted according to the dosage regimen proposed in humans.

Comments to the Sponsor

1. It has been proposed by the Sponsor that pyridostigmine bromide should not be used for more than 14 days on a continuous basis (recommended dose is every 8 hours). The Sponsor should clarify the reason (s) for this assumption since the need for pyridostigmine bromide may be much longer than 14 days.

2. The consequences of continuous inhibition of acetylcholinesterase between 20 to 40% beyond 3 weeks is currently unknown in humans. Long term monitoring of the subjects taking pyridostigmine bromide may be necessary.

3. There is no direct evidence that acetylcholinesterase inhibition is an appropriate surrogate marker in humans, i.e., protection from the adverse effects of nerve gas is related to the inhibition of acetylcholinesterase in RBC. Furthermore, the assumption that since 20-40% inhibition of acetylcholinesterase protects monkeys from nerve gas, the same may not be true in humans.

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Labeling Comments

The following labeling comments are only for the use of **military personnels.**

The Sponsor is requested to perform the following **revisions** on the submitted labeling:

The pharmacokinetics, bioavailability and pharmacodynamics informations provided by the Sponsor under the Clinical Pharmacology section should be **replaced** with the following:

Draft Labeling

1 page(s) of revised draft labeling has been redacted from this portion of the review.

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the labeling changes.

Please forward Comments 1-3 and Labeling Comments to the Sponsor.

Iftekhar Mahmood, Ph.D. /S/ 8/8/96

FT initialed by Mohammad Hossain, Ph.D. /S/ 8/8/96

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

First draft prepared on July 19, 1996.
RD initialed by Mohammad Hossain, Ph.D. on July 25, 1996.

Biopharm Day: Aug 7, 1996.

CC: NDA 20-414, HFD-120, HFD-860 (Mahmood, Hossain, Malinowski), HFD-340 (Viswanathan), and HFD 870: Chron, Drug, Reviewer and FOI (HFD-19) files (Clarence Bott, HFD-870, PKLN, RM 13B-31).

Study #1

TItle: Safety, tolerance, pharmacokinetics and pharmacodynamics of intravenous pyridostigmine and oral doses of standard and sustained-release pyridostigmine in healthy men and the influence of food on oral pyridostigmine pharmacokinetics.

Objectives: The study was undertaken to evaluate the rate and extent of absorption of pyridostigmine bromide and the degree and time course of erythrocyte acetylcholinestrase inhibition following a standard tablet (immediate release), a sustained-release preparation and IV dose of pyridostigmine bromide.

Formulations:

Three pyridostigmine bromide preparations were used in this study.

(i) Intravenous pyridostigmine bromide (Regonol^{R}), Lot No 2860589460, Hoffman-LaRoche, Inc.

(ii) A 90 mg sustained-release preparation produced by the —— Lot No WR 250710BA BL58714 WRA-034-05099.

(iii) A 30 mg standard tablet, Lot No WR 250710BB BM03509 038641, ——

Study Design:

The study was an open-label study. Sixteen male volunteers (9 whites & 7 blacks), ranging from 20 to 35 years in age and 10% of the ideal body weight (determined by Metropolitan Life Insurance Company) took part in this study. Each subject received 6mg of pyridostigmine salt in 24 ml normal saline (250 µg/ml), over 6 hrs (the amount of pyridostigmine bromide base ranged from 3.936 to 4.512 mg). Next day a single dose of a standard 30 mg pyridostigmine bromide tablet or a 90 mg sustained-release preparation was given and then two days later, the subjects began receiving multiple dosing with the same tablet. The first eight subjects received the sustained-release tablet and the next eight received the standard tablet. For IV and single dose study, the subjects were not allowed to eat or smoke 8 hours before and 4 hours after the dose. Concurrently with the first dose during multiple dosing the subjects were given a standard breakfast consisting of 8 fl.oz of 2% milk, 4 fl.oz of orange juice, two slices of wheat toast with margarine and jelly, and two scrambled eggs. The standard tablet was given at every eight hours for 48 hrs (total of 6 tablets) and with the sustained-release tablet was given at every 12 hours for 48 hrs (total of 4 tablets). Five ml blood samples were drawn at regular intervals in heparinized vacutainers and centrifuged for ten minutes. The plasma was separated and stored at -80^{o}C. Blood samples were drawn for 14 hrs and 24 hrs following IV and oral administration of pyridostigmine bromide, respectively.

An — assay of pyridostigmine bromid was developed at the —
— The minimum quantitation limit was — ng/ml as free base (— ng/ml as pyridostigmine bromide). Accuracy was 8 to 12% and the precision was 3 to 14% in the concentration range of ng/ml. Pyridostigmine bromide was stable in
—

Erythrocyte acetylcholinesterase activity was measured at the —
— based upon the protocol established by the US Army Medical Research Institute for Chemical defense. The assay was linear between 2.94 and 14.70 µM/mL/min of product formed with a CV of less than 2%.

Results:

1. Pharmacokinetics:

Following intravenous administration of pyridostigmine, the plasma concentration kept rising for three hours, followed by a plateau for the next three hours. A two compartment model was fitted to plasma concentration-time data. The area under the curve was calculated by trapezoidal rule. Following oral administration of pyridostigmine, the sustained release pyridostigmine, despite a three fold higher dose than the standard tablet took longer to reach peak indicating slower absorption from the sustained release form. Food decreased the AUC and C_{max} for the standard tablet by 25 and 19%, respectively, whereas a 16% decrease in C_{max} and 35% increase in AUC was observed between fed and fasting conditions with sustained release preparation. However, food prolonged the T_{max} for both the formulations by 2 fold. The mean absolute bioavailability for the standard tablet was $17 \pm 6\%$ and $12 \pm 2\%$ under fasting and fed state, respectively. The mean bioavailability for the sustained release preparations was 8 $\pm$ 3% and $10 \pm 4\%$ under fasting and fed state, respectively. The following table summarizes the different pharmacokinetic parameters of pyridostigmine.

TABLE 1

Parameters	IV infusion	standard tablet (30 mg)	Sustained Release (90 mg)
t1/2 (hrs)	3.2 ± 3.4	-	-
AUC (0-24 h) (ng.hr/ml)	119 ± 22 (gr 1)	108 ± 52 (fast)	-
	125 ± 27 (gr 2)	-	141± 45 (fast)
AUC (First dose fed)		72 ± 12 (0-8 h)	183 ± 81 (0-12 h)
AUC (steady state fed)		103 ± 20 (0-8 h)	217 ± 86 (0-12 h)
V_c (liters)	19.1 ± 12.3	-	-
T_{max} (hrs)	-	1.3 ± 0.3 (fast)	2.2 ± 0.8 (fast)
		2.5 ± 1.3 (fed)	4.0 ± 1.2 (fed)
		4.4 ± 7.2 (fed, SS)	3.2 ± 1.9 (fed, SS)
C_{max} (ng/mL)	-	22.4 ± 6.9 (fast)	37.6 ± 15.4 (fast)
		16.2 ± 3.9 (fed)	31.3 ± 12.2 (fed)
		20.7 ± 4.1 (fed, SS)	33.1 ± 11.7 (fed, SS)
Absolute	-	0.17 ± 0.06 (fast)	0.08 ± 0.03 (fast)
Bioavailability		0.12 ± 0.02 (fed)	0.10 ± 0.04 (fed)
Relative	-	-	0.55 ± 0.34 (fast)
Bioavailability			0.86 ± 0.41 (fed)

gr 1 refers to group of 8 subjects who received IV infusion and standard tablet.
gr 2 refers to group of 8 subjects who received IV infusion and sustained release tablet.

2. Pharmacodynamics:

The degree of inhibition of erythrocyte acetylcholinestrase activity following intravenous infusion and oral administration was used as a pharmacodynamic end point. The inhibition after IV infusion increased over the first 3-5 hours, then plateaued while after infusion was stopped the inhibition fell over the next 6-8 hours. The administration of the standard tablet with food decreased the extent of acetylcholinestrase inhibition compared to fasting, whereas no effect on

acetylcholinestrase inhibition was observed with sustained release formulation between the fasting or fed condition. The duration of inhibition between 20 to 40% following IV and oral administration was as follows:

IV infusion (group 1)	5.47 ± 0.51 hrs (maximum inhibition 34 ± 3%)
IV infusion (group 2)	4.85 ± 0.58 hrs (maximum inhibition 36 ± 4%)
Standard tablet (fast)	3.77 ± 1.19 hrs (maximum inhibition 38 ± 9%)
Standard tablet (fed)	3.40 ± 1.21 hrs (maximum inhibition 26 ± 2%)
Sustained release (fast)	3.68 ± 0.77 hrs (maximum inhibition 41 ± 11%)
Sustained release (fed)	4.46 ± 1.54 hrs (maximum inhibition 44 ± 13%)

The mean duration of inhibition greater than 20% during the multiple dose was 5.6 hours with standard tablet compared to 9.1 hours with the standard-release tablets.

Comments:

In this study, the investigators have determined the pharmacokinetics of pyridostigmine following intravenous and two different oral formulations. The sustained release (90 mg) preparation was formulated at the ——— were the manufacturer of the 30 mg standard tablet.

The reported AUCs for IV, standard tablets and sustained release tablets are from time (0-t) rather than time (0-∞). However, the overall contribution of the tail (last concentration/elimination rate constant) was about 10% to the total AUC.

The investigator has not reported the values of C_{max} and T_{max} following multiple dosing of either the 30 mg tablet or the sustained release preparation. No attempt was taken by the investigator to report the AUC(0-8) or AUC (0-12) for the standard tablet or the sustained release preparation to make a comparasion between fed and fasting state.

Overall the pharmacokinetic analysis of the data has not been done properly.

Study # 2

Title: A study to evaluate the safety, tolerance, pharmacokinetics and pharmacodynamics of pyridostigmine when given in single and multiple doses to males and females in different weight groups.

Objectives: To determine the safety and tolerance of 30 mg pyridostigmine bromide, when given every 8 hours for 64 doses to healthy male and female subjects in different weight groups (high, medium, low). In addition, the objective was to determine the multiple dose pharmacokinetics and pharmacodynamics (red blood cell acetylcholinesterase inhibition) of pyridostigmine bromide when given to male and female volunteers over a 22 day period.

Study Design: This was a multiple-dose randomized placebo control trial in 90 male and female subjects (between 18-44 years). There were 45 male and 45 female subjects. Subjects were divided into 6 groups of 15 subjects each according to gender and weight category (high, medium and low weight).

Parameters	Male	Weight (lbs)	Female	Weight (lbs)
High	200-230	212 ± 9	170-200	184 ± 10
Medium	160-180	169 ± 6	135-160	143 ± 6
Low	110-140	134 ± 7	95-120	111 ± 7

Male high weight = MH; Male medium weight = MM; Male low weight = ML
Female high weight = FH; Female medium weight = FM; Female low weight.

In each group 10 subjects were randomized to pyridostigmine bromide (30 mg, q8h for 21 days plus a single dose on day 22) and 5 subjects to placebo. Vital signs, laboratory tests (serum chemistry, hematology and urinalysis), electrocardiograms, and adverse reactions were recorded throughout the study to assess safety.

Study Medication:

The lot numbers of the active and placebo tablets were as follows:

a. Pyridostigmine bromide (Active), 30 mg, Hoffmann-La Roche, Lot #325039, manufactured **August 1985** (WR250710BF)

b. Pyridostigmine bromide (Placebo), 30 mg, Hoffmann-La Roche, Lot # C181554-01, manufactured **1994** (WR250710BH).

