Promethazine Affects Autonomic Cardiovascular Mechanisms Minimally

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ABSTRACT
Promethazine hydrochloride, Phenergan, is a phenothiazine derivative with antihistaminic (H₁), sedative, antiemetic, anticholinergic, and antimotion sickness properties. These properties have made promethazine a candidate for use in environments such as microgravity, which provoke emesis and motion sickness. Recently, we evaluated carotid baroreceptor-cardiac reflex responses during two Space Shuttle missions 18 to 20 hr after the 50 mg intramuscular administration of promethazine. Because the effects of promethazine on autonomic cardiovascular mechanisms in general and baroreflex function in particular were not known, we were unable to exclude a possible influence of promethazine on our results. Our purpose was to determine the ground-based effects of promethazine on autonomic cardiovascular control. Because of promethazine's antihistaminic and anticholinergic properties, we expected that a 50-mg intramuscular injection of promethazine would affect sympathetically and vagally mediated cardiovascular mechanisms. Eight healthy young subjects, five men and three women, were studied at rest in recumbency. All reported drowsiness as a result of the promethazine injection; most also reported nervous excitation, dry mouth, and fatigue. Three subjects had significant reactions: two reported excessive anxiety and one reported dizziness. Measurements were performed immediately prior to injection and 3.1 ± 0.1 and 19.5 ± 0.4 hr postinjection. We found no significant effect of promethazine on resting mean R-R interval, arterial pressure, R-R interval power spectra, carotid baroreflex function, and venous plasma catecholamine levels.

Promethazine hydrochloride, Phenergan, is a phenothiazine derivative with antihistaminic (H₁), sedative, antiemetic, anticholinergic, and antimotion sickness properties. As an antihistamine, promethazine interferes with the binding of histamine to the H₁ receptor by competitive antagonism, thereby alleviating histaminic actions such as bronchoconstriction (O'Neill et al., 1985) and intestinal contractions (Rychlik et al., 1991) and enhancing immunosuppressive activity (Rychlik et al., 1988). Promethazine has been used widely during labor (Zimmer et al., 1990), for pediatric sedation (O'Brien et al., 1991), and for premedication (Dodson and Eastley, 1978). One of promethazine's additional premedicant advantages is its antiemetic property, which has been linked to moderate anticholinergic activity (Peroutka and Snyder, 1982). Anticholinergic activity has long been a key feature of antimotion sickness agents (Wood and Graybiel, 1968).

The antiemetic and antimotion sickness properties of promethazine have made it a candidate for use in environments, such as microgravity (Davis et al., 1988), which provoke these symptoms. The incidence of space motion sickness during the first 44 flights of the Space Shuttle was 73% (Davis et al., 1993). Although numerous medication, medication combinations, and routes of administration have been tested (Graybiel and Lackner, 1987; Wood et al., 1987), intramuscular injection of promethazine is the current treatment of choice for space motion sickness (Wood et al., 1992; Davis et al., 1993) and has been administered on the Space Shuttle since 1989 (Bagian, 1991). Reasons for this choice include promethazine's ability to provide relief after the onset of nausea and vomiting (Graybiel and Lackner, 1987), its long duration of action (Wood et al., 1992), and its apparent lack of significant adverse reactions under the operational conditions of spaceflight (Lackner and Graybiel, 1994).

Although a number of ground-based investigations has addressed the effects of promethazine on performance (Clarke and Nicholson, 1978; Kotzan et al., 1986; Hyman et al., 1988), few have addressed the effects of promethazine on autonomic cardiovascular mechanisms. Those that do exist use animal models (Goldberg et al., 1969; Aronson and Hanno, 1979; Covert et al., 1988) or use promethazine in combination with other medications (Sunahara et al., 1987).

ABBREVIATIONS: Baroreflex, carotid baroreceptor-cardiac reflex response; STS, Space Transportation System.
To our knowledge, no study has investigated the cardiovascular effects of promethazine alone in humans on the ground or during spaceflight; nonetheless, cardiovascular experiments are performed on the Space Shuttle relatively soon after the administration of intramuscular promethazine.

Recently, we evaluated carotid baroreceptor-cardiac reflex responses (baroreflexes) during two Space Shuttle missions, STS-40 and STS-55 (Space Transportation System), 18 to 20 hr after the 50 mg intramuscular administration of promethazine (Fritsch and Eckberg, 1992; Eckberg et al., 1994). Because the effects of promethazine on autonomic cardiovascular mechanisms in general and baroreflex function in particular were not known, we were unable to exclude a possible influence of promethazine on our results. Our purpose was to determine the ground-based effects of promethazine on autonomic cardiovascular control. Because of promethazine’s antihistaminic and anticholinergic properties, we expected that a 50-mg intramuscular injection of promethazine would alter sympathetically and vagally mediated autonomic cardiovascular mechanisms. All measurements were performed at rest in recumbency because this most closely approximated the circumstances during our microgravity measurements.

