Pyridostigmine Bromide Intake during the Persian Gulf War Is Not Associated with Postwar Handgrip Strength

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Many Persian Gulf War veterans took pyridostigmine bromide (PB) during the Persian Gulf War. Previous research suggests that PB intake and insecticide exposure may reduce muscular strength. During 1994 and 1995, we examined the relationships between self-reported PB intake, self-reported exposures, and handgrip strength among 527 Gulf War veterans (GWVs) and 969 nondeployed veterans of that era (NDVs). We found that 25.4% and 6.7% of the GWVs and NDVs, respectively, reported generalized muscle weakness (for 1 month or longer) since the Gulf War (July 1990). Many veterans also reported exposure to insecticide during the war. Dominant handgrip strength was measured three times with a hand-held dynamometer in subjects standing with the elbow bent at a right angle. Multiple linear regression revealed that handgrip strength was negatively associated with age ($p = 0.001$) and female gender ($p < 0.001$). Handgrip strength was also found to be positively associated with height ($p < 0.001$), but it was not associated with PB intake ($p = 0.558$). Exposure to insecticides had no major effect on handgrip strength. These data suggest no association between PB intake and postwar handgrip strength.

Introduction

Veterans of the Persian Gulf War have returned home reporting a wide variety of symptoms. Although there are many theories regarding the cause of these symptoms, an etiologic agent or exposure has yet to be determined. As part of a larger study of the prevalence of self-reported symptoms and exposures in U.S. Navy Seabees (construction workers), this study was initiated to examine the possible associations between wartime pyridostigmine bromide intake and postwar handgrip strength in Seabees who participated in the Persian Gulf War.

Pyridostigmine bromide was issued to U.S. and British soldiers to protect against possible nerve gas attacks. Soldiers were instructed to take one 30-mg tablet every 8 hours just before the commencement of the air war. As a pretreatment used to minimize the effects of anticholinesterase nerve agent exposure, pyridostigmine bromide is known to enhance the standard therapeutic regimen of atropine and pralidoxime by inhibiting cholinesterase at the neuromuscular junction. Evidence that some individuals may be more genetically susceptible to pyridostigmine bromide than others and the potential for pyridostigmine bromide to have synergistic effects with other chemicals has led some researchers and veterans to hypothesize that it may be a cause of postwar morbidity. Researchers have also observed that stress may make the blood-brain barrier permeable to pyridostigmine bromide in animal models, contributing to the alleged toxicity of this agent. Furthermore, they suggest that pyridostigmine bromide might increase central nervous system-based symptoms (headaches, drowsiness, inability to concentrate). Others suggest that pyridostigmine bromide may induce symptoms by affecting the peripheral nervous system.

Even though recent human and animal studies have suggested that pyridostigmine bromide could be responsible for detrimental neurological effects, such as fatigue and muscle weakness, little is known about its role in long-term morbidity. Therefore, we used an objectively collected handgrip strength measurement to investigate the potential chronic effects of pyridostigmine ingestion by itself and in conjunction with other exposures.
Methods

Study Population

The study population consisted of active duty Seabees who in 1994 and 1995 had remained on active duty since the time of the Persian Gulf War. Seabees were studied because of their diverse deployment experiences and because they were among the first veterans to report symptoms after returning from the Persian Gulf. Both Gulf War veterans (GWVs) and nondeployed veterans (NDVs) of the same era were selected from 14 Seabee commands located in Port Hueneme, California, and Gulfport, Mississippi.

Questionnaire

Subjects were asked to complete an eight-page questionnaire, undergo handgrip strength testing, lung function testing, and height and weight measurements, and provide blood and urine specimens. The survey collected demographic, health risk, and deployment exposure data. Pyridostigmine bromide ingestion and insecticide spray exposure data were assessed from July 1990, as was exposure to the burning of insecticide coils used to repel and kill insects. Only those individuals answering "definitely" on the questionnaire were considered to have been exposed.