The study medication was stored at refrigeration temperature under secure conditions at ——.

Blood Sampling:

Blood samples for pyridostigmine and RBC acetylcholinesterase (AChE) levels during single dose (Day 1) were drawn at time 0, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours post dose.

On Days 3 through 21 samples were drawn on Days 4, 7, 9, 11, 14, 16 and 21 at approximately 5 minutes prior to the 9 am dose.

Blood samples for pyridostigmine and RBC AChE levels on Days 22-25 were drawn at 0, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 18 hours post dose.

Blood samples were also drawn on the following days:

Day 23: 24, 28, 36 and 40 hr.

Day 24: 48, 52, 56, 60 and 66 hr.

Day 25: 72 hr.

Diet:

All subjects were fasted from midnight until two hours post the first dose on day 1 and last dose on Day 22 of test medication. Water was allowed ad lib. All other doses required fasting from one hour prior to dosing and until one hour post dosing. Standardized meals were served throughout the study.

Concomitant medications:

Subjects were asked not to take any medication for one week prior to the initiation of this study. Subjects were not allowed any medication during the study other than the study medication. Any concomitant medications used during the study were authorized by the Principal Investigator and were recorded in subject's study records.

Analytical Methods:

Pyridostigmine plasma concentrations were assayed at the ——.

Pyridostigmine plasma concentrations were assayed by using —— ——. The assay was sensitive to 1.6 ng/mL of pyridostigmine bromide with a coefficient of variation (CV) 10 % over a concentration range of —— ng/mL.

Red blood cell acetylcholinesterase activity was assayed in the laboratory of the U.S. Army Medical Research Institute of Chemical Defense. The red blood cell acetylcholinesterase activity was measured by standard enzymatic techniques with a lower limit of quantitation of

— U/mL.

Data Analysis:

Pharmacokinetics:

Cmax (maximum plasma concentration) and Tmax (time to maximum plasma concentration) were found by examination of the plasma profiles.

Pharmacodynamics:

The percent inhibition of acetylcholinesterase activity was calculated from the AChE data. The AChE activity on Day 1, 0 hour (Pre-dose) was used as the baseline. The AChE activities in subsequent samples was subtracted from the baseline and %inhibition was calculated as follows:

Baseline AChE activity = Ab

AChE activity in a subsequent sample = Ai

Percent Inhibition for the Ai th. sample = ((Ab - Ai)/Ab) X 100

Results:

Pharmacokinetics:

The pharmacokinetic parameters C_{max} and T_{max} for pyridostigmine were estimated directly from the plasma concentration vs time data on Day 1 and Day 22. On Day 1, the C_{max} was 25% lower in male-high weight group compared to the low and medium groups, whereas in female-high weight group the Cmax was almost 50% lower than the low and medium groups. This difference was statistically significant ($p > 0.05$). However, negligible and statistically nonsignificant differences were seen for T_{max} on Day 1. Neither the C_{max} nor the T_{max} showed any statistical differences among groups on day 22.

The oral clearance was 324 ± 121 l/hr and 339 ± 138 l/hr in males and females, respectively. The clearance was independent of gender and weight in low and medium weight groups. However, in both male and female high weight group, the clearance was higher by 26% and 68%, respectively.

The mean steady-state concentration of pyridostigmine during Days 4-22 was between 5 to 10 ng/mL. The accumulation ratio of pyridostigmine bromide was 1.6 on day 22.

Summary of Pharmacokinetic Parameters (Day 1)

Parameters	Low	Medium	High
C_{max} (ng/mL)			
Male	21.1 ± 5.8	21.3 ± 4.8	16.1 ± 5.6
Female	27.8 ± 11.8	25.3 ± 10.3	14.6 ± 6.3
T_{max} (hrs)			
Male	2.05 ± 0.44	2.20 ± 0.35	2.4 ± 0.91
Female	1.75 ± 0.59	2.25 ± 0.63	2.05 ± 0.60
Clearance (l/hr)			
Male	308 ± 99	278 ± 53	387 ± 166
Female	270 ± 81	294 ± 123	453 ± 135
Clearance (l/hr)	All wt groups		
Male	324.4 ± 120.9		
Female	338.7 ± 138.5		

Summary of Pharmacokinetic Parameters (Day 22)

Parameters	Low	Medium	High
C_{max} (ng/mL)			
Male	26.9 ± 7.5	30.1 ± 10.9	20.9 ± 5.3
Female	32.9 ± 7.2	31.7 ± 13.5	25.1 ± 11.2
T_{max} (hrs)			
Male	1.80 ± 0.63	1.85 ± 0.94	2.2 ± 0.48
Female	1.65 ± 0.47	1.95 ± 1.07	2.3 ± 0.59
Clearance (l/hr)			
Male	309 ± 111	261 ± 111	324 ± 94
Female	238 ± 59	300 ± 129	308 ± 127

ALL WT GROUPS & males & females

	Day 1	Day 22
AUC (ng.hr/mL) (8hrs)	78.0 ± 28.8	117.7 ± 42.9
Oral Clearance	331.6 ± 129.1	290.2 ± 107.5
Accumulation Factor	-	1.6 ± 0.6

Pharmacodynamics:

The percent inhibition of acetylcholinesterase activity showed considerable variability among subjects. However, the mean data did not show any obvious differences in different groups. Following a single dose the maximum inhibition of acetylcholinestrase activity ranged from 29-45% in different weight groups and this inhibition was achieved in 2-3 hours post dose. Following a single dose the targeted inhibition of 20-40% lasted up to 4-5 hours post dose. Following multiple dosing the maximum inhibition of acetylcholinestrase activity ranged from 41-49% in different weight groups and the targeted inhibition of 20-40% lasted up to 7-8 hours post dose. The mean percentage inhibition of acetylcholinestrase activity during days 4-22 of the study (trough levels) was 18-26% in various groups. The inhibition of RBC acetylcholinestrase activity was independent of gender. However, in the high weight group the inhibtion of acetylcholinestrase activity was lower by 15% in males and by 26% in females compared to low weight group.

Time for maximum inhibition of acetylcholinestrase activity for some subjects on Day 22 was more than 8 hours. Majority of the subjects had T_{imax} of 1-3 hours. Based on this general observation subjects with $T_{imax} > 8$ hours were considered as outliers. There were 5 subjects in this category and their data are presented below:

Subject #	Group	T_{imax} (hours)
47	MM	10
13	MH	72
60	FL	10
42	FH	72
65	FH	28

MM = Male medium weight; MH= Male high weight.
FH = Female high weight ; FL = Female low weight.

The summary of pharmacodynamic parameters of pyridostigmine bromide with and without outliers is presented in the following Table.

Summary of Pharmacodynamic Parameters

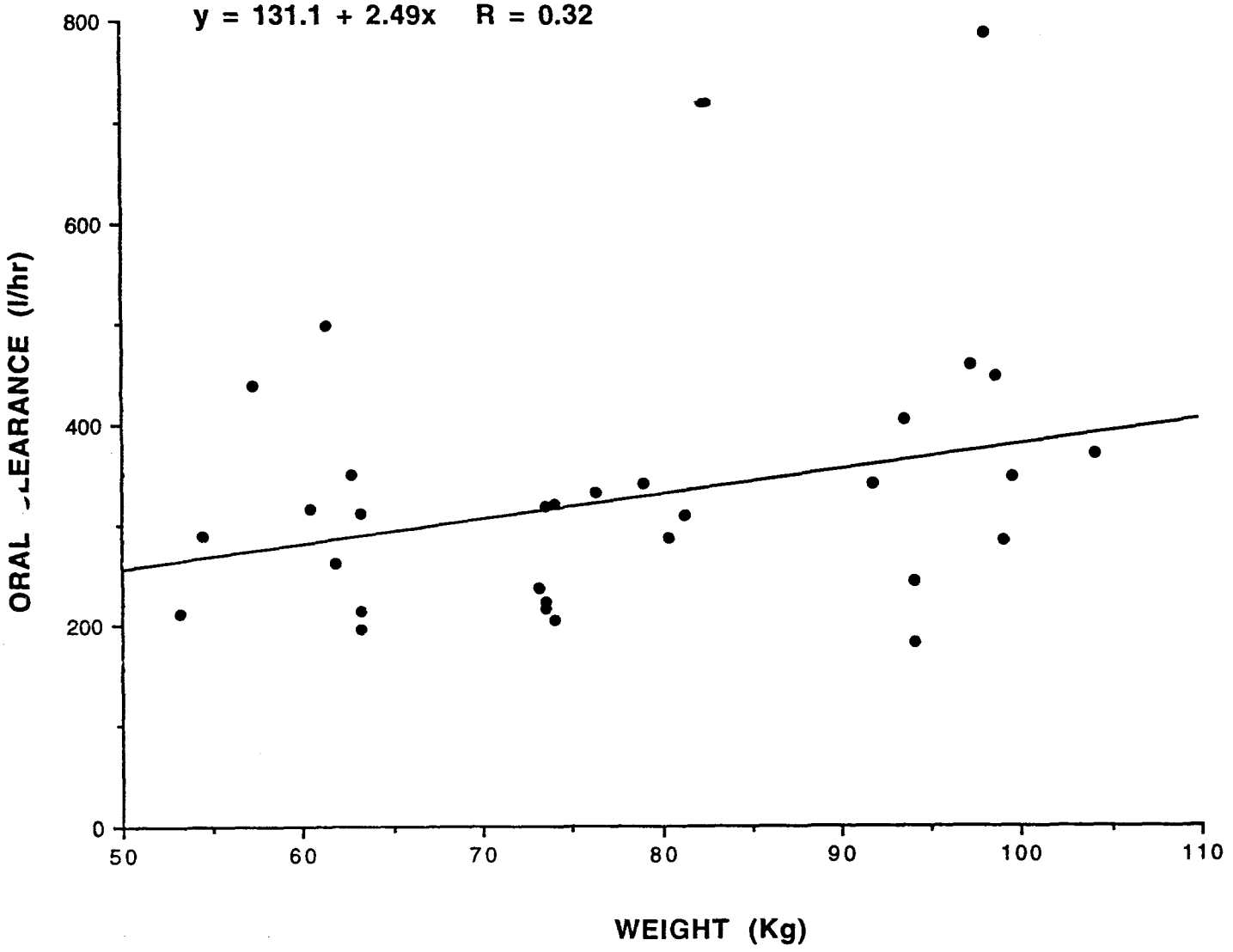
Parameters	Low	Medium	High
Day 1:			
I_{max} (% Inhibition)			
Male	37.9 ± 7.0	36.0 ± 5.2	32.0 ± 7.3
Female	38.8 ± 6.7	44.7 ± 6.5	28.7 ± 8.2
Ti_{max} (hrs)			
Male	2.1 ± 0.52	2.65 ± 0.34	2.60 ± 0.88
Female	2.45 ± 0.99	2.15 ± 0.41	2.0 ± 0.33
Day 22: (All subjects)			
I_{max} (% Inhibition)			
Male	48.5 ± 5.9	44.9 ± 7.9	41.4 ± 5.7
Female	43.2 ± 5.9	48.6 ± 11.2	42.7 ± 9.9
Ti_{max} (hrs)			
Male	2.45 ± 1.09	3.0 ± 2.53	9.9 ± 21.83
Female	3.3 ± 3.06	2.4 ± 1.33	11.95 ± 22.59
Day 22: (Without outliers)			
I_{max} (% Inhibition)			
Male	48.5 ± 5.9	45.4 ± 8.2	41.4 ± 5.7
Female	43.2 ± 6.3	48.6 ± 11.2	41.7 ± 9.6
Ti_{max} (hrs)			
Male	2.45 ± 1.09	2.22 ± 0.62	3.0 ± 0.83
Female	2.56 ± 2.07	2.4 ± 1.33	2.44 ± 0.86

