

8.10.5 Summary of Safety Findings from Operation Desert Storm Studies

During Operation Desert Storm, PB was administered to 250,000-300,000 American military personnel facing possible nerve agent exposure. The doctrinal regimen was one 30 mg tablet q8h. Multiple follow-up surveys were conducted during which several hundred military medical personnel, soldiers, and aviators were queried. The results of these surveys, summarized below, indicated that while non-incapacitating, mostly gastrointestinal, symptoms occurred, these effects did not interfere with the physical and mental tasks required of either soldiers or aviators.

8.10.5.1 Keeler, J. R., *et al.* (1991). Pyridostigmine Used as a Nerve Agent Pretreatment Under Wartime Conditions (Ref. 8.15.41).

The objective of this retrospective study was to determine the adverse effects of pretreatment with pyridostigmine bromide for nerve agent exposure during a wartime setting.

Commanders of the US XVIII Airborne Corps instructed 41,650 soldiers to take pyridostigmine tablets at the onset of Operation Desert Storm hostilities in January 1991. The dosage of pyridostigmine was one 30 mg tablet q8h while under the threat of nerve agent attack (for 1-7 days). Therefore, the total dosage ranged from 1 to 21 tablets, with 34,000 soldiers reportedly taking the medication for 6 to 7 days. Overall 234,000 person-days of pyridostigmine administration occurred. Approximately 30 medical officers (physicians and physician assistants) were queried retrospectively about their impressions, the incidence of general physiological response to pyridostigmine, and potential adverse effects observed in the soldiers taking the pyridostigmine pretreatment.

Regardless of the total dosage or pattern of pyridostigmine administration, gastrointestinal changes including increased flatus, loose stools, abdominal cramps, and nausea were reported by about half the troops. The noteworthy other reported effects

were urinary urgency, headaches, rhinorrhea, diaphoresis, and tingling of the extremities. All of these were observed at an incidence of between the range of less than 5 to 30%. These effects were considered tolerable.

Approximately 1% of the soldiers believed they had effects that warranted medical attention, but fewer than 0.1% had symptoms serious enough to discontinue the drug. Although non-incapacitating symptoms often occurred, these effects did not noticeably interfere with the performance of the full range of the physical and mental tasks required by these soldiers in their military mission performance. A higher incidence of minor intestinal and urinary symptoms than expected may be related to the influence of stress factors present in a combat situation.

**8.10.5.2 Office of The Surgeon General, Department of the Army (1992).
Summaries of Three Separate Surveys Concerning the Use of
Pyridostigmine During Operation Desert Shield/Storm (Ref. 8.15.64)**

Three separate surveys were conducted retrospectively with regard to medical care givers, soldiers, and aviators who used pyridostigmine bromide during Operation Desert Shield/Desert Storm.

**Survey 1: A Survey of Medical Caregivers Conducted With Regard to the Use of
Pyridostigmine Bromide During Operation Desert Shield/Desert Storm**

Forty-two surveys were sent retrospectively to selected medical personnel involved in Operation Desert Shield/Storm. Twenty three respondents reported responsibility for over 8366 military medical personnel. Of this number, 5825 took PB during ODS. Among the respondents, patient visits with pyridostigmine usage ranged from 0 to 50. At most, 0.5% of 5,825 subjects had complaints severe enough to require

discontinuation of the drug, hospitalization, or evacuation. All the respondents considered the drug to have been well tolerated.

As was expected, most side effects reported by the respondents were gastrointestinal in nature. Two respondents listed asthma or exacerbation of asthma as side effects of the drug. The side effects appeared to be most severe in individuals of smaller size. Seventeen soldiers inadvertently took 90 mg of the drug at one time without any sequelae.

Survey 2: Results of Survey of Soldiers Deployed in Operation Desert Storm Regarding Pyridostigmine Bromide Use

A brief questionnaire was administered to 149 soldiers, over two-thirds of whom were aviators, at the conclusion of Operation Desert Storm. Questions were asked about chemical defense, work/rest schedules, and the aspect of pharmacological support in heat stress/physical training during Operations Desert Shield and Desert Storm. The average age of the respondents was 30.56 (19-55) years. Approximately 95% of the respondents were males. Of the 133 who took pyridostigmine, 50 experienced side effects principally consisting of nausea, diarrhea, abdominal cramps, muscle cramps, and muscle weakness. In addition, headache was reported by 10 respondents.

