

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-414

MEDICAL REVIEW

120-DAY SAFETY UPDATE

Review of Safety Data

NDA	20-414
SPONSOR	Department of the Army
DRUG	Pyridostigmine
INDICATION	Protection against anticholinesterase nerve gas agents
MATERIAL SUBMITTED	120-Day Safety Update
CORRESPONDENCE DATE	9/24/96
DATE RECEIVED	9/24/96
DATE REVIEWED	9/25/96
MEDICAL OFFICER	Richard M. Tresley

Introduction

Pyridostigmine bromide (PB) has been proposed to produce anticholinesterase inhibition in humans as part of a medical program to protect US military personnel against the effects of organophosphorus nerve agent poisoning. The US Department of the Army, under the guidance of _____ conducted a single-site randomized, multiple-dose, double-blind, placebo-controlled study involving 90 healthy males and females: 60 volunteers received PB 30 mg q 8 hr x 21 consecutive days, and 30 placebo. Volunteers were further subdivided by weight category (low, medium, and high) to determine if possible side effects might be attributable to subject size (namely, whether larger amounts of drug on a mg/kg basis could account for adverse events). The acute study was completed in December 1995. At the conclusion of the trial, each volunteer was assigned four outpatient follow-up visits (including a safety examination, vitals, and laboratory battery [SMA-19, CBC, routine urinalysis]) at three-month intervals; five of the 90 subjects did not return at all, 69 completed all four follow-up visits.

The 120-day safety update examines (1) the results of the four follow-up visits, (2) animal mutagenicity testing, and (3) a recently published study, conducted in chickens, by Abou-Donia MB, Wilmarth KR, Jensen KF, et al, "Neurotoxicity resulting from coexposure to PB, Deet, and Permethrin: implications of Gulf War chemical exposures" (Journal of Toxicology and Environmental Health 48 [1996]:35-56). To date, briefly, results of the reverse mutation assay, the chromosome aberration test using CHO, and the micronucleus cytogenetic assay in mice were negative. The mouse lymphoma assay was negative in the absence of hepatic microsomal enzymes, but positive in the presence of drug metabolizing enzymes. A CHO/HGPRT assay is currently ongoing to investigate the potential of PB to cause gene mutations; results are expected in October 1996. Examination of these data and the Abou-Donia article falls under the general purview of Dr. Barry Rosloff (Pharmacology).

Review of Clinical Data

Four subjects from the Lassiter study are singled out for special attention:

<i>Subject No</i>	<i>Confinement Dates</i>	<i>Complaint</i>	<i>PI's Assessment</i>	<i>Impression</i>
Subject #84	14 Mar 1995-7 Apr 1995: asymptomatic.	Six weeks following conclusion of the study (12 June 1995), subject reported a pruritic rash (described as "bullous lesions" around her waist, in the webs of her hands, and in the left antecubital fossa) and was later referred to a dermatologist who, after a biopsy, diagnosed a fixed drug reaction and treated her with topical steroids with rapid resolution over a week. She was described as asymptomatic in follow-up visits on 10 July 1995 and 3 October 1995.	"Highly unlikely related to PB, because of the temporal sequence. "It is impossible to rule this unequivocally unrelated, however, so the adverse experience was rated as 'possibly related'" (page 4).	Probably not related. Note: most PB allergic reactions are caused by the bromide molecule. Bromide rashes are not generally bullous in character (personal communication from Dr. Roger Goetsch, FDA CDER Dermatology). The sponsor does not state whether the subject had taken any other drugs during the six-week interval in question.
Subject #28	29 Nov 1994-24 Dec 1994: asymptomatic.	Subject notified the sponsor on 19 April 1995 that she was 2-3 months pregnant and had been admitted to the hospital for IV hydration after severe nausea and vomiting. She failed follow-up until 7 June 1996, at which time she had returned from Mexico where she had given birth to a healthy full-term male who was reported by his pediatrician as "developing normally and is healthy" (page 4).	Not PB related.	Not PB related (emesis gravidarum?).

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Subject #72	Dates of confinement and subject condition not provided.	Seen on 11 Sep 1995 with a 21-lb weight loss and anemia (Hgb 10; HCT 31.1). He noted a recent blood donation and ascribed his malnutrition to financial straits. He failed to report to the hospital to which he had been referred by the study center. Seen again at the study center on 20 Dec 1995 with Hgb 10.4/HCT 32.3, and on 25 Apr 1996 with Hgb 11.9/HCT 36.8. Denied symptoms on both occasions; reported blood donations and participation in drug studies to improve his finances.	Not PB related.	Not PB related.
Subject # 88	21 Mar 1995-15 Apr 1995: asymptomatic.	On her 17 Jan 1996 visit, she stated that she was 6+ months pregnant. On her last clinic visit, 29 Mar 1996, she was no longer pregnant; there is no information about her child. Lost to follow-up.	?	?

A review of the vitals and laboratory data on the other subjects has not turned up any abnormalities that could be considered PB related. There were no differences between gender or weight classes.

Conclusion

The one-year follow-up of subjects from the Lassiter study has revealed no significant safety issues.