Methods

Subjects. Eight healthy subjects, five men and three women, whose average age and weight (±S.E.) were 25 ± 1 yr (range: 20-32) and 67 ± 4 kg (range: 52-86), were studied at rest in recumbency. Subjects abstained from alcohol, caffeine, and exercise at least 24 hr before and during their participation in this investigation. All three women used oral contraceptives; no other medications were used by any subject. None of the subjects were smokers. This investigation was approved by the human investigation committees of the Hunter Holmes McGuire Department of Veterans Affairs Medical Center and the Medical College of Virginia and was in accordance with the Declaration of Helsinki. All volunteers gave their informed written consent to participate.

Experimental protocol. An interrupted time series experimental design was used. Measurements were made immediately before and during their participation in this investigation. All three women used oral contraceptives; no other medications were used by any subject. None of the subjects were smokers. This investigation was approved by the human investigation committees of the Hunter Holmes McGuire Department of Veterans Affairs Medical Center and the Medical College of Virginia and was in accordance with the Declaration of Helsinki. All volunteers gave their informed written consent to participate.

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Adverse reactions to promethazine. Several side-effects were reported by the subjects. All reported drowsiness; most also reported nervous excitement, dry mouth, and fatigue. In all but one case, these symptoms disappeared by 19.5 hr postinjection. Three subjects had significant reactions. Two reported excessive anxiety 3.1 hr postinjection. One of these subjects panicked upon placement of the face mask and could not perform 10 min of controlled respiration. A third subject complained of dizziness during both postinjection experimental conditions.

Subject elimination. One subject did not permit postinjection blood samples to be drawn. This same subject had great difficulty with the fit of the mask during all controlled respiration periods. Subsequent analysis of these data revealed results so extreme that their validity were questioned. These aberrant data were tested and met the criteria of an outlier as defined by the maximum normal residual (Snedecor and Cochran, 1989). As a result, we excluded all of this subject’s mean R-R interval, arterial pressure, R-R interval periodicity, and carotid baroreflex response data.

Mean R-R interval and arterial pressure. Mean R-R interval and arterial pressure (sphygmomanometer) levels for the three experimental conditions are given in Table 1. No significant differences were found among the three experimental conditions. The Wilcoxon signed rank test was used in the few instances that assumptions for parametric tests were violated. Differences were considered significant when P < 0.05; two-tailed tests were used. Sample size estimates for each variable were performed using the minimum difference between group means and standard deviations from the baseline, 3-hr and 18-hr treatment periods from the first seven subjects. For the estimates, alpha was set to 0.05 and power was set to 0.80.

Results

TABLE 1

<table>
<thead>
<tr>
<th>Autonomic cardiovascular effects of promethazine</th>
<th>Preinjection</th>
<th>Postinjection</th>
</tr>
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<tbody>
<tr>
<td>Arterial pressure (mmHg)</td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>114 ± 5</td>
<td>109 ± 2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>65 ± 2</td>
<td>63 ± 1</td>
</tr>
<tr>
<td>Carotid distending pressure (mmHg)</td>
<td>251 ± 38</td>
<td>226 ± 28</td>
</tr>
<tr>
<td>Spectral power (10^3 sec^2/mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory frequencies (0.2–0.3 Hz)</td>
<td>4.5 ± 0.9</td>
<td>5.6 ± 1.6</td>
</tr>
<tr>
<td>Low frequencies (0.05–0.15 Hz)</td>
<td>2.9 ± 0.6</td>
<td>3.6 ± 1.6</td>
</tr>
<tr>
<td>Very low frequencies (&lt;0.05 Hz)</td>
<td>4.3 ± 0.8</td>
<td>2.7 ± 0.8</td>
</tr>
<tr>
<td>Carotid baroreflex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (msec)</td>
<td>251 ± 36</td>
<td>226 ± 28</td>
</tr>
<tr>
<td>Maximum slope (msec/mmHg)</td>
<td>5.2 ± 0.9</td>
<td>4.9 ± 0.8</td>
</tr>
<tr>
<td>Catecholamines (µg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>212 ± 26</td>
<td>226 ± 28</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>29 ± 10</td>
<td>19 ± 6</td>
</tr>
</tbody>
</table>

Fig. 1. Original record showing (A) neck pressure profile, electrocardiogram and R-R interval responses of one subject to one stimulus sequence and (B) the averaged response of the subject to seven stimulus sequences. The range, maximum slope, and operational point, , are displayed.
R-R interval periodicities. R-R interval spectral power from the respiratory (0.20-0.30 Hz), low (0.05 to 0.15 Hz) and very low (<0.05 Hz) frequency bands are given in Table 1 for the preinjection and postinjection conditions. Averaged power spectra are shown in Figure 2. There were no significant differences among experimental conditions for any of the frequency bands. β-Statistical error was not suspected because sample size estimates were more than 100 for each frequency band.