Conclusions:

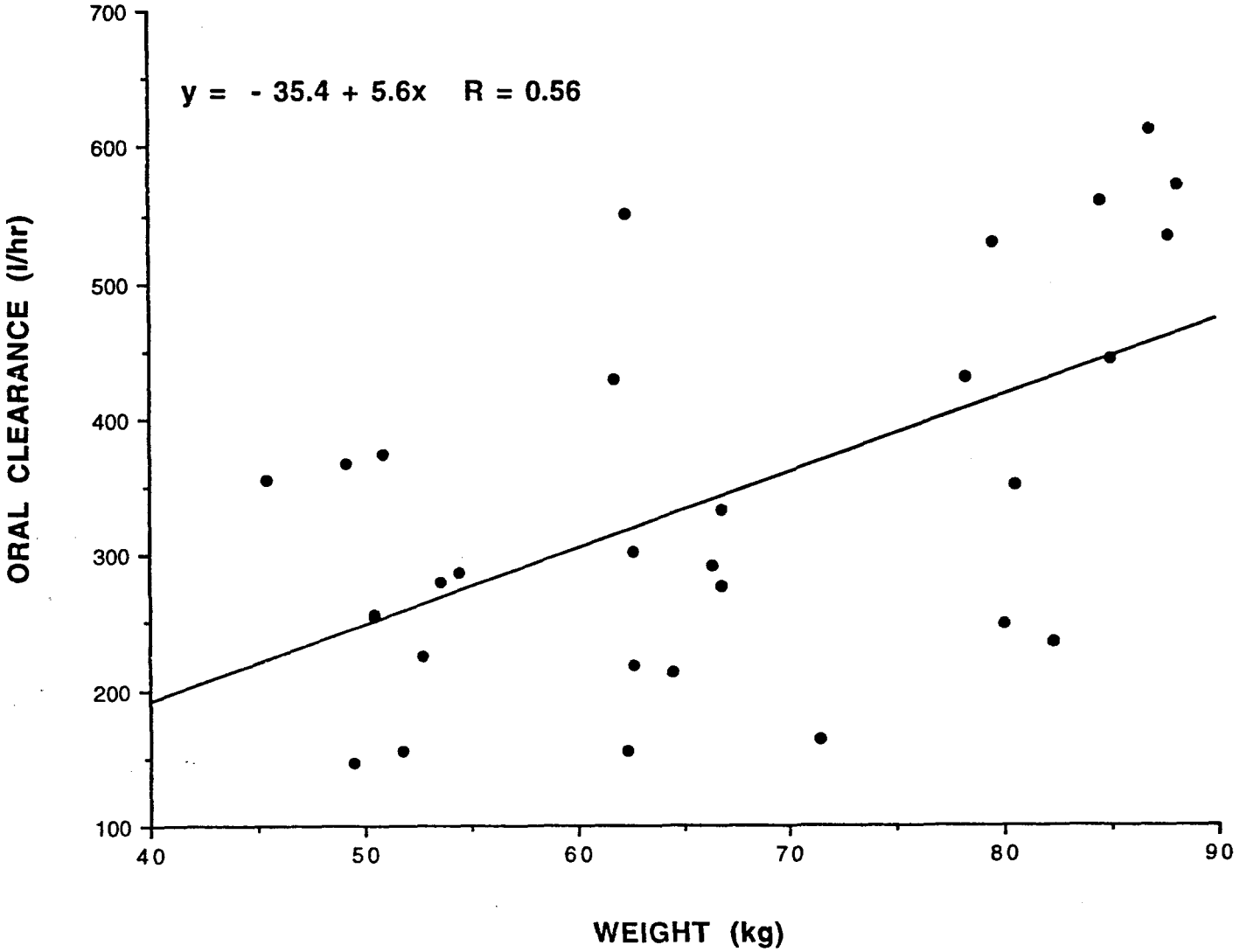
The pharmacokinetics of pyridostigmine bromide appears to be independent of weight and gender in low and medium weight subjects. However, the C_{max} was lower by 25% in high weight males and by 50% in high weight females compared to low and medium weight groups. In both male and female high weight groups, the clearance was also higher by 26% and 68%, respectively.

The percent inhibition of acetylcholinesterase showed that 20-40% inhibition was achieved in 2 to 3 hours post dose. This level of inhibition was maintained upto 4 to 5 hours and 7 to 8 hrs following a single and multiple dose, respectively.

Clearance vs weight of pyridostigmine in male subjects (n =30)



Clearance vs weight of pyridostigmine in females (n = 30)



Results:

The maximum plasma concentration of pyridostigmine reached in two hours with a lag time of 15 to 30 minutes. The mean pyridostigmine plasma concentration ranged from 17.4 ± 4.8 to 38.3± 13.9 ng/ml, whereas the mean AUC ranged from 83.7 ± 28.2 to 165.1 ± 63.8 ng.hr/ml. The maximum inhibitiom (39 to 57%) of acetylcholinesterase activity reached in 2 to 3 hours and returned to normal after 16 hours post dose. The pharmacokinetic and pharmacodynamic parameters following four doses of pyridostigmine syrup have been summarized in the following Table.

TABLE

Pyridostigmine Dose (syrup)

Parameters	0.40 mg/kg	0.57 mg/kg	0.73 mg/kg	0.90 mg/kg
T_{max} (hrs)	2.06 ± 0.8	2.1 ± 1.1	2.89 ± 9.6	1.7 ± 0.5
C_{max} (ng/ml)	17.4 ± 4.8	22.8 ± 7.5	28.9 ± 46.7	38.3 ± 13.9
AUC (0-24) (ng.hr/ml)	83.7 ± 28.2	110.6 ± 40.8	129.6 ± 46.7	165.1 ± 63.8
$T_{inhibition}$ (hr)	2.6 ± 0.9	2.5 ± 1.0	2.1 ± 0.8	1.8 ± 0.7
I_{max} (%)	39.4 ± 7.4	46.2 ± 8.0	52.2 ± 9.4	56.6 ± 8.9
$AUC_{(0-24)}$ inhibition (%hr)	237 ± 54.1	307.2 ± 90.2	307.8 ± 91.1	370.3 ± 99.8

Based upon C_{max} and $AUC_{(0-24)}$, the pharmacokinetics of pyridostigmine was linear from 0.40 mg/kg to 0.90 mg/kg (30 to 60 mg). The maximum %inhibtiom of acetylcholinesterase activity (I_{max}) increased with increasing dose.

In order to evaluate the comparative bioavailability of the syrup and tablet formulations at the 30 mg dose level, eighteen subjects received 30 mg tablet or 30 mg syrup of pyridostigmine bromide. The results of the study showed that the relative bioavailability of the tablet to the syrup was 121 ± 45%. Furthermore, the pharmacodynamic end points, e.g. I_{max}, $AUC_{(0-24)}$ inhibition and $T_{inhibition}$ were identical between the two dosage forms. The pharmacokinetic and pharmacodynamic parameters following 30 mg dose of pyridostigmine tablet and syrup have been summarized in the following Table.

TABLE

Parameters	Tablet	Syrup
T_{max} (hrs)	3.0 ± 0.9	2.5 ± 0.8
C_{max} (ng/ml)	23.8 ± 9.7	21.9 ± 46.8
AUC (0-24) (ng.hr/ml)	91.6 ± 37.1	92.5 ± 46.8
$T_{inhibition}$ (hr)	2.9 ± 0.6	2.5 ± 0.6
I_{max} (%)	40.4 ± 8.5	39 ± 8.9
$AUC_{(0-24)}$ inhibition (%hr)	235.6 ± 79.4	237.6 ± 81.2

Conclusion:

This study indicates that the pharmacokinetics of pyridostigmine syrup are linear over the single dose range of 30 to 60 mg. Furthermore, the pharmacokinetics and pharmacodynamics of 30 mg dose of pyridostigmine tablet and syrup are comparable.