Survey 3: Results of the Study of Nerve Agent Pretreatment Pyridostigmine (NAPP) in Aviation

There were over 118 aviators in this study, of whom only 108 took the pyridostigmine tablets. Forty-eight of the 108 aviators were taking medications in addition to pyridostigmine. The majority on other medications were taking Cipro (ciprofloxacin). Twenty-six of the 108 aviators had side effects mostly headaches and diarrhea related to pyridostigmine. Of the 26 who suffered side effects, 9 were taking other medications with eight of the nine taking Cipro and one, vitamins. The effects

observed in the eight aviators or reported by the eight aviators who were on Cipro medication cannot be definitively related to pyridostigmine use alone. The average number of PB tablets taken by the aviators who experienced the side effects was 10.46, which is only slightly less than the average number taken by all the aviators (10.9). The range for the number of tablets taken by the aviators experiencing side effects was similar to that of the range for the total group. Aviators who experienced the side effects did not differ in the number of missions they flew while on pyridostigmine administration from the aviators in general, indicating the side effects did not affect their ability to perform their missions.

The overall side effects attributed to pyridostigmine bromide from all three surveys can be summarized as follows: gastrointestinal effects such as nausea, diarrhea, abdominal cramps, bloating, gas, and stomach problems were the most common symptoms observed, ranging from a high incidence of 7.6% for nausea and 7.2% for diarrhea to 3.4% for bloating and gas. The side effect reports of fatigue were 1.4%; watering of the eyes, 1%; and increased heart rate and runny nose, 0.7%. The most predominant central nervous system effect was headache at 6.2%, followed by vertigo at 1.4%. Other noteworthy side effects reported were muscle cramps, twitching, and urinary urgency frequency, all at 0.7%.

8.10.5.3 Sharabi, Y., *et al.* (1991). Survey of Symptoms Following Intake of Pyridostigmine During the Persian Gulf War (Ref. 8.15.74).

Two separate studies were carried out. In the first study 250 soldiers of one unit, ages 18-22 years, were examined 24 hours prior to the initiation of 30 mg of pyridostigmine therapy q8h. They were asked to fill out a questionnaire containing a list of possible symptoms and complaints, grading them from one to three. In the second study, conducted in another unit, 21 soldiers took the same regimen of pyridostigmine. Nine had complaints that related to medication, whereas 12 denied any

complaints and therefore served as a control group. A similar questionnaire was filled out, and, in addition, blood AChE activity was measured.

In the first study 213 of the 250 soldiers answered the questionnaire. They consumed an average of 2.89 ± 0.67 tablets during the 24-hour period. The most frequent symptoms were nonspecific and included dry mouth, general malaise, fatigue, and weakness. The typical pyridostigmine effects such as nausea, abdominal pain, frequent urination, and rhinorrhea were relatively infrequent. The majority of symptoms were generally mild and appeared around 1.6 hours subsequent to each intake of the drug. The time of appearance and severity were unrelated to whether the soldier took pyridostigmine before or after a meal.

In the second study, which measured the cholinesterase activity, there was no significant difference in the level of AChE inhibition between the soldiers who were complaining of symptoms and those who were asymptomatic. Anxiety and stress, which accompany a war situation, could have contributed to the appearance of the significant symptoms.

8.10.5.4 Almog, S., *et al.* (1991). Acute Pyridostigmine Overdose: A Report of Nine Cases (Ref. 8.15.1).

Nine patients were admitted to emergency rooms within 10-180 minutes following an acute intentional pyridostigmine overdose during the Persian Gulf war. Six of the patients were males, and the overall age range was 17-19 years. The dosage of pyridostigmine ingested ranged from 390 to 900 mg (13-30 tablets, 30 mg each). Three of the patients presented a mixed drug intoxication. All of the patients underwent gastric emptying followed by administration of activated charcoal.

The pyridostigmine ingestion produced mild to moderate cholinergic symptoms such as abdominal cramps, diarrhea, emesis, nausea, hypersalivation, urinary

incontinence, fasciculations, muscle weakness, and blurred vision. No central nervous system manifestations were observed. Symptoms developed within several minutes and lasted up to 24 hours.

Atropine (1-8 mg) had to be administered to three of the patients to counteract muscarinic effects. The values for the decrease in cholinesterase activity ranged between 25 and 79% and returned to normal values within 24-48 hours after the ingestion. In the three patients with a mixed drug ingestion, symptoms were principally related to other drugs such as oxazepam, acetaminophen, atropine, and propranolol. All the patients recovered within several hours to 5 days and were discharged with a referral to further psychiatric care. No obvious correlation was found between the extent of the cholinesterase inhibition and the incidence of severity of the cholinergic symptoms. Clinical recovery was faster than the spontaneous recovery of the enzyme. The pyridostigmine poisoning was self-limiting and well tolerated by the young healthy adults.