Water Potentiates the Pressor Effect of Ephedra Alkaloids

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Background—The use of ephedra alkaloids in over-the-counter preparations has been associated with potentially serious cerebrovascular events. Because of its potential association with hemorrhagic strokes, phenylpropanolamine has been largely substituted for by pseudoephedrine, but it is not clear whether this is indeed a safer alternative. It would be important to understand the cardiovascular effects of ephedra alkaloids, but these are normally masked by baroreflex buffering mechanisms. We therefore investigated the effects of ephedra alkaloids in patients with autonomic impairment and explored their potential interaction with water ingestion.

Methods and Results—The cardiovascular effects of phenylpropanolamine or pseudoephedrine, alone and in combination with water, were determined in 13 subjects with impairment of baroreflex function due to autonomic failure. Phenylpropanolamine, 12.5 to 25 mg PO, increased systolic blood pressure (SBP) by 21±14 mm Hg after 90 minutes. However, when ingested with 16 oz of room temperature tap water, phenylpropanolamine increased SBP by 82±2 mm Hg. Pseudoephedrine, 30 mg PO, increased SBP on average 52±9 mm Hg when taken with 16 oz of water and by as much as 88 mm Hg.

Conclusions—Ephedra alkaloids increase blood pressure significantly in individuals with impaired baroreflex function. Concomitant ingestion of ephedra alkaloids and water produced a greater increase in blood pressure. If used cautiously, this interaction can be beneficial in the treatment of orthostatic hypotension. On the other hand, it could contribute to the cardiovascular complications associated with the use of ephedra alkaloids, given that baroreflex function varies widely in normal individuals and is impaired in several medical conditions. (Circulation. 2004;109:1823-1825.)

Key Words: blood pressure • pharmacology • stroke

Serious cerebrovascular toxicity has been reported in people taking dietary supplements that contain ephedra alkaloids. In a case-control study, phenylpropanolamine ingestion was associated with an increased risk for hemorrhagic strokes in women. An increase in blood pressure after drug ingestion may contribute to this risk. The increase in blood pressure produced by any pressor agent is normally attenuated by baroreflex buffering that leads to a compensatory decrease in heart rate and sympathetic tone. Accordingly, the pressor effect of phenylpropanolamine is augmented in patients with impaired baroreflex function due to autonomic failure. Even in otherwise healthy people, the ability of the baroreflex to buffer changes in blood pressure varies 10- to 20-fold. Thus, a subgroup of healthy subjects may be particularly sensitive to pressor agents such as phenylpropanolamine. Individuals with impaired baroreflex function are also hypersensitive to “trivial” stimuli that occur during daily life. For example, water drinking elicits a profound pressor response in patients with autonomic failure. We reasoned that concomitant ingestion of water and ephedra alkaloids may induce a particularly large pressor response. Phenylpropanolamine has largely been replaced in the US market by pseudoephedrine. It is not certain, however, whether pseudoephedrine has an improved safety profile. We therefore examined the potential interaction between phenylpropanolamine and pseudoephedrine and water drinking.

Methods

We studied 13 patients (age 66±3 years, 8 men) with autonomic failure due to multiple system atrophy (n=5) or pure autonomic failure (n=8) referred for severe orthostatic hypotension, to determine the use of short-acting pressor agents in their treatment. Patients with pure autonomic failure had isolated severe impairment of autonomic reflexes without a discernible cause (eg, medications, secondary causes of neuropathy). Patients with multiple system atrophy had either parkinsonian or cerebellar features, in addition to autonomic failure. All studies were approved by the institutional review board of Vanderbilt University. Written informed consent was obtained. All tests were conducted with patients in the seated position after an overnight fast, on separate days. Blood pressure was determined every 5 minutes by an automated brachial blood pressure cuff. In a first study in 4 patients, we compared the effect of 480 mL of tap water given together with placebo, 50 mL of tap water together with phenylpropanolamine, and 480 mL of tap water together with phenylpropanolamine in a crossover fashion. Room-temperature water was used and was ingested in less than 5 minutes. The dose of phenylpropanolamine was individualized in each patient (12.5 or 25

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mg) to avoid excessive hypertension. This study was terminated because phenylpropanolamine was, in effect, taken off the market. In a second study, 9 patients received 30 mg of pseudoephedrine, and, on separate days, they drank either 50 or 480 mL of tap water 15 minutes after pseudoephedrine ingestion. Results are presented as mean±SEM. ANOVA with repeated measurements was used for multiple comparisons. The level of significance was set at α=0.05.