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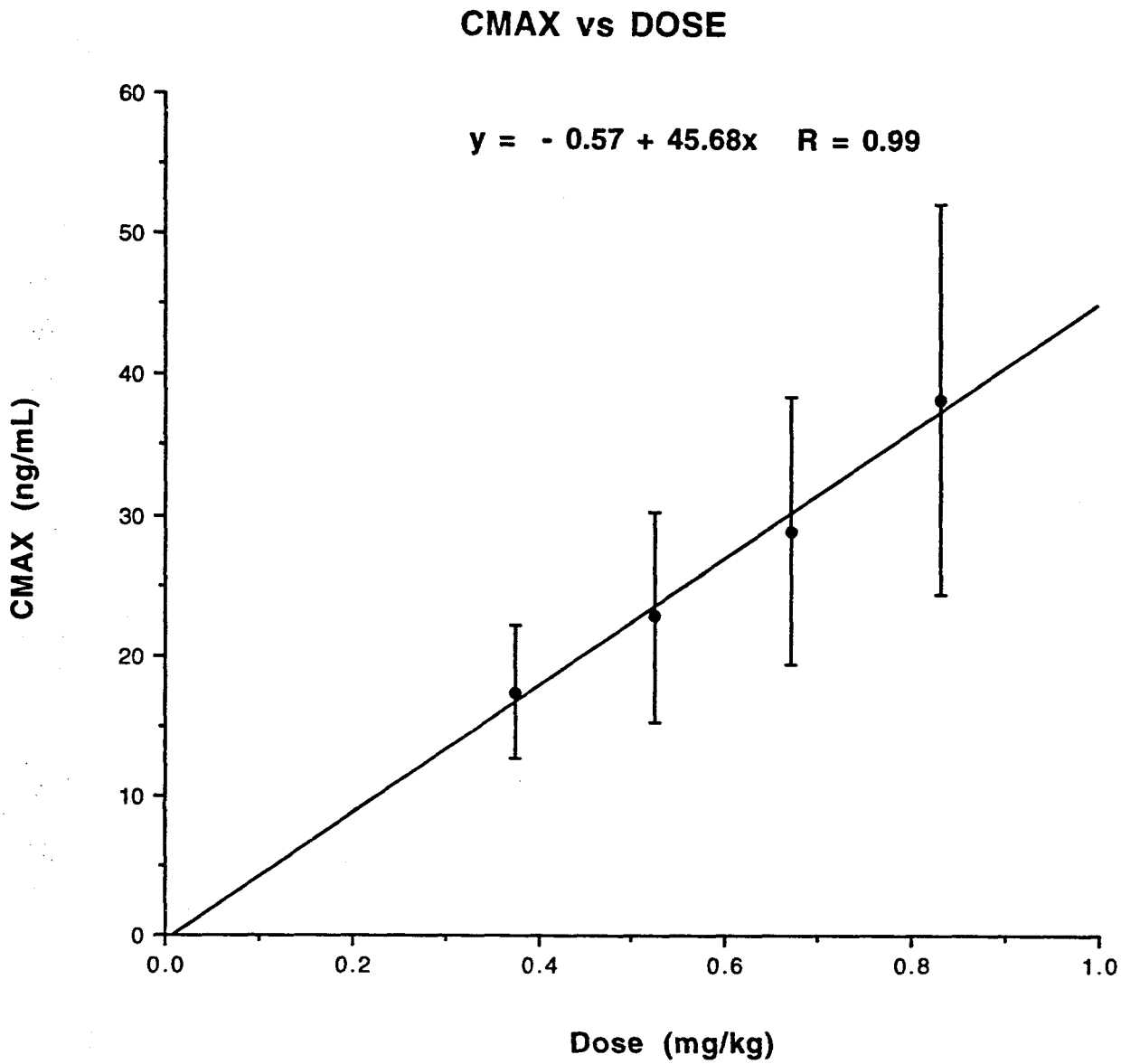
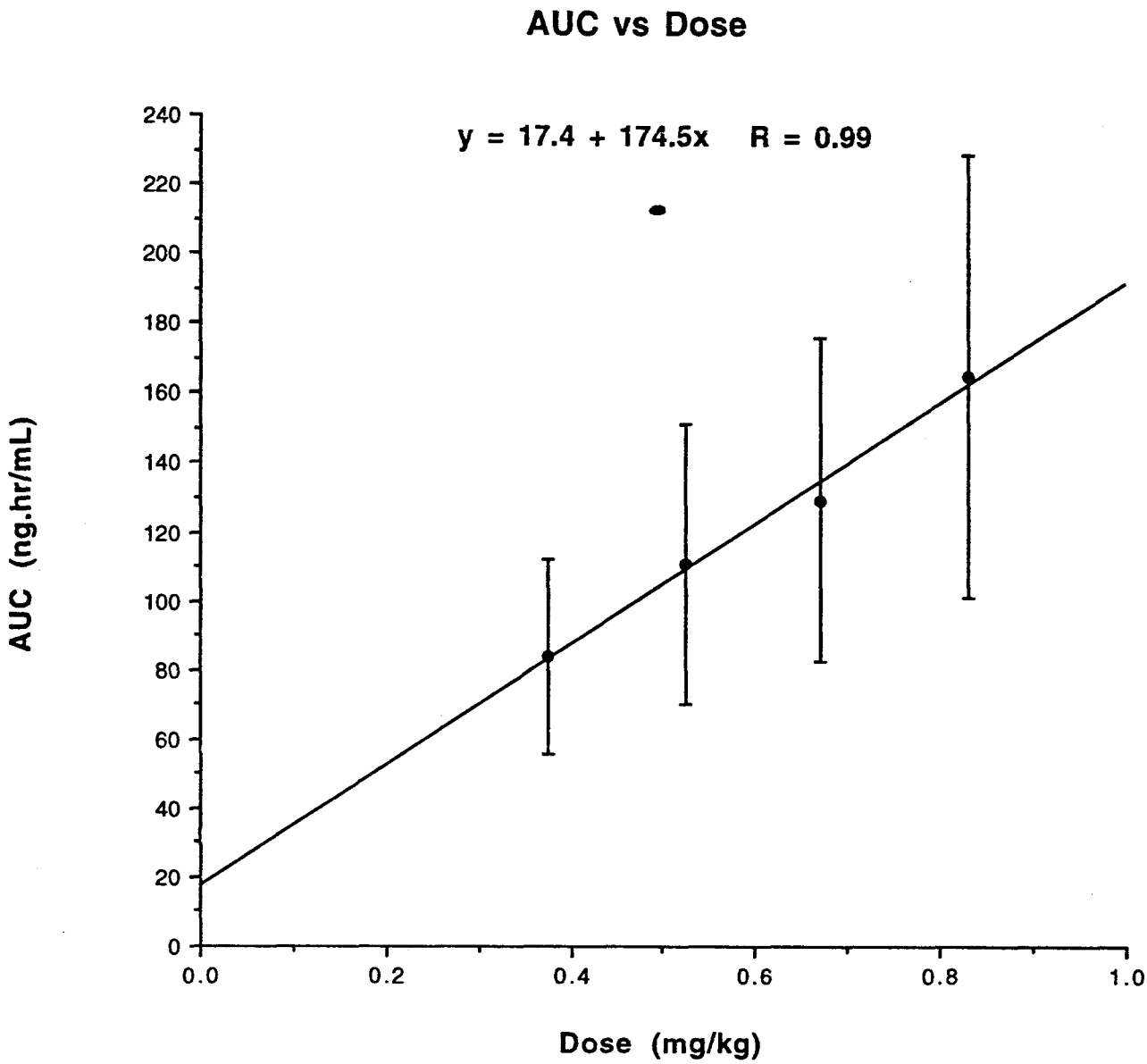

CMAX vs DOSE
y = - 0.57 + 45.68x R = 0.99
CMAX (ng/mL)
60
50
40
30
20
10
0
0.0
0.2
0.4
0.6
0.8
1.0
Dose (mg/kg)


AUC vs Dose
y = 17.4 + 174.5x R = 0.99
AUC (ng.hr/mL)
240
220
200
180
160
140
120
100
80
60
40
20
0
0.0
0.2
0.4
0.6
0.8
1.0
Dose (mg/kg)

13 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
CLINICAL REVIEW OF NDA

Generic (Brand) Name:	Pyridostigmine Bromide (Mestinon)
Indication:	Protection against anticholinesterase nerve gas agents
NDA Classification:	3P
NDA Number:	20-414
Original Receipt Date:	March 7, 1994
Resubmission Date:	May 24, 1996
Clinical Reviewer:	Richard M. Tresley, MD
Review Completed:	August 1, 1996

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1 Materials Utilized in Review

Volume	*Submission Date*	*Material*
2.47	May 24, 1996	Integrated Summary of Safety
2.47, 1.48-63, 2.86-88	March 7, 1994 May 24, 1996	Clinical Data
2.47	May 24, 1996	Integrated Summary of Benefits/Risks
2.88	May 24, 1996	Labeling

2 BACKGROUND

A. *Indication*

The proposed indication for pyridostigmine bromide (PB) 30-mg tablets is "to produce acetylcholinesterase inhibition (AChEI) in humans as part of a medical program to provide protection for U.S. military personnel against the effects of organophosphorus nerve agent poisoning. It is also used for the treatment of *myasthenia gravis*, as well as for the reversal of nondepolarizing muscle relaxants."

B. *Related NDAs and INDs*

NDA/Mestinon (Roche) 9,829 (approved 6-Apr-55)
60 mg tablet, myasthenia gravis
NDA/Mestinon (Roche) 11,665 (approved 1-Jan-59)
180 mg tablet, sustained release
NDA/Mestinon syrup (Roche) 15,193 (approved 11-Jun-63)
60 mg/5 ml syrup
NDA/Mestinon (Roche) 9,830 (approved 2-Oct-72)
5 mg/ml im/iv injectable
NDA/Regonol (Organon) 17,398 (approved 14-Aug-73)
5 mg/ml im/iv injectable
INDs submitted by the Office of the Surgeon General, Dept. Of the Army:
--Pyridostigmine bromide (Roche/ [redacted] (submitted 26-Jan-84)
30 mg tablet
--Pyridostigmine bromide [redacted] (submitted 9-Sep-87)
Sustained-release tablet, various oral formulations
ANDA/[redacted] now Solvay Duphar) 89,572 (approved 27-Nov-90)
30 mg tablet
(withdrawn by Solvay Duphar, January 1994)

C. *Administrative History*

Original IND ([redacted]) received	January 26, 1984
FDA Interim Rule	December 21, 1990
(Waiver of informed consent, where not feasible, in battlefield or combat-related situations.)	
Initial NDA submitted	March 7, 1994
FDA Refuse to File Action	May 5, 1994
NDA resubmitted	May 24, 1996

D. *Proposed Directions for Use*

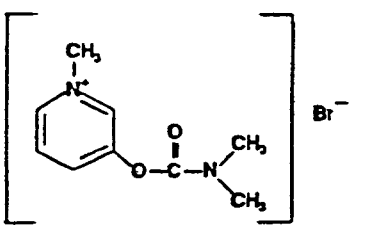
[redacted]

E. *Foreign Marketing Experience*

"Mestinon 30-mg tablets are currently supplied to the military in the United Kingdom, Canada, Switzerland, and Denmark" (v. 2.2, p. 9).

3 CHEMISTRY

Pyridostigmine [redacted] molecular formula, $C_9H_{13}BrN_2O_2$; and molecular weight, 261.2. Following is its molecular structure:



Inactive ingredients in the tablet form [redacted] lactose, magnesium stearate, [redacted] starch, precipitated silica, talc, and purified water.

4 ANIMAL STUDIES AND TOXICOLOGY

Pyridostigmine bromide and its derivatives have been in the market place for over 40 years

as a treatment for myasthenia gravis. The acute *oral* LD_{50} ranges from 18 mg/kg in mice to 80-87 mg/kg in rats and rabbits -- or 14-67 times the intended daily dosage of 1.3 mg/kg for humans. The *iv* LD_{50} in mice was 1.5 mg/kg; and the *ip* LD_{50}, 3.3 mg/kg in mice, 3.9 mg/kg in adult rats, and 4.6 mg/kg in adult rats. Death usually occurred within 24 hours, but occasionally as late as six days after dosing.

In two-week toxicity testing in rabbits, mortality occurred at 1 mg/kg iv on Day 1 in 2 of 6 animals, but not at 0.5 mg/kg/d for two weeks. In 1 of 14 dogs given PB at 6 mg/kg/d in capsule form, death occurred on Day 23 presumably as a result of "drug-induced intussusception." There were no deaths or signs of toxicity, over a two-week period, in rats administered up to 4 mg/kg/d in drinking water and dogs at 1 mg/kg/d iv; or over a four-week period in dogs given 1 mg/kg/d im.

In 13-32 week studies of oral dosing, mortality occurred at dosing initiation (Day 2) in 2 of 20 rats given 60 mg/kg/d by gavage; however, when the dose was reduced to 30 mg/kg/d, no deaths were seen over a 13-week period. There were also no deaths or signs of toxicity in rats given 32 mg/kg/d (by dietary admixture) for 21 weeks, in monkeys at 16 or 32 mg/kg/d (by gavage) for 16 weeks, or in dogs at 1.5 mg/kg/d (in capsules) for 13 weeks. In monkeys, no deaths or signs of toxicity were observed with doses up to 4 mg/kg/d x 5 days weekly for 16-19 weeks, followed by doses up to 32 mg/kg (NOEL) for 16 additional weeks.

No reproductive or teratogenic effects were noted in rats or rabbits at doses toxic to the parental animals. No evidence of mutagenicity was observed in the Ames (with and without metabolic activation) and micronucleus tests.

PB has been fielded as a prophylactic for nerve agent poisoning by the military in the UK, Israel, and the US briefly during the Persian Gulf War; but its mechanism of action and the effective dose rely exclusively on animal data. Used alone, PB neither reduces the toxic effect, nor acts as an antidote, nor significantly changes the LD_{50} of the nerve agent. However, the sponsor contends, using animal data to support his conclusion, that if PB is taken prior to nerve agent exposure and if the nerve agent challenge is followed by the current antidotes (atropine and 2-PAM), therapy is more effective than without pretreatment. PB thereby raises the LD_{50} of the nerve agent.