Carotid baroreflex function. Baroreflex stimulus-response relations, shown in Figure 3, represent the average of seven subjects. Baroreflex range, maximum slope, and operational point for preinjection and postinjection conditions are given in Table 1. There were no significant differences among experimental conditions for range, maximum slope or operational point. β-Statistical error was not suspected because sample size estimates were more than 100 for range, maximum slope, and operational point. In addition, significance was not altered by including the results of the eliminated subject.

Plasma catecholamines. Plasma norepinephrine and epinephrine levels are given in Table 1. There were no significant differences among experimental conditions for plasma norepinephrine or plasma epinephrine. β-Statistical error was not suspected because sample size estimates were greater than 100 for plasma norepinephrine and 29 for plasma epinephrine.

Discussion

We studied the effects of promethazine on resting mean R-R interval, arterial pressure, R-R interval periodicities, carotid baroreflex function, and plasma catecholamine levels in humans. The major and surprising finding is that promethazine did not change any of the autonomic cardiovascular functions we measured. However, a number of adverse reactions were reported. Because of the antihistaminic and anticholinergic properties of promethazine, we had expected a significant influence during the peak plasma concentration 3 hr postinjection (Schwinghammer et al., 1984) with minimal influence 18 to 20 hr post-injection. The halflife of a 50 mg intramuscular injection is 9.76 hr (Schwinghammer et al., 1984).

Reactions to promethazine. All subjects reported drowsiness 3.1 hr postinjection followed by restful sleep that night. Most also reported nervous excitation, dry mouth, and fatigue. In all but one case, these symptoms disappeared by 19.5 hr postinjection. What prompted the greatest concern were the three of eight subjects who had significant reactions: two had excessive anxiety 3.1 hr postinjection and one had dizziness 3.1 and 19.5 hr postinjection. These symptoms were not surprising, such reactions are well established (Schroeder et al., 1985; Wood et al., 1985). However, the large percentage of adverse reactions was unexpected. This should be of concern when promethazine is used in situations where mental and physical performance must be at a high level, such as in the Space Shuttle, even though the reported incidence of sedation and adverse reactions during spaceflight appears to be much less than on earth (Bagian and Ward, 1994). This disparity is especially puzzling because the effective intramuscular dosage of 50 mg for space motion sickness (Graybiel and Lackner, 1987) is more than that recommended clinically for the control of nausea and vomiting (Wood et al., 1992). Altered pharmacokinetics and pharmacodynamics during spaceflight may explain these differences (Derendorf, 1994; Tietze and Putcha, 1994).

Mean R-R interval and arterial pressure. Mean R-R interval and arterial pressure for the preinjection and postinjection conditions were not different, although there was a nonsignificant postinjection drop in systolic pressure (Table 1). In a study of awake resting dogs, promethazine decreased mean R-R interval and increased blood pressure (Goldberg et al., 1969); we had expected similar results.

R-R interval periodicities. Fluctuations of R-R intervals are used widely as indexes of the level of autonomic traffic to the heart. This usage has its origin in a study published by Katona and Jih (1975) that showed that in anesthetized dogs with spontaneous breathing, respiration-related R-R interval periodicities are related linearly to absolute vagal firing rates. R-R interval periodicities are not only related to respiration, but are also related to the rhythmic fluctuations of systemic arterial blood pressure (Koepchen, 1984). There is substantial disagreement regarding mechanisms responsible for fluctuations centered around 0.10 Hz. Some argue that
they are mediated predominately by fluctuations of sympathetic neural traffic (Pagani et al., 1986), although we and others have shown that vagal-cardiac motoneurons, probably mediated by a baroreflex mechanism, play an important role (Pomeranz et al., 1985; Koh et al., 1994; Sleight et al., 1995). R-R interval periodicities of less than 0.05 Hz have been related to thermoregulation (Kitney and Roppe, 1977) and to local fluctuations in peripheral vascular resistance associated with the regulation of blood flow through vascular beds (Akselrod et al., 1985). The renin-angiotensin system also appears to play a significant role in the control of these local fluctuations (Akselrod et al., 1981).