Handgrip Strength Test

Handgrip strength was measured using a hand-held dynamometer (Jamar, Lafayette, Indiana). Measurements were taken with the subject standing, using the dominant hand, and with the subject's elbow bent at a right angle. The average of three successive efforts was used in the analyses. Height and weight measurements were taken using a medical scale.

Statistics

Demographic and exposure data were compared univariately using $\chi^2$ tests. Exposure data and handgrip strength tests were compared using Wilcoxon rank sum tests. Multivariate linear regression was performed with the SAS statistical package using handgrip strength as the dependent variable and forcing dichotomous variables into the model to obtain parameter estimates for each covariate. Parameter estimates were also obtained for the interactions between pyridostigmine bromide ingestion and insecticide spray exposure and between pyridostigmine bromide ingestion and burning insecticide exposure.

TABLE I

SELECTED CHARACTERISTICS OF REGULAR ACTIVE DUTY U.S. NAVY SEABEES DEPLOYED TO THE PERSIAN GULF, BY SELF-REPORTED PYRIDOSTIGMINE BROMIDE (PB) INTAKE (N = 527)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any PB Intake (n = 171)</th>
<th>No PB Intake (n = 356)</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>28.4</td>
<td>29.5</td>
<td>0.961</td>
</tr>
<tr>
<td>Handgrip (kg)</td>
<td>53.8</td>
<td>53.6</td>
<td>0.545</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.3</td>
<td>174.8</td>
<td>0.092</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.4</td>
<td>84.5</td>
<td>0.073</td>
</tr>
<tr>
<td>Symptoms reported</td>
<td>3.9</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p values were computed by the Wilcoxon rank sum test.

Results

A total of 1,497 study subjects were enrolled, 527 GWVs (628 men and 927 NDVs (438 women). Adjusting for an 80% availability at the two Seabee enrollment sites, it was estimated that 53% of the eligible Seabees participated. Demographic characteristics were similar among GWVs and NDVs and among participants and nonparticipants in the study (data not shown). Additionally, the Seabee population was symptomatic, with 25.4% of the GWVs and 6.7% of the NDVs reporting unusual fatigue or generalized muscle weakness for at least 1 month or more since July 1990 (data not shown).

Among GWVs, 171 subjects self-reported taking pyridostigmine bromide and 356 subjects reported no use of pyridostigmine bromide. GWVs who took pyridostigmine bromide were not significantly different from those who did not take pyridostigmine bromide with respect to age, average handgrip strength, height, and weight (Table I). However, veterans who took pyridostigmine bromide self-reported a greater number of symptoms than those who did not. We attempted to capture self-reported data regarding the quantity of pyridostigmine bromide ingested. However, more than 75% of the subjects who reported pyridostigmine bromide ingestion failed to respond or could not remember how many tablets they had taken. Among the 42 subjects who reported the quantity of pyridostigmine bromide tablets ingested, the mean handgrip strength was not associated with ingested quantity. As a result, pyridostigmine bromide ingestion was used as a categorical variable in subsequent analyses.

The subjects were next stratified into three groups: GWVs who reported pyridostigmine bromide intake (GWVs/PB+), GWVs who did not report pyridostigmine bromide intake (GWVs/PB−), and NDVs who did not report pyridostigmine bromide intake (NDVs/PB−). No NDVs reported pyridostigmine bromide intake. There was little difference in handgrip strength among these three groups: NDVs/PB− had a mean grip strength of 54.0 kg, GWVs/PB+ had a mean grip strength of 53.8 kg, and GWVs/PB− had a mean grip strength of 53.5 kg.

Among GWVs, 25 reported being exposed to burning insecticide and 170 reported exposure to insecticide spray. When self-reported exposure to insecticide spray and exposure to pyridostigmine bromide were jointly considered, we did not see a significant interactive effect on handgrip strength (Fig. 1). Similarly, we examined the combination of exposure to burning insecticide and pyridostigmine bromide and also found no significant interactive effect on handgrip strength (Fig. 2).