Essentially, the carbamate PB binds to the same active site on the acetylcholinesterase enzyme as the organophosphorus agents; as long as the PB molecule occupies the site, the nerve agent cannot bind to the enzyme. The attachment of the carbamate is reversible and within minutes to hours, the carbamate spontaneously leaves or is hydrolyzed (decarbamylated), allowing the enzyme to function normally. In contrast, after a nerve agent attaches, the agent-enzyme bond is irreversible and the enzyme can be replaced only by *de novo* synthesis. Thus the attachment of PB provides temporary protection of the enzyme from the nerve agent.

According to the sponsor, primates were found to be most sensitive to pretreatment and therapy, guinea pigs next, followed by rabbits and rats. PB pretreatment appeared to be most beneficial in the pretreatment of animals challenged by soman (GD), which produces an agent-enzyme complex refractory to oxime reactivation (nerve agent "aging"). The sponsor uses a measurement known as the protective ratio (LD_{50} in a group of animals challenged with an agent and treated::LD_{50} of a group of animals challenged with an agent and not treated) to indicate beneficial effect. In three studies in guinea pigs challenged with soman and then treated with atropine/2-PAM, the protective ratios were 3.4, 1.7, and 3.0; when pretreatment with PB was given, along with the standard therapy, the protective ratios improved to 6.4, 6.8, and 11.0. In two studies in rabbits, the addition of PB pretreatment raised the protective ratios from 1.4 and 2.2 to 2.7 and 3.1; and, in rhesus monkeys, from 1.6 to over 40. After tabun (GA) challenge, the protective ratios after standard atropine/2-PAM therapy were 2.4 in rabbits and 4.4 in guinea pigs; but PB pretreatment raised these ratios to 3.9 and 12.2, respectively. Standard therapy (atropine/2-PAM) given to sarin (GB)- and VX-challenged guinea pigs produced protective ratios of 30-50,

which were not significantly altered by PB pretreatment. These animal studies will be reviewed in detail by Dr. Barry Rosloff.

In the definitive efficacy trial in rhesus monkeys, animals were randomized to four groups: control (no treatment); atropine (0.40 mg/kg)/2-PAM (25.71 mg/kg) in divided doses (2/3 at 1 minute after soman, 1/3 total dose at 10 minutes after soman), low-dose PB (1.2 mg q8 hr x 6 doses) + atropine/2-PAM (as above), and high-dose PB (1.2 mg, followed in 8 hours by 1.8 mg, then in 16 hours by an additional 2.4 mg/kg q8 hr x 6 doses) + atropine/2-PAM as above. Animals in both the low- and high-dose PB pretreatment groups were well protected from soman-induced convulsions and death: at the highest soman doses given to atropine/2-PAM-only animals (27-52.2 mcg/ml soman), 4/5 had convulsions and died at 48 hours, whereas no (0/11) PB-treated animals died. At the maximum soman doses given (501-617 mcg/ml), just 2/36 PB-treated animals died.

Trials that would include extensive exposure to organophosphorus nerve agents have not been conducted in humans for ethical reasons; however, results are available from early British studies that exposed volunteers to very low-level doses of sarin. Thus the pretreatment dosing regimen of PB proposed in the NDA for humans, as well as the use of AChEI as surrogate marker, have been derived entirely from pharmacokinetic, pharmacodynamic, and efficacy studies in rhesus monkeys and extrapolated to man: pretreatment with PB at 30 mg q8h, the sponsor alleges, provides an RBC acetylcholinesterase inhibition level (AChEI) of 15-20% which -- in combination with the appropriate antidotes -- should give protection against nerve agent poisoning.

According to Dr. Rosloff, who will be analyzing the material in detail, the most recent animals studies cited in the NDA may show that much lower pretreatment levels of AChEI are equally protective in primates. This would cast doubt on the significance of AchEI as a surrogate marker and also raise questions about the proposed 30 mg q8 dosing regimen.

5 DESCRIPTION OF CLINICAL DATA SOURCES

Pyridostigmine bromide and its derivatives have been in the market place for over 40 years as a treatment for myasthenia gravis in daily dosages that can be as high as 600 mg. In NDA 20-414, the sponsor alieges that a PB dosing regimen of 30 mg q8 hours (90 mg/day) is safe in healthy men and women and will yield an AChEI of 15-20% -- equivalent to the level in primates that has been shown to provide adequate protection against organophosphorus poisoning. The sponsor marshals support for this contention, as well as for the safety of PB in normal subjects, from numerous trials in the US and abroad, ranging from one to 30 days in duration and encompassing "800-850 volunteers, 435 of whom were studied under military service and environmental stress conditions" [v. 2.47, p. 230]. I can only account for 668 subjects total, including the published sources that have been cited; it should be noted, however, that I have not included in my count studies in which the exact number of treated subjects is not known for sure. I have broken down the NDA data into dose, duration, and numbers of subjects as follows:

Dose	*Duration*	*No. of subjects*	
		NDA Studies	*Published Citations*
30 mg tablet	1 dose	570	39
30q8 tablet	5 days	447	
30q8 tablet	6 days	380	
30q8 tablet	7 days	351	

30q8 tablet	10 days	310	
30q8 tablet	14 days	149	
30q8 tablet	21 days	137	
30q8 tablet	28 days	77	
60 mg tablet	1 dose	26	12
90q12 tablet	2 days	8	
10, 20, 30 mg liquid formulation	1 dose of each on 3 different days		5
6 mg iv	1 dose	16	

A table of all the sponsor's studies, adapted from data pages in the NDA (v 2.47, pp 235-54), can be found in section 7 below.

To buttress further the claim for safety, the sponsor cites published reports of the estimated 250,000 US military personel who took PB 30 mg q8h for periods of 1-7 days under wartime conditions during the Persian Gulf War. This material is discussed in section 8B.

6 SUMMARY OF HUMAN PHARMACOKINETICS

After a single oral dose of 0.57 mg/kg of PB syrup (40 mg dose for humans), the C_{max} in humans is 22.79 ng/ml vs 26.6 ng/ml in the rhesus monkey (after gavage). The I_{max} for RBC AChEI at this dose is 43% for the monkey and 46.2% for humans. The protective effect of PB was still found to be present in monkeys with an RBC AChEI as low as 10% (Olson, 1995; v 2.82, p 152-v 2.83, p 173), and there is no apparent reduction in the protective effect when RBC AchEI is inhibited by as much as 51%. The sponsor alleges that the PB 30 mg q8h dosage regimen provides the 20-40% desired level of RBC AChEI that would provide increased protection against nerve agent poisoning in animals (Lassiter, 1996; v 2.84, p 123); however, initial, and even subsequent multiple doses, of PB do lead to extremely variable levels of PB and AChEI (Parker, 1989, v 2.86, p 185; Lassiter, 1996, v 2.84, p 123).

Results from the largest study (Lassiter [1996], v 2.84, p 99]: single-site, randomized, double-blind, placebo-controlled) show C_{max} and T_{max} ranges, for a single Roche PB 30 mg tablet, as 16.1-27.8 ng/ml and 1.8-2.4 hours, respectively. For multiple dosing at 30 mg q8h x 22 days, the ranges for C_{max} and T_{max} were 21.0-34.0 ng/ml and 1.6-2.3 hours. I_{max} parameters ranged from 28.7-44.7% on Day 1 to 41.7-48.6% on Day 22.

This subject will be dealt with in greater detail by Dr. Iftekhar Mahmood.

7 OVERVIEW OF CLINICAL STUDIES

The following table, adapted from the sponsor's submission, summarizes the human safety data which has been used in support of the NDA. The number of subjects, as well as the number of treated versus placebo, are indicated when the information is available; in many cases, actual

numbers are not specified in the studies. Key to abbreviations:

inc = *increased*	DB = *double blind*	sxs =*symptoms*	n_{tr} = on drug
dec = *decreased*	PC = *placebo controlled*	HR =*heart rate*	n_{pl} = on placebo
rh = *relative humidity*	CO = *crossover*	PFT =*pulmonary*	
withdr =*withdrawals*	BC = *baseline controlled*	*function tests*	

A. *Safety Studies Conducted by the US Army and Air Force*

Study Title	*Type*	*Subjects*	*Dose*	*Results*	*P.I./Ref.*
Safety, tolerance, PK and PD of PB when given in single and multiple doses to males and females in different weight categories	DB, PC	45 M 45 F (n_{tr}=60 n_{pl}=30)	30q8h x 64 doses	Few mild side effects (see Section 8C below); no deaths or serious adverse reactions.	Lassiter (1996), v 2.84, p 99
PB does not alter thermoregulation during exercise in cold air	DB, PC, CO	7 M	30q8h x 7 days	No differences between treated and placebo for core temp; HR; metabolic rate (with low and moderate exercise in 5°C, 40% rh, 1.1 m/s wind speed); or plasma glucose, glycerol, FFA. No AEs cited.	Roberts (1993), v 1.62, p 1
Chronic PB administration: side effects among soldiers working in a desert environment	DB, PC, CO	24 M	30Q8h x 5 days	Few marginal statistically--but not clinically--significant performance decrements (see Section 8F below).	Cook (1992), v 1.58, p 136
Cardiovascular and thermoregulatory responses to repeated ACh administration	PC, CO	4 M	30Q8h x 3 days (10 doses)	On PB, both resting and post high-intensity exercise HR dec by 11±7 beats/min, core temp by 0.23±12°C; sweating inc 12±18% during exercise in 35°C.	Kolka (1992), v 1.61, p 36 (published report)
Physiological effects of wearing the aircrew uniform integrated battlefield while flying the UH-60 simulator in a controlled heat environment	DB, PC, CO	2 M	30 mg x 1 dose	In 35°C, rh 50%, one subject had inc core temp on PB, one did not; both had inc sweat rate on PB.	Thornton (1992), v 1.62, p 29

Effects of PB on physiological responses to heat, exercise, and hypohydration	PC, CO	6 M	30 mg x 1 dose	Mod exercise in 35°C under 4 conditions: 20% rh, hydrated *ad libitum ;* 20% rh, euhydrated; 75% rh, euhydrated; 20% rh, hypohydrated 3% body wt. PB dec HR by 3 beats/min overall, but did not affect core temp, sweating, HCT, Hgb, tot protein, osmolality, *ad libitum* drinking, rate of O_2 uptake, or subjective ratings of temp, discomfort, exertion.	Wenger (1992), v 1.62, p 9 (published report)
Effects of PB on visual performance	BC	4 M	30q8h x 3 days	No significant change in refractive error or pupil diameter.	Wiley (1992), v 1.62, p 90
Effects of PB on A-10 pilots during execution of a simulated mission: performance	DB, PC, CO	24 M	30q8h x 3 doses	No operationally significant effects.[1]	Brooks (1992), v 2.86, p 6
Multiple dose PB administration: cardiovascular effects at rest during heat and altitude exposure	PC, CO	9 M	30q8h x 10 doses	Resting HR and core temp slightly dec in hot environment; core temp also dec at sea level and at acute altitude (see Section 8F below).	Kolka (1991), v 1.61, p 41
Respiratory and skeletal muscle function after acute PB administration	PC	10 M	30 mg x 1 dose	No significant effect on PFTs, handgrip or leg-extension strength, or CK, LDH, AST testing.	Levine (1991), v 1.61, p 72
Effects of PB on human thermoregulation during cold water immersion	PC, CO	6 M	30 mg x 1 dose	Marked abdominal and leg cramping with cold stress (see Section 8F below).	Prusaczyk (1991), v 1.61, p 287
PB: Effects on physiological responses to repeated exercise heat stress	DB, PC, CO	7 M	30q8h x 19 doses	No significant effect on memory or mathematical processing tasks.[1]	Wenger (1991), v 2.87, p 60
Human temperature regulation during exercise after oral PB administration	PC	4 M	30 mg x 1 dose	Very slight dec in HR.	Kolka (1990), v 1.61, p 29