Results
All patients had severe disabling orthostatic hypotension, with an average decrease in systolic blood pressure of 84±8 mm Hg (range 34 to 142 mm Hg, from 156±6 to 72±5 mm Hg). Heart rate increased from 70±4 to 80±5 bpm, an inappropriate increase given the magnitude of hypotension. Patients had an exaggerated depressor response during phase II of theValsalva maneuver (−60±7 mm Hg, range −25 to −105 mm Hg, versus −20±6 mm Hg in normal subjects) and an impaired baroreflex-mediated increase in heart rate relative to the fall in blood pressure (0.18±0.02 versus 2.90±0.62 bpm/mm Hg in normal subjects). All these findings are consistent with a profound impairment in baroreflex regulation of both heart rate and vasomotor tone.

Phenylpropanolamine (16±2.8 mg) taken with 50 mL of water increased seated systolic blood pressure by 21±14 mm Hg after 90 minutes (Figure 1). When the same patients ingested 480 mL of water without phenylpropanolamine, systolic blood pressure rapidly rose, reaching a maximum increase of 24±13 mm Hg above baseline after 25 minutes. The combination of phenylpropanolamine and 480 mL of water resulted in a rapid and profound pressor response of 82±2.3 mm Hg after 70 minutes (P<0.0001 between interventions by ANOVA). No change in heart rate was observed during 480 mL of water or phenylpropanolamine alone; heart rate decreased by 7±1 bpm in patients receiving phenylpropanolamine and 480 mL of water.

When patients ingested pseudoephedrine with 50 mL of water, seated systolic blood pressure increased to a maximum of 22±10 mm Hg after 55 minutes, from a baseline seated blood pressure of 108±7 mm Hg (Figure 2). Water drinking after ingestion of the pseudoephedrine augmented the pressor response substantially. The maximal increase in systolic blood pressure was 52±9 mm Hg after 60 minutes, from a baseline seated blood pressure of 95±5 (P<0.001 between interventions). Heart rate decreased by 6±1 and 7±1 bpm with pseudoephedrine alone and pseudoephedrine plus 480 mL of water, from a baseline of 73±6 and 73±5 bpm, respectively. Blood pressure returned toward baseline values by 2 hours.

Discussion
The novel finding of the present study is that water drinking profoundly enhances the pressor response to the ephedra alkaloids phenylpropanolamine and pseudoephedrine in subjects with impaired baroreflex function. Systolic blood pressure increased on average 82 mm Hg when phenylpropanolamine was taken with water and 52 mm Hg when 30 mg of pseudoephedrine was taken with water (range 37 to 88 mm Hg). To the best of our knowledge, an acute interaction of similar magnitude has not been reported for any other cardiovascular drug and a component of the regular diet. The interaction between ephedra alkaloids and water drinking may be explained by the fact that water itself can raise blood pressure. We observed recently that drinking 480 mL of water increases systolic blood pressure more than 30 mm Hg in patients with severe autonomic failure. Water drinking also increases blood pressure moderately in otherwise healthy older subjects but very little in younger subjects. The pressor response appears to be mediated by the sympathetic nervous system, because water drinking increases muscle sympathetic nerve traffic and venous plasma norepinephrine concentrations in healthy subjects. Moreover, ganglionic blockade with trimethaphan abolishes the pressor response. The present study demonstrates that combination of the sympathetic response elicited by water drinking and the adrenergic stimulus provided by ephedra alkaloids elicits an additive, and perhaps synergistic, effect on blood pressure.

We studied the interaction between ephedra alkaloids and water drinking in a population with greatly impaired baroreflex function, which made them hypersensitive to vasoactive medications. Denervation hypersensitivity can also contribute to enhanced pressor response to adrenergic agonists in these patients. It is likely that these responses are masked in...
healthy subjects with intact baroreflex function. However, baroreflex function varies substantially even in the general population. The variability in baroreflex function is explained by genetic factors; age; medical conditions such as obesity, hypertension, diabetes, and heart failure; and other variables. Moreover, the doses of ephedra alkaloids that are used for various indications substantially exceed the doses applied in the present study. For instance, we used 30 mg of pseudoephedrine in the present study, the lowest dose found in over-the-counter nasal decongestants, and doses up to 240 mg are available as slow-release preparations. It is possible, therefore, that water drinking may also increase the response to ephedra alkaloids in otherwise healthy subjects with low normal baroreflex function and more so in patients with impaired baroreflex function.

Our findings may have important clinical implications. If used cautiously, we can exploit this interaction to our advantage in the treatment of patients with orthostatic hypotension. Conversely, inadvertent ingestion of pressor agents and water may cause potentially dangerous pressure surges in subjects with impaired baroreflex function and in patients with autonomic failure (eg, diabetic neuropathy). Future studies would need to assess whether this interaction contributes to the cardiovascular risks associated with these drugs in the general population.

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