/s/

Richard M. Tresley, MD
Medical Reviewer

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2. Proposed Phase IV Efficacy Studies

As specified in 21 CFR 314.610(b)(1) the sponsor submits very brief outlines of clinical studies to be conducted in the event of a nerve gas exposure in subject that took PB pretreatment. Final protocols will be submitted in the future. The sponsor outlines four proposals. I am uncertain whether the proposals will all be part of a single protocol or different studies. For now I will assume they are different studies.

The first study proposed by the sponsor is a retrospective comparative survey of adverse effects of PB experienced by individuals from selected units at post-deployment. The primary objective will be to determine if there is a difference in the self-reported adverse effects of individuals who took PB against those who did not. The sponsor does not state whether these selected units will or will not have been exposed to nerve agents. The data will be collected once soldiers have returned to their home station.

In the second proposed study the sponsor intends to perform a retrospective survey of all health care providers involved with the treatment of nerve gas casualties. Health care providers will be questioned while they are still in the theatre of operations. They will be requested to provide their perception of "*clinical benefit derived from use of PB pre-exposure vs. service members who took post-exposure antidote.*" I am not certain what the sponsor means by this statement. I assume they mean a comparison of nerve-gas-exposed subjects that took PB to nerve-gas-exposed subjects that did not take PB. Hopefully all nerve-gas-exposed subjects take the antidote as directed. PB is not thought to be beneficial unless post exposure antidotes are taken and in fact may be harmful without antidote treatment. Clarification will be needed.

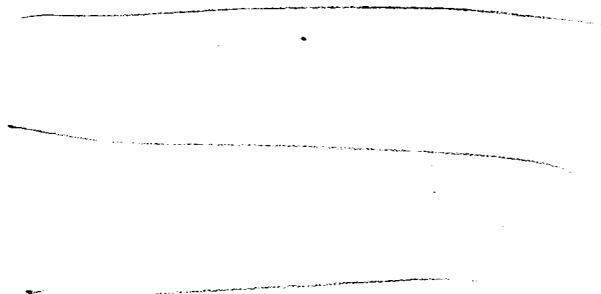
In a third proposed study the sponsor intends to compare the survival data and use multivariate statistical modeling techniques to elucidate clinical benefit from PB pretreatment after nerve agent exposure. Initially survival in the area of exposure based on PB use and nerve agent of exposure will be studied. The sponsor states that as more information on the exposure is obtained, an overlay of chemical agent exposure can be used to create a model of PB efficacy assuming that reliable information is available regarding the following factors; (1) use of PB by exposed units, (2) duration of PB use prior to exposure, (3) specific nerve agent deployed, (4) data on the dispersion and concentration of the nerve agent, (5) units exposed, (6) level of personal and collective protection in exposed units, (7) percent strength of units prior to nerve agent attack, (8) casualties in exposure area, (9) other weapons used by enemy and friendly forces, (10) other factor that would affect survivability (ex available medical resources).

Finally, in the fourth proposed study the sponsor intends to retrospectively compare medical records of soldiers who took PB and those who did not take PB. The primary objective will be to determine is there is a difference in the incidence of adverse events reported in individuals who took PB and were required to seek medical attention compared to individuals who did not take PB. Again the sponsor does not state whether this review would occur in individuals exposed to nerve agents or not.

The above four proposed studies are only briefly summarized by the sponsor. Significant details will be required to determine whether the designs are sound scientifically. On the surface it appears the first and fourth studies will be useless in assessing the efficacy of PB in the setting of nerve agent exposure. The second and third studies have the potential of providing the information we require however more details will be needed before I can provide relevant comments. Since these efficacy studies will essentially be epidemiological in nature I recommend we obtain an Epidemiology consult to evaluate the designs once the final protocols are received by the Agency.

3. Licensure Transition Logistics Plan

The sponsor officially requests permission to distribute the current stockpiled investigational drug product after approval. They argue that the current world situation does not permit them the time to remove, repro cure, and restock pyridostigmine tablets already prepositioned near hostile environments in time for it to be available for deployed troops. The sponsor proposes to provide all recipients of PB an interim label (see following figure) that clearly states that PB was approved based on efficacy in animals and the indication it was approved for. This interim label will be used in conjunction with the previous label already included in the investigational product. This issue has already been discussed internally and with the sponsor and has tentatively been approved. The interim label has been previously submitted, reviewed and also tentatively approved.



Assuming the sponsor receives final approval to temporarily distribute investigational drug product the sponsor proposes the following "Licensure Transition Logistics Plan" to replace all "investigational PB product" with newly products PB product over a 5 year period. The Interim Label will be printed on a 4¼ X 1⁵/₈ pastel green laminated card that will fit into the protective sleeve of the PB blister pack. The production, distribution, review and execution of the distribution of the interim label we be coordinated by the Joint Readiness Clinical Advisory Board (JRCAB). Each Service is responsible for submitting a detailed distribution plan for PB. Once (if) PB is approved the Department of Defense will release a "Medical Materiel Quality Control Message" through logistics channels directing each Service to distribute the Interim Label to all sites possessing investigational PB tablets and to dispense/issue these with each sleeve of PB tablet dispensed.