Effects of PB on A-10 pilots during execution of a simulated mission: physiology	DB, PC, CO	24 M	30q8h x 1 day	Slight dec in HR; handgrip unchanged; flight tasks executed without problem. Mild sxs without impact on military duties: stomach gas and eructation (6), fatigue or muscle fatigue (6), confusion or giddiness (5); 1 each: rapid heartbeat ; sweating; dry mouth; inc bowel activity; tingling itching; irritability; blurred vision.	Harriman (1990), v 2.86, p 139
Performance effects of PB during and after acceleration stress	DB, PC, CO	5 M	30q8h x 4 doses	No significant effects.	Boll (1989), v 2.86, p 1
Chemical defense pretreatment drugs in the aerospace environment: an overview of biochemical analyses from PB studies conducted for the USAF School of Aerospace Medicine	DB, PC	?not given	Cf. various regimens: (1) liquid: 10-, 20-, 30-mg qod. (2) tablet: (a) 30 mg x 1; (b) 30 q8h x 4 doses; (c) 30q8h x 9 doses.	Single or initial PB doses result in extremely variable levels of PB and AchEI. Results from altitude and spatial disorientation studies with in-flight simulator experiences showed no differences between treated and placebo.[1]	Parker (1989), v 2.86, p 185
Effects of PB on the somatogravic illusion	DB, PC, CO	?not given	30q8 x 4 doses	No significant vestibular and visceral disturbances caused by abnormal acceleratory flight patterns.[1]	Previc (1989), v 2.88, p 1
PB effect on HR and vagal tone in aircrew	DB, CO	12 M	30 mg x 1 dose	Few marginal statistically, but not clinically, significant effects on HR and vagal tone during various segments of flight simulator.[1]	Dellinger (1988), v 2.86, p 51
Effect of PB on in-flight aircrew performance	DB, PC, CO	21 M	30 mg x 1 dose	No significant effect on fatigue or workload.[1]	Gawron (1988), v 1.59, p 1

Effects of ACh and atropine derivatives on visual function in human subjects	DB, PC, CO	?not listed	60 mg x 1 dose	No significant effect of stationary visual function.[1]	Morrison (1988), v 1.61, p 110
Interactive effects of PB and altitude on performance	DB, PC, CO	12 M	30q8 x 4 doses	Slight dec in finger-tapping test and short-term memory recall at operationally relevant altitudes, but overall performamce not significantly affected.[1]	Schiflett (1987), v 2.88, p 15
Chemical warfare prophylaxis: PB levels and ACh activity in single and multiple dose protocols	DB, PC	?not given	Cf. various regimens: (1) 10-, 20-, 30- mg liquid doses qod; (2) 30 mg tablet x 1 dose; (3) 30qh x 4 doses (tablets); (4) 30q8 x 9 doses (tablets)	Single dose or the initial dose in a multiple-tablet regimen resulted in very variable levels of PB and AchEI in pilots evaluated in both pre- and post-in-flight simulator experience; this "should be of concern to investigators interpreting performance and physiological data in such studies and aircrew facing potential chemical agent exposure."[1]	Parker (1987), v 1.61, p 273
Interaction of PB with mild hypoxia and rapid decompression	DB. PC, CO	12 M	30q8 x 4 doses	No significant PFT changes with moderate dec in barometric pressure.	Krutz (1987), v 2.86, p 180
Effects of a single oral dose of PB on contrast sensitivity	DB, PC, CO	14 M	60 mg x 1 dose	No effect on visual contrast sensitivity.[1]	Kay (1985), v 1.60, p 207

Effects of PB on psychomotor and visual performance [in pilots]	DB, PC, CO	24 M	30q8h x 5 days	Mild performance decrements in dual task studies: (1) primary attention task + secondary arithmetic addition task led to decline in the addition task results; (2) primary visual motor tracking task + secondary memory search task led to decline in the memory search task results. Could potentially impact on flight performance; requires further research, per P.I.[1]	Graham (1984), v 1.60, p 74

[1] I am not familiar with tests of pilot competence, and therefore have depended upon the assessments of the P.I., who is usually a military officer familiar with the duties and responsibilities of military personnel under study.

B. *Safety Studies Sponsored by the* [redacted]

Evaluation of PB as a pretreatment for nerve agent poisoning in man. In-house studies.	PC	76 M/F (n_{tr}=56 n_{pl}=20)	30q8h x 1-8 days ± 2-Pam/ atropine/ diazepam	No clinically significant events, with/without low-level sarin exposure (see Section 8G below). No adverse effects noted.	Blake (1985), v 1.58, p 9
Effect on man of 4 weeks' treatment with PB (3 x 30 mg po daily)	DB, PC	28 M (n_{tr}=14 n_{pl}=14)	30q8h x 4 weeks	Mild GI sxs with PB[1]: nausea/diarrhea, flatus, runny nose, headache. No clinically significant dec on number facility and grammatical reasoning tests. Marginal statistically, but not clinically, significant changes in uric acid (1 subject), Ca++ (1), total protein (1), MCV (1), MCHC (1).	Gleadle (1985), v 1.60, p 1
Evaluation of postural hand and finger tremor in subjects receiving PB	DB, PC	24 M	Cf. dose regimens: (1) 60 mg a 1 dose; (2) 30q8h x 2 weeks	Marginally statistical inc in physiological (normal) postural hand tremor after single 60 mg dose, but no effect observed with multiple 30-mg doses.	Findley (1984), v 1.58, p 211

Three studies [in three different centers] of the effects of 4 weeks' treatment with PB, 3 x 30 mg daily	DB, PC	97 M (n_{tr}=63 n_{pl}=34)	30q8 x 28 days	Mild sxs[2] with PB: less energetic, sweated more, less alert, more stools, more micturation, unduly hot, headache, depressed, difficulty concentrating, more tense, confused, bowel discomfort, felt sick, dizzy on standing, tight chest, runny nose, distant vision difficulty, unusual vision dimness, unwell in any way. Few changes in chemistry and hematology values of marginal statistical, but none of clinical, significance.	Gleadle (1983), v 1.59, p 206
Study of the effects of three weeks' treatment with PB on men undergoing moderate to strenuous exercise	DB, PC	24 M (6 withdr--from treated or placebo group?; reason?) (n_{tr}=14 n_{pl}=10)	30q8h x 3 weeks	Subjects engaged in bridge building and demolition exercises. Mild sxs[1] with PB: less energetic; more tired, sweated more, less alert, bowel discomfort, felt sick, vomited, chest tightness, runny nose, "unwell in any way."	Gleadle (1983), v 1.59, p 171
Car driver behavior following PB administration	DB, PC	48 M	30q8h x 1-7 days	No significant hazard to drivers.	Wetherell (1983), v 1.62, p 46
Effects of 10 days' treatment with PB on servicemen performing normal duties	DB, PC	34 M (n_{tr}=17 n_{pl}=17)	30q8h x 10 days	Mild sxs with PB: inc stools.[3] No significant abnormalities on the number facility and grammatical reasoning tests.	Kemp (1982), v 1.60, p 251
Physiological aspects of an investigation into the effects of PB pre-treatment on work capacity in the heat	DB, PC	18 M	30q8h x 2 weeks	Mod exercise in 35°C, 55% rh, with full NEC protective clothing: mild dec in resting HR (6-7 beats/min), not clinically significant; no clinically significant effect on PFTs, chemistry, hematology.	Duggan (1982), v 1.58, p 142

Effect on heart rate of neuromuscular blockade reversal by PB	DB, PC	40 F	10 mg im x 1 dose	In anesthetized women post-GYN surgery, atropine should be given with PB to prevent bradycardia; this combination may provide more stable HR than neostigmine + atropine.	Long (1981), v 1.61, p 95
Investigation of a possible interaction between PB pretreatment and a thermally stressful environment	DB, PC	18 M	30q8 x 2 weeks	Statistically, but not clinically significant, dec in resting HR (6-7 beats/min); no clinically significant abnormalities in chemistry, hematology, or on number facility or grammatical reasoning tests.	Jolly (1981), v 1.60, p 170
Selected clinical and biochemical observations in men taking PB	DB, PC	18 M	30q8h x 10 days	No clinical significant changes on hematology, LFTs, BUN, creatinine. No subject complaints.	Moylan-Jones (1981), v 1.61, p 216
A laboratory study of the performance of men taking PB orally (30 mg, 8 hourly) for 2 weeks	DB, PC	24 M	30q8h x 14 days	Marginal statistically, but not clinically, significant dec in the O'Connor Finger Dexterity Text and peak expiratory flow. No significant abnormalities in number facility, grammatical reasoning, short-term memory, perceptual motor-speed and coordination, attention, grip strength, other PFTs, pupil size. No symptom differences between placebo and treated groups.	Kemp (1981), v 1.61, p 1
Effect of PB upon exercise ventilation and cardiac frequency in healthy men	DB, PC, CO	7 M	30q8h x 2 weeks	Dec in resting and exercise HR by 6 beats/min. No clinically significant changes in PFTs, sweating, temp.	Martin (1980), v 1.61, p 99
A trial of PB pretreatment for nerve agent poisoning in man	DB, PC	84 M	30 mg x 1 dose	Low-level exposure to sarin; for results, see below.	Moylan-Jones (1975), v 1.61, p 210

[1]Symptoms have not been pooled for the total study, but rather are listed by week (a representative day was selected per week) and in the order that they appear on the individual questionnaires that subjects were asked to fill out. An accurate, comprehensive list of symptoms could therefore not be drawn up for the whole study over the

entire period.

[2]Symptoms have not been pooled for the total study, but rather are listed by week (a representative day was selected per week), by center site, and in the order they appear on the individual questionnaires that subjects were asked to fill out. There is no way to compile an accurate, comprehensive list of symptoms for the whole study over the entire period.

[3]This was the only symptom for which the number of complaints in the treated group exceeded placebo.