We expected the antihistaminic activity of promethazine to alter vascular resistance (Royblat et al., 1991) and the anticholinergic activity of promethazine to reduce vagally mediated baroreflex responses. The result would be altered R-R periodicities or spectral power. Contrary to expectations, the injection of promethazine did not significantly alter respiratory, low, or very low R-R interval spectral power (Table 1; Fig. 2). This lack of influence by promethazine on respiratory and low frequency periodicity indicates that the antihista-
minic and anticholinergic activity associated with prometh-
azine has minimal impact on efferent cardiovagal activity and carotid baroreceptor-cardiac reflex responsiveness.

**Carotid baroreflex function.** The key reason for this investigation was to determine the effects of a 50-mg intramuscular injection of promethazine on vagally mediated carotid baroreceptor-cardiac reflex responsiveness. We recently performed carotid baroreflex measurements during two Space Shuttle missions (STS-40 and STS-55) 18 to 20 hr after the administration of promethazine. To account for the potential influence of promethazine on those results, our study recreated the dosage and timing between administration of promethazine and measurement of the carotid baroreflex that occurred during our Space Shuttle investigations. In addition, we investigated the influence of promethazine on the baroreflex during its peak plasma concentration. Our results indicate that promethazine does not influence carotid baroreflex function. The range, maximum slope, and operational point were not significantly different at any time after the injection of promethazine (Table 1). Thus, it is likely that baroreflex changes measured during spaceflight were not influenced by promethazine.

**Plasma catecholamine levels.** We did not collect blood for plasma catecholamine analysis originally, but for other purposes. Because of this, blood was collected immediately after needle insertion. The decision to use the stored plasma for catecholamine analysis was supported by the results of Johnson et al. (1977) which showed that, after 30 min supine rest, plasma norepinephrine and epinephrine levels from blood collected immediately after venipuncture were not different from blood collected 30 min after venipuncture. In our study, plasma norepinephrine levels were not changed appreciably by promethazine. Although not significant, plasma epinephrine levels were lower 3.1 hr postinjection and had not returned to preinjection values after 19.5 hr (Table 1).

**Potential limitations.** Because this investigation was performed only at rest in recumbency, it was limited in scope and did not address the effects of promethazine on autonomic cardiovascular mechanisms during other conditions. Stimuli, such as motion sickness, which evoke strong autonomic re-

**References**


Akselrod, S., Gordon, D., Ubel, F. A., Shannon, D. C., Barger, A. C., and Cohen, R. J.: Power spectrum analysis of heart rate fluctuation: a quantita-

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The design of the investigation, without a control group, placebos, or cross-overs, did not account for the effects of time or circadian variability on the results. All subjects began the investigation in the early afternoon at least 2 hr after a meal. Therefore, the preinjection and 3 hr postinjection measure-
ments were performed in the same afternoon. The 18 to 20 hr postinjection measurements were performed early the next morning. We know that carotid baroreflex responses are reproducible (Eckberg et al., 1992) and do not exhibit circadian variability (Kasting et al., 1987), but we acknowledge that the other measurements might have been influenced. Spectral analyses of R-R interval periodicities are also reproducible (Honziková et al., 1990), especially under the conditions of controlled breathing (Öri et al., 1992). However, R-R interval periodicities do exhibit circadian variability. Hayano et al. (1990) reported that in measurements performed during controlled breathing (15 breaths/min) in the supine position the respiratory frequency component was greater in the morning than in the late afternoon but the low frequency component did not change with the time of day. Our 18 hr respiratory frequency component, collected in the morning, was actually the smallest of the three treatment periods; therefore, the possibility exists that circadian variability masked a significant treatment effect.

After completion of our analyses, we addressed the possi-
bility that a β-statistical error occurred and that we might have found statistically significant differences if we had studied more subjects. Sample size estimates for each parameter in Table 1 were performed using the minimum difference between group means and standard deviations from the baseline, 3-hr and 18-hr treatment periods from the first seven subjects. For the estimates, alpha was set to 0.05 and power was set to 0.80. The results of this analysis indicated that the minimum sample size for plasma epinephrine was 29 and for systolic pressure was 31; all others required more than 100 subjects. Thus, it seems highly unlikely that our negative results resulted from β-statistical errors.

In conclusion, we studied the effects of a large intramuscular dose of promethazine on autonomic cardiovascular mechanisms in a group of healthy young men and women. Because of promethazine’s antihistaminic and anticholinergic properties, we expected that a 50-mg intramuscular dose would affect sympathetically and vagally mediated cardio-
vascular autonomic control substantially. We found no significant effect of promethazine on resting mean R-R interval, arterial pressure, R-R interval periodicities, carotid baroreflex function, or plasma catecholamine levels.

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