To further investigate the possibility of pyridostigmine bromide or a combination of exposures having a negative effect on handgrip strength, we constructed a multivariate linear regression model using handgrip strength as the dependent variable. Age and sex were found to have a negative effect on handgrip strength, whereas height was positively associated. Pyridostigmine bromide, insecticide spray, and burning insecticide were not important independent or interaction term predictors of handgrip strength (Table II).

Discussion

Pyridostigmine bromide prophylaxis is an important component of the U.S. defense against chemical warfare. However,
recent news articles and scientific reports attributing symptoms and illnesses to pyridostigmine bromide ingestion have stirred debate about its safety.12,15,19-22 Based on animal studies, it has been suggested that pyridostigmine bromide could have potentially deleterious effects in humans if taken in high dosages, especially if taken in combination with other chemicals.21 More recent studies have focused on the health effects of agents on animal health, such as DEET, in combination with high doses of pyridostigmine bromide.12,16 These studies suggest the potential for synergistic effects between ingested pyridostigmine bromide pills and organophosphates, pesticides, and insect repellents, such as DEET. It has even been theorized that pyridostigmine bromide may alter the function of the enzyme butyrylcholinesterase, permitting other toxins to cross the blood-brain barrier.17,22 Some researchers have hypothesized that GWVs may suffer from delayed chronic neurotoxic syndromes, specifically those attributable to these wartime exposures.21

In contrast, a wide body of literature demonstrates that pyridostigmine bromide has long been used safely as an effective agent in the treatment of myasthenia gravis. Myasthenia gravis patients have few side effects despite taking much higher doses of the drug than did GWVs.1,11 Certainly, the Food and Drug Administration did not anticipate chronic symptoms from pyridostigmine bromide ingestion when it endorsed the use of pyridostigmine bromide by U.S. troops in the Persian Gulf.6,15 Although some scientists regard pyridostigmine bromide as potentially dangerous by itself or in combination with other chemicals or factors, our findings are consistent with the pyridostigmine bromide safety literature.

Our analyses provide evidence that pyridostigmine ingestion does not seem to affect handgrip strength by itself or in conjunction with other exposures; however, this study does have limitations. As reported in the first Seabee study,2 the data are subject to recall bias because of the self-report nature of the survey. Furthermore, in some of the comparisons, although we tried to assess the combination of pyridostigmine bromide and other factors on handgrip strength, we were unable to determine if these exposures were concurrent. Because of the small sample size of individuals who reported being exposed to both agents, our statistical power to detect small differences was limited. Because this survey was conducted only among active duty personnel, our findings may not represent the health of veterans who have left active service.

Similarly, our study had several strengths. The use of an objective outcome, handgrip strength, has been shown to be an easy and reliable instrument for measuring muscle strength.25,26 Seabees were a good population to study because they had experienced many unique exposures during their deployments both inside and outside of the Persian Gulf region. Because they were on active duty, these Seabees were less likely
to have other confounding exposures that might be related to the civilian occupations of reserve populations. These Seabees had not previously participated in any research surveys. This is in contrast to some reserve Seabees units, which have been surveyed multiple times and whose ailments have been described in both the national media and the scientific literature.8,17

In summary, we have studied wartime exposures, including ingestion of pyridostigmine bromide, insecticide spray exposure, and burning insecticide exposure, as reported among GWVs and NDVs and compared them with handgrip strength 4 years after the war. A moderate proportion of subjects in both groups reported weakness and increased fatigue for at least 1 month or more since the war (July 1990). We found no evidence that pyridostigmine bromide ingestion, alone or in combination with acetylcholinesterase exposures, was associated with evidence of muscle weakness several years later. These data do not support the hypothesis that pyridostigmine bromide ingestion, by itself or in conjunction with other exposures, is a cause of chronic weakness.

Acknowledgment

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References