C. *Safety Studies from Published Literature*

Effect of PB on acceleration tolerance and performance	DB, PC	8 M (3 withdr--treated or place-bo?--due to schedule con-flicts)	30q8h x 3 days	At high sustained Gz+ exposures, no adverse effect on acceleration tolerance or motor and cognitive performance. No significant clinical changes in HR, EKG, PFTs, grip strength. No difference in symptoms between treated and placebo groups.	Forster (1994), v 2.86, p 126
Exacerbation of asthma after pyridostigmine during Operation Desert Storm	? (no con-trols)	16 M/F (10 with asthma; 6 healthy)	30 mg x 1 dose	PB associated with asthma exacerbation: 7/10 asthmatics with inc chest tightness 2-6 h post PB; 5/7 required use of inhalers; 3/10 with severe tightness, wheezing, dyspnea: 1 bed-bound x 12-18 h post PFTs, 1 recovered 8 h post PFTs, 1 placed on steroids 36 h post PFTs, admitted to hosp and then evacuated home. Other sxs (reported by 5/264 other unit members who also took PB): rhinorrhea, headache, diarrhea.[1]	Gouge (1994), v 2.86, p 134
The influence of PB administration on human neuromuscular functions--studies in healthy human subjects	DB, PC, BC	35 M	30q8h x 9 days	*Only a brief review of the study was available in the NDA:* "PB at a dosage of 30 mg 3 times daily for 9 days produces a 20-30% AChEI, and no significant neuromuscular effects occur" by *unspecified* "electrophysiological" and "electromyographical" tests.	Glikson (1991), v 2.63, p 208

The effect of PB on respiratory function in healthy asthmatic volunteers	DB, PC, CO	25 M	12 healthy adults = 60 mg x 1 dose; 13 asthmatics = 30 mg x 1 dose	Marginal statistically, but not clinically, significant dec in HR (6 beats/min) at rest only. In healthy subjects, marginal statistically, but not clinically, significant dec in FEV_1 post 60 mg PB at rest and after exercise. In asthmatics, no statistically significant differences were observed between the placebo and PB groups either at rest or after exercise. No list of adverse effects. Note: the asthmatics received atropine post exercise after(?) PFTs.	Ram (1991), v 1.61, p 294
Heat-exercise performance of PB-treated subjects wearing chemical protective clothing	DB, PC, CO	8 M	30q8h x 4 doses	After 170 min exercise-heat stress (33°C, rh 60%; two 50-min walks @1.39 m/s, 0% grade), no significant differences in HR, core temp, or sweat rate. No adverse effects noted.	Epstein (1990), v 1.58 p 206
Effect of repeated doses of 30 mg PB on pilot performance in an A-4 flight simulator	DB, PC, CO	10 M?	30 q8h x 4 doses	No change in flight performance, by instructor evaluation. "Mild" sxs with PB: limb weakness (2), trembling fingers (1), tongue twitching (1), flatus (1), inc salivation (1), difficulty in concentration (1).[2]	Izraeli (1990), v 1.60, p 166

[1]Without controls, it is difficult to determine whether the asthma was exacerbated solely by the PB ; there may have been other contributing factors, such as the dust and sand of the desert environment.

[2]The washout period may not have been long enough to exclude the possibility of drug effects influencing the symptom complex of subjects placed on placebo following drug exposure.

8 SAFETY FINDINGS

The safety evaluation centers on information provided by the sponsor in the Integrated Summary of Safety, published articles about the Gulf War experience, and case report forms and narrative summaries for deaths, serious adverse events, and discontinuations. Although the sponsor claims that "800-850" subjects were enrolled in its studies (some studies are reported for which the number of enrolles is unknown, "NA"), only 668--excluding published reports for the Gulf War, where the numbers involved are imprecise--could be readily accounted for.

In discussing adverse events, the sponsor does not define "serious and unexpected"; some

of the events he lists, such as mild nausea and diarrhea (see Section 8A below), are commonplace for PB and therefore would not necessarily fit the regulatory definition (CFR 314.80).

A. *Serious and Unexpected Adverse Events*

No deaths were reported in any of the studies conducted by the sponsor or during the supporting studies tabulated for the NDA. Available in the market place for the treatment of myasthenia gravis for almost 40 years, PB has compiled a long record of safety. Myasthenics average about 600 mg/day, whereas the total recommended dose in this NDA does not exceed 90 mg/day. Following is the experience of adverse events during the supporting military studies which the sponsor has classified as serious or unexpected (there are no more than four case report forms for the entire NDA and these can be found in v 2.75, pp 71-106):

Age	*PB Dose*	*Adverse Event*	*Outcome*	*Reviewer's Impression*
26 F	30q8 x 64 doses	Numerous bullous lesions around waist, webs of hands, left antecubital fossa. Occurred 8 weeks after final dose of PB.	Per dermatologist, "fixed drug eruption" (path bx report). P.I. Rated event as "possibly related."	Unlikely allergic reaction to PB, given the distant temporal interval.
24 M	30q8 x 3 doses	One pilot, standing while being hooked up by the technician prior to entering the flight simulator, experienced the following symptoms 90 min after his 30-mg dose: nausea, lightheadedness "with fever" (feverish sensation?), tongue numbness, loss of consciousness x 3-4 min, urinary and fecal incontinence, stiffness in torso and arms, post-event confusion and queasiness x 2 hours, superficial contusions and abrasions from fall.	Pt taken to ER and then hospitalized overnight. Returned to baseline after 2 hours. No reported residua. Labs and neurologic workup (neurologic exam and EEG only) reportedly negative.	Although the event has been classified as "cholinergic" and "syncopal," the actual symptoms might be consistent with a seizure (both urinary and fecal incontinence; stiffness in torso and upper arms; post-event confusion and queasiness x 2 hr). From the Poisindex, coma and seizures have been reported "in severe cases." This scenario ("in severe cases"), however, seems unlikely here, given the relatively low dose. However, one cannot entirely rule out the possibility that the event could have been medication related.

21 M	9 mg iv	Visual distortion x 5 min, followed by LOC x 2-5 min? while sitting on a bench, waiting for bus 18 after dosing.	Returned to baseline in 5? min and able to take bus home; subsequent labs (RBC AchEI, EEG, blood and tox tests) reportedly normal.	Probably syncope; unlikely related to drug exposure, given the distant temporal interval between dose administration and clinical event. The military medical reviewer (Brent G. Petty, MD) doubted any drug reaction for the same reason and suggested "migraine equivalent" as a diagnosis; however, there was no history of migraine, and syncope associatedwith migraine is very unusual.
21 M	30 mg x 1 dose	Chest tightness x 15 min.	Resolved; normal HR, BP, and physical exam.	Possibly related to PB.
24 M	30 mg x 1 dose	Intermittent abdominal cramping x 2 hr.	Resolved; normal physical exam.	Directly related to PB.
N=16 M	6 mg iv x 1 dose, followed the next day by either 30 q8* x 2 days (n=8) or 90q12** x 2 days (n=8)	1) HCT dec >5% over course of study (6 pts*; 4**); (2) tinnitus post 1st dose (1*); (3) forehead rash resolving on PB (1**); (4) flatulence, abdominal cramps, heartburn (1*); (5) nausea, diarrhea (1**); (6) slight in AST (2*; 1**); headache** (1).	Dec HCT probably due to phlebotomy, per study P.I. AST follow-up available for 1/3: returned to normal 9 days post end of study. Other clinical symptoms resolved quickly.	Probably related; apparently all quickly resolved. The dec HCT was probably due to phlebotomy, per the study P.I. Most of the adverse events found here would not appear to be "serious or unexpected," despite placement in this section by the sponsor.

B. *Pyridostigmine Experience During the Persian Gulf War (as reported in published sources)*

Although the NDA only touches cursorily upon the prophylactic use of pyridostigmine during the Gulf War, there have been a number of published sources that discuss the experience in some detail.

During Operation Desert Storm in January 1991, at least 250,000 US military personnel supposedly took PB at the recommended dosage of 30 mg q8h for periods of 1-7 days. According to Keeler, in a published retrospective study of soldiers during the Gulf War, "[o]ne percent of

this military population had effects from pyridostigmine for which they sought medical advice. Fewer than 0.1% had effects sufficient to warrant discontinuation of the drug" (JL Keeler et al, "Pyridostigmine Used as a Nerve Agent Pretreatment Under Wartime Conditions," JAMA 299(1991):695).

Keeler's article specifically reviews the history of the XVIII Airborne Corps, comprised of 41,650 soldiers (6.5% female) who reportedly took PB 30 mg q8 hr for 1-7 days (compliance allegedly 99% at the start of hostilities), with 34,000 soldiers reportedly taking the medication for 6-7 days. In very general terms, Keeler breaks down the incidence of side effects as follows: GI symptoms (flatus, loose stools, abdominal cramps, and nausea), ≥50%; urinary urgency and frequency, 5-30%; headaches, rhinorrhea, diaphoresis, tingling of the extremities, <5%; need for medical visit, 1%; and discontinuation on medical advice, <0.1%. "There were no medical evacuations among this corps because of problems with pyridostigmine (Keeler, p 694)." Keeler cites a signle example of a possible overdose. One "medical specialist" took two PB tablets to make up for a missed dose and, apparently experiencing "mild cholinergic crisis," then self-administered atropine by autoinjector intramuscularly and reported to his medical treatment facility. No further symptoms were reported (Keeler p 694).

One possible unexpected side effect which the study associated with the medication was hypertension in two otherwise normotensive recruits, both of whom reportedly experienced acute elevations in blood pressure (180-220/110-120 mm Hg). The elevated blood pressures were discovered incidentally, it sems, when the soldiers sought medical attention for epistaxis and "profuse bleeding" from a shaving nick. One of the recruits discontinued the drug for two days with resolution of the hypertension, then was rechallenged with PB with recurrence of significant hypertension. Platelets, CBC, and coagulation labs were all normal for both soldiers (Keeler, p 694).

One unit physician discontinued medication in 28 soldiers: 3 with exacerbated acute bronchitis, 1 with asthma, 2 with allergic reactions (not further described, but possibly due to the bromide salt formulation), 2 with hypertension, and 20 with intolerable nausea and diarrhea. One physician discontinued his own therapy because of GI side effects and headaches.

Since the war, some veterans have complained about a vague constellation of symptoms that have been loosely grouped together under the rubric "Gulf War Syndrome." Although investigated by various organizations, including the armed forces medical corps and the NIH, its etiology still remains a mystery, and its course not well defined.

C. *Adverse Events by Organ System*

This list of adverse events, mainly divided between muscarinic and nicotinic effects, and their incidence is derived from the Lassiter (1996) trial. A randomized, double-blind, placebo-controlled trial (45 men and 45 women, divided equally into treated [60] and placebo [45] groups), it is the most recent, and one of the largest and apparently one of the more reliable, of the studies put forth by the sponsor. By organ system (n_R=60):

Skin: rash[1], 2%; dry skin, 2%; alopecia[2], 2%
Eyes: eye pain, 2%

[1]Patients, according to the PDR, have developed rashes due to an allergy to the bromide radical. Whether this is the case here is not known; however, as there were no withdrawals, it is likely that the rash resolved without treatment while the patient was still on drug.

[2]Apparently resolved spontaneously; it should be noted that 3% on placebo also complained about alopecia.

Cardiovascular: dizziness, 3%
Pulmonary: none.
Digestive: nausea, 3%; diarrhea, 6%; abdominal pain, 6%
Neurologic: headache, 13%; hypertonia, 5%; amblyopia, 2%; hypesthesia, 2%
Musculoskeletal: myalgia, 2%; hip/leg/forearm/back pain, 2%; neck pain, 2%; twitch, 3%
GU: urinary frequency, 2%.

Other symptoms not felt by the sponsor – correctly, most likely – to be associated with drug effects: epistaxis (1 subject); dysmenorrhea (3 subjects).

It was not possible to combine the data fromseveral studies to provide a more representative representative collection of symptoms and their incidences because of serious differences in data presentation. In one large double-blind, placebo-controlled multicenter study (Gleadle, 1983 [v 1.59, p 206]) symptoms were not pooled together for the total study but rather were listed by week (a representative day was selected per week) and in the order that they appear on the individual questionnaires that subjects were asked to fill out. An accurate, comprehensive list of symptoms could therefore not be drawn up for the whole study over the entire period. Kemp (1982; v 1.60, p 251) provided two different tables of symptoms: one, like Gleadle's, was divided by questionnaire and day, and a second pooled GI symptoms for the whole period of the trial. In another study by Gleadle (1983; v 1.59, p 171), there were six withdrawals but nowhere was it specified whether they dropped out of the placebo or the treated arm of the trial. Finally, the Harriman (1990; v 2.86; p 13) study, like many others presented by the sponsor, was a placebo-controlled crossover trial; but the washout period was not long enough to exclude the possibility of drug effects influencing the symptom complex of subjects placed on placebo following drug exposure.