The sponsor states they are aware they FDA expects all investigational PB to be replaced as soon as possible. However they argue that complete and immediate replacement is not feasible given the present threat level. Additionally, the sponsor states that complete replacement of investigational PB within a brief period of time would fail to provide the manufacturer of PB "with consistent demand for the product and would not support a warm base of production and capabilities to meet contingency surge requirements." They propose to replace the present stockpile over a 5 year period with approximately 20% of the inventory replaced each year.

The Department of Defense proposes to use investigational PB inventory during this 5-year transition period. Over the next 2 years the DOD plans to open existing bags of product, insert blister packs into new cardboard sleeves containing the "NDA-approved" wording, replace the current patient insert, replace the desiccant and reseal each bag. Bags will be replaced if necessary for either esthetics reasons or if resealing the old bags is impossible. Thus all investigational PB will be relabeled within a maximum of 2 years and replaced in a maximum of 5 years. This relabeling will be accomplished when warranted by the Shelf Life Extension Program (SLEP) testing and extension of expiration dating, or within 2 years, whichever ever occurs first. The oldest stocks of investigational PB would be immediately replaced with properly labeled and licensed product once available from the manufacturer.

In addition the above replacement plan the sponsor offers the following alternative plans for our consideration. The first alternative plan is the preferred by the sponsor.

1. Continue using the interim patient insert for the investigational PB during the 5-year transition period. Only products meeting SLEP testing and extension during this transition period will be retained for this purpose.
2. Purchase 100% replacement of existing investigational PB inventory within 12 months, or when sufficient appropriately labeled licensed product is available.

In my opinion the Licensure Transition Logistics Plan appears to be a reasonable compromise between the needs of the Department of Defense, the manufacturer and the Agency. Care should be used during the process to ensure that the oldest stock is replaced first.

4. Financial Statement

The sponsor submits FDA form 3454, "Certification of Financial Interests and Arrangement of Clinical Investigators" under Item 19. The sponsor states that the "clinical studies in this application were not covered clinical studies as described in 21 CFR 54.2.

21CFR 54.2 (e) defines covered clinical studies as any study of a drug (or device) in "humans" submitted in a marketing application that the sponsor or FDA relies on to establish that the product is effective or any study in which a single investigator makes a significant contribution to the demonstration of safety. I am uncertain whether the sponsor's statement is acceptable to the Agency. Although I concur no single investigator

contributed the majority (or significant proportion) of the total safety data I reviewed, individually most studies were dominated by a single investigator at a single site. On the other hand all of the safety studies were completed prior to this requirement. More concerning however is the lack of a financial disclosure statement for the efficacy studies completed. Although the efficacy studies were done in animals, and therefore no financial statement is required to satisfy 21CFR54.2(e), they are essential to the approval of this product. The Animal Rule is silent on whether financial disclosure statements are required but it would seem reasonable that they would be required in this setting.

5. Additional Comments and Conclusions

- The sponsor states in the cover letter that they would be amendable to postmarketing restrictions to assure safe use of PB assuming it was approved. Restrictions they envision could include restricted distribution to certain health facilities or health care practitioners with special training or experience, distribution conditioned on the performance of specific medical procedures, including medical follow up, and distribution conditioned on specified record keeping.

As I discussed in my original safety review I do not believe this product is safe for use in the general population since its safe use and effectiveness can only be realized when it is used in conjunction with protective clothing, rapid use of antidotes, immediate evacuation from the poisoned area, and prompt medical care. The use of this product requires appropriate training on how to use each of these therapies, how to recognize the symptoms of organophosphate nerve agent poisoning, an adequate evacuation plan, and the propositioning of health care resources. This tasking is already part of the military doctrine for PB use. In my opinion the distribution of this product should be limited to the military and hazardous material workers and potentially trained first responders. The training program the military now requires should be maintained. Distribution should be monitored for continued safety and efficacy assessment whenever possible. Potential non-military users of this product should be certified in its use in conjunction with all the other elements needed for the safe and effective use of this product prior to distribution.

- My review of the Professional Package Insert, Patient Package Insert, Interim Label and container labels has already been completed in a separate document and has been forwarded to the team leader and project manager.
- The sponsor's plan to distribute the current stockpiled investigational drug product with an interim label that clearly states that PB was approved based on efficacy in animals and the indication it was approved for appears acceptable to me.
- The sponsor's plan (summarized in section 3) to replace all investigational product with newly made approved product over a five year period appears acceptable to me.
- The sponsor proposes to use a 10-year date of expiration on the label. I defer to the Chemistry reviewer as to whether the supporting stability data is sufficient to support this request. Presently the investigational drug product is labeled with a date of manufacturing and expiration dates are being determined by repeated stability testing as part of a Shelf Life Extension Program.
- The sponsor briefly outline four Phase IV studies under Item 20 of the submission (summarized in section 2). Two of the studies do not appear to evaluate the efficacy

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/s/

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1/9/03 03:23:00 PM
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Concur. Since the efficacy data from animal studies was collected prior to the publication of the "Animal Rule," the investigators could not have predicted the pivotal nature of results...Financial Disclosure therefore seems moot for these studies.