D. *Vital Signs*

Information is taken from the randomized, double-blind, placebo-controlled study comprising 90 normal volunteers (60 treated, 30 placebo), which is the pivotal study the sponsor provides in support of its claim for the safety and tolerability of the proposed regimen (Protocol 94-09,dated 4/96; Lassiter and Garg, investigators; see v. 2.84, pp. 100-306). The study has also been used to determine the pharmacokinetics and pharmacodynamics of both single- and multiple-dose regimens of PB.

Much of the data has been presented in an inadequate fashion. The entire cohort was categorized by gender (45 males/45 females) and weight (low, medium, and high; 10/group), creating 30 small groups. Though vitals were taken daily, only data with marginal statistical significance on a particular day were reported; within-patient and within-study data are also placed together, without distinction. There is no way to compare these single entries. Total pooling of individual study results was not done.

Nonetheless, despite the poor presentation, the within-study differences (treated from placebo) and within-patient differences (baseline from treatment) that achieved marginal statistical significance are largely compatible with the usual quotidinal fluctuations, and so appear really to have little clinical importance (e.g., 5-6 beats in HR or 5-10 mm Hg [120 to 115 or 110] in SBP that fall within the normal expected ranges).

Subtle changes in heart rate have also been noted consistently under various environmental conditions (see Section 8F below). These difference, too, appear to have little clinical importance.

E. *Laboratory Parameters*

Chemistry, hematology, and EKG data in this section have also been set forth inadequately (in the same manner as described in Section 8D above). Individual observations -- within-patient and within-study differences, single-day variations -- are listed only because they achieve statistical significance; however, no real biological or clinical importance can be attached to them. A lengthy review of chemistry (including hepatic enzymes), hematology, urinalysis (abnormal only in cases of an incidental UTI or menstrual period), and EKG profiles reveals no clinically significant abnormalities. Hormonal data (thyroid function tests, cortisol, prolactin, growth hormone, testosterone, estradiol, progesterone, and IGF-1) remained normal throughout the Lassiter study (v 2.85, pp 307-15).

F. *Adverse Effects Due to Environmental Changes*

Dose	*Adverse Effects*	*Comments*
30 mg x 1	3 hr after dose, experienced muscle cramps in legs and abdomen, following 1-hr cold exposure (10°C + 1 m/s wind).	Resolved in 1 hr after "simple rewarming techniques. Pt withdrawn from study (because of adverse event?).
30q8 x 7 days	4 hr/d in heat (42°C, 20% rh), followed by 2 hr/d moderate exercise (40% max aerobic exercise): lower resting DBP (-4 mm Hg), smaller pupil diameter (-0.5 mm), higher core temp. (-0.1°C), dec handgrip (-3%).	3/7 subjects had only 4 days of PB due to "equipment failure."
30q8 x 3 days	At 35°C, resting core temperature dec (-0.22°C) and HR (-11 beats/min), compared to placebo. At 31°C, both core temp (-0.24°C) and HR (-8 beats/min) were lower at sea level ; and at 10,000 ft, core temp was lower (-0.15°C).	

G. *British Studies Evaluating Pyridostigmine as Pretreatment for Nerve-Agent Poisoning Involving Low-Level Exposure to Organophosphate Poisons (Sarin)*

In 1975 and 1985, the _____ conducted two trials of PB -- parts of which were double-blind and placebo-controlled -- in troops who were exposed to very low levels of sarin. In the earlier trial, 56 men (divided into groups of four, two members of which were pre-treated with a single dose of PB 30 mg and two with placebo) were exposed to sarin at a very low-level concentration time of 5 mg·min/m^3. Twenty-eight controls were given PB only, without

sarin exposure. Mean AChEI produced by the carbamate and sarin were additive (PB alone: 22.7%; PB + sarin: 44.2%; placebo + sarin: 21.6%). AChE enzyme recovery in the sarin-placebo group lagged slightly behind the PB-alone and PB-sarin groups after 24, 48, and 72 hr:

RBC ChE Depression after Exposure (All Volunteers)

% Depression ± Standard Deviation

	Control	Post Exposure	24 hours	48 hours	72 hours
Placebo + GB	0	21.6 (± 6.24)	21.5 (± 5.85)	20.8 (± 4.35)	18.5 (± 5.96)
Pyridostigmine + GB	0	44.2 (± 5.13)	17.5 (± 6.44)	17.4 (± 4.82)	15.2 (± 6.91)
Pyridostigmine Alone (30 mg)	0	22.7 (± 7.36)	3.1 (± 3.13)	1.4 (± 1.26)	-

Whether any significant clinical events occurred is unknown; no adverse effects are reported. Ophthalmologic examination (e.g., pupil diameter) showed no significant differences between subgroups.

The second trial compared five groups: (1) PB 30 mg q8h po x at least 3 doses + pralidoxime mesylate 500 mg im + atropine sulphate 2 mg im+ diazepam 10 mg po; (2) PB 30 mg q8h po x 5 days + 2-PAM 500 mg im + atropine 2 mg im + diazepam 5 mg po; (3) PB 30 mg po q8h x at least 15 doses or placebo, followed by sarin vapor 5 mg·min/m^3; (4) PB 30 mg q8h po or placebo, followed by sarin vapor 5 mg·min/m^3 and an EEG; (5) PB 30 mg q8h po x at least 5 doses, followed by sarin vapor 5 mg·min/m^3 (3/10 subjects received dummy exposure to sarin, and 1/10 received placebo in place of PB), followed immediately by 2-PAM 500 mg im + atropine 2 mg im + diazepam 5 mg po. In contrast to the earlier study, the effects of PB and sarin on AchEI were not additive:

A comparison of the mean blood cholinesterase inhibitions at:

Time post 07.00 h dose	3 h		4 h		8 h		72 h	
Treatment	Mean	SD	Mean	SD	Mean	SD	Mean	SD
GB + placebo pyridostigmine bromide	-	-	18.2	5.6	16.3	3.9	19.7	4.4
Pyridostigmine bromide alone	41.1	7.4	35.6	6.9	21.0	8.1	-	-
GB + pyridostigmine bromide	40.7	4.2	44.0	4.9	27.0	7.8	12.5	5.7

(Results of the EEGs were not available.)

There was no significant effect on mean resting HR (standing) before exercise (120 steps/min on a 12-in high box), after 5 min of exercise, or at 5 min after the end of exercise; and, following exposure to sarin, there were no statistically significant differences in mean heart rate at rest or at the end of exercise between PB-treated and placebo patients. No statistically change in BP was noted in PB-treated subjects; however, 1.5 hours after administration of the triple therapy, following exposure to sarin, a statistically significant rise in diastolic blood pressure was noted (in reaching 99 in one subject with a baseline of 87, then dropping to 89 1.5 hours later; otherwise, 85 was the mean for the group). Respiratory function tests (measured by spirometry and flowmeter) in subjects treated with PB showed no significant change over placebo, and there were no observed changes following sarin exposure. No significant effect on pupil size was recorded in PB-treated subjects.

Thirteen of 56 subjects (23%) on active treatment, compared to two out of 20 (10%) on placebo, complained of mild side effects, most commonly borborygmi (1 active) , tiredness (2 active), and diarrhea (2 on active, 2 on placebo). Other complaints among treated subjects: nausea (1), runny nose (1), dilated pupils (1), muscle twitching (1), hot flashes/pyrexia/headache (1), disturbed sleep (1). One subject (#83/81), whose AChEI was greater than 60%, was reported to have experienced no untoward effects (v 1.58, p 37). There was no evidence for PB accumulation in any of the subjects.

Finally, the study makes no mention of adverse events in subjects who received triple therapy (along with PB) -- namely, PB, 2-PAM, and diazepam. However, the study does comment that the triple therapy had no significant effect on blood cholinesterase inhibition levels.

H. *Analysis of Dropouts*

Few of the studies presented by the sponsor discuss dropouts. Gleadle (1983; v 1.59, p 171) mentions 6 withdrawals; however, he fails to indicate from which arm of the study, placebo or treatment, they derive or the reasons for their withdrawal. Forster (1994; v 2.86, p 126) notes three withdrawals from a trial comprised of eight subjects as a result of scheduling conflicts.

I. *Drug Abuse and Overdose Potential*

While no abuse potential is indicated in the 1996 PDR, overdosage of PB can result in cholinergic crisis and lead to muscle weakness which, when the muscles of respiration are involved, can end in death. There are only two references to overdosages in the NDA, both of which occurred in the setting of the Gulf War theater. Keeler, in a retrospective study already cited, mentions one "medical specialist" who took two tablets to make up for a missed dose and, experiencing a "mild cholinergic crisis," self-administered atropine by autoinjector intramuscularly and then reported to his medical treatment facility. There were no further effects.

The other reference is to an article reporting nine cases (6 male, 3 female) of PB overdosage in Israel, all of which occurred in the setting of suicide attempts (S Almog et al, "Acute Pyridostigmine Overdose: A Report of Nine Cases," Isr J Med Sci 29 [1991]:659-63). The amounts of PB ingested ranged from 390-900 mg (13-30 tablets of 30-mg strength); three of the patients presented with a picture of mixed drug intoxication (propranolol, acetominophen, or atropine [via self-injector]). Symptoms reportedly developed within several minutes and lasted up to 24 hours and included abdominal cramps, diarrhea, emesis, nausea, urinary incontinence, hypersalivation, fasciculations, muscle weakness, and blurred vision. Every patient underwent gastric emptying, followed by the administration of activated charcoal. One patient with mixed

drug intoxication (PB, 630 mg, and propranolol, 4 g) went into cardiac arrest but was succesfully resuscitated and apparently required insertion of a temporary pacemaker. All patients recovered within several hours to 5 days and were discharged with referrals for follow-up psychiatric care (p 661). Almog adds that "[n]o clear correlation was found between the extent of cholinesterase inhibition and the incidence or severity of the cholinergic signs. The clinical recovery was faster than the spontaneous recovery of the enzyme (p 659)."

9 CONCLUSION

PB appears generally to be safe when administered at 30 mg every 8 hours for periods up to 2 weeks, judging by the studies listed above and the 40 years of experience in myasthenics at much higher doses and for much longer duration. However, as a preliminary but uncontrolled study like Gouge's ([1994], v 2.86, p134) points out, the widespread use of PB among soldiers can possibly result in some serious medical problems in select recruits, especially if the men and women are not screened for underlying diseases (e.g., asthma) that may be exacerbated by the medication. Other trials (Graham [1984], v 1.60, p 74; Schiflett [1987], v 2.88, p 15) hint at subtle cognitive difficulties experienced by pilots on PB that could potentially impact on flight performance; more studies are needed to assess this problem fully.

10 RECOMMENDATIONS

PB appears to be safe, as noted in Section 9. However, approval of the NDA awaits the opinion of Dr. Rosloff, who has examined the efficacy data in animals for AChEI as surrogate marker.

/S/

Richard M. Tresley, MD
Medical Reviewer

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