Safety and Tolerance of Oral Dextromethorphan in Patients at Risk for Brain Ischemia

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Experimental ischemia models have shown the antitussive dextromethorphan to be an N-methyl-D-aspartate antagonist with neuroprotective properties. We treated 10 patients with a history of recent stroke or transient ischemic attack with oral dextromethorphan (60 mg q.i.d.) for 3 weeks in a placebo-controlled, double-blind, crossover tolerance study. We documented no clinical evidence of toxicity attributable to dextromethorphan in this preliminary study. (Stroke 1991;22:1075-1077)

Experimental evidence indicates that the excitatory neurotransmitter glutamate may play an important role in mediating ischemic neuronal damage.1 Both in vitro and in vivo ischemia models have demonstrated that antagonists of the N-methyl-D-aspartate (NMDA) subclass of glutamate receptors have neuroprotective properties.1,2 Recently, the dextrorotatory morphinan dextromethorphan has been shown to be an NMDA antagonist capable of attenuating hypoxic neuronal injury in cell culture3 and reducing infarct size in animal stroke models.4 The primary metabolite of dextromethorphan, dextrorphan, is also an NMDA antagonist with neuroprotective properties in experimental ischemia models.4

A number of safety issues regarding the use of NMDA antagonists in clinical trials have been raised.3 In particular, the NMDA receptor appears to play an important role in synaptic plasticity; therefore, NMDA antagonists could interfere with learning and memory function. Also, because phencyclidine is an NMDA antagonist, it is possible that NMDA antagonists in general may cause psychotomimetic effects. However, dextromethorphan has an established safety record in humans at antitussive doses and thus appears to be an attractive compound for initial clinical investigation.

Although it is difficult to extrapolate human dose requirements from animal data, it is likely that dextromethorphan doses higher than typically used for antitussive effects will be required for neuroprotection. Therefore, it is important to investigate the safety and tolerance of higher doses of dextromethorphan before a clinical study designed to detect the efficacy of dextromethorphan in acute stroke is initiated. As a first step, this study evaluated 60 mg q.i.d. dextromethorphan, twice the usual antitussive dose, in patients at risk for brain ischemia.

Subjects and Methods

We used a randomized, double-blind, crossover design to enroll ten patients between the ages of 50 and 75 years with a history of stroke or transient ischemic attack (TIA) within the past year. Exclusion criteria included severe cardiac, pulmonary, hepatic, or renal disease; significant laboratory abnormalities; or active psychiatric disease. We excluded patients taking monoamine oxidase inhibitors, but allowed other medications. Dextromethorphan hydrobromide capsules were used.

After we obtained informed consent, patients underwent a baseline neuropsychiatric evaluation consisting of the Benton Revised Visual Retention Test, Rey Auditory Verbal Learning Test, Serial Digit and Digit Span tests, and the psychotism items from the Minnesota Multiphasic Personality Inventory (MMPI). Dextromethorphan 30 mg p.o. q.i.d. was then begun. If no significant side effects were reported after 1 week on 30 mg q.i.d., patients were randomized to either dextromethorphan 60 mg q.i.d. or an identically appearing placebo for the next 3
weeks. At the end of 3 weeks, the neuropsychologic evaluation and routine laboratory studies (complete blood count, chemistry panel, urinalysis) were repeated, and a trough (6 hours after dose) dextromethorphan level was obtained. The study medication was tapered over the next week. Patients were then crossed over to the alternate therapy for the next 3 weeks. Subsequently, neuropsychologic and laboratory tests were repeated.

Results

Ten patients with a variety of previous stroke and TIA locations were enrolled in the study (see Table 1). Seven of the 10 patients enrolled completed the entire study. Of the three patients who withdrew before completion, one dropped out (patient 3) during the unblinded lead-in week because of side effects consisting of decreased concentration and blurred vision. Two patients dropped out during the blinded phase of the study, one while on placebo (patient 5) and one while taking dextromethorphan (patient 6). Patient 6 developed chest pain, diaphoresis, and shortness of breath approximately 20 minutes after taking his first 60-mg dextromethorphan capsule. A myocardial infarction was ruled out, and the final diagnosis was anxiety reaction.

Of the seven patients who completed the study, four had no side effects during either the dextromethorphan or placebo phase, two reported side effects only while on placebo, and one had adverse effects only while on dextromethorphan (see Table 1). There was no difference in the severity of adverse effects reported on dextromethorphan compared to placebo, and no withdrawal reactions were reported. Of the patients who completed the study, only one patient was able to identify correctly the dextromethorphan from the placebo phase of the study. No significant laboratory abnormalities attributable to dextromethorphan occurred. Pill counts revealed greater than 80% compliance throughout the study in all patients.

Neuropsychologic evaluation failed to reveal any significant difference in performance on any of the tests at the end of the dextromethorphan phase as compared to the placebo phase (Wilcoxon matched pairs signed ranks test).

Discussion

This study represents an initial attempt to administer dextromethorphan at higher than antitussive doses to patients at risk for brain ischemia. We chose patients with a history of stroke or TIA because they have clinical characteristics similar to the patient population of interest in a stroke treatment trial. In this study, there were no differences in the number or severity of adverse effects reported when dextromethorphan 60 mg q.i.d. was compared to placebo. Because of concern that NMDA antagonists might interfere with synaptic plasticity, neuropsychologic testing focused on learning and memory tests. In addition, the psychoticism items from the MMPI were included because of concern that NMDA antagonists might have phencyclidinelike effects. We detected no neuropsychologic abnormalities attributable to dextromethorphan in this small pilot study. It is possible that neuropsychologic changes might be detected in a larger study, although we note that no patient had a change on any test that would be considered clinically significant. As this study was being completed, it was reported that NMDA antagonists can induce vacuoles in neurons in the retrosplenial and cingulate cortices in experimental animals. These morphologic changes appear to be predominantly transient and reversible; however, their significance remains to be determined.

Despite uniform dosing, serum dextromethorphan levels varied considerably among patients. This variability probably results from several factors, including

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Stroke location</th>
<th>DM</th>
<th>Placebo</th>
<th>DM (ng/ml)</th>
<th>DX (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>Right subcortical</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>Brain stem</td>
<td>None</td>
<td>None</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3*</td>
<td>68</td>
<td>Brain stem TIA</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>Left subcortical</td>
<td>None</td>
<td>None</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>5†</td>
<td>52</td>
<td>Left hemisphere TIA</td>
<td>...</td>
<td>Dizzy, drowsy, slurred speech</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6‡</td>
<td>59</td>
<td>Left frontal</td>
<td>Chest pain, diaphoresis</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
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</tr>
<tr>
<td>8</td>
<td>66</td>
<td>Right hemisphere TIA</td>
<td>None</td>
<td>Drowsy</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>Right subcortical</td>
<td>Drowsy</td>
<td>None</td>
<td>189</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>67</td>
<td>Right subcortical</td>
<td>None</td>
<td>Decreased coordination, drowsy</td>
<td>145</td>
<td>10</td>
</tr>
</tbody>
</table>

Serum dextromethorphan (DM) and dextrorphan (DX) levels drawn after 3 weeks on dextromethorphan 60 mg q.i.d. (6 hours after final dose). TIA, transient ischemic attack.

* Dropped out during unblinded lead-in week; †dropped out during placebo phase; ‡dropped out during DM phase.
the variable rate of metabolism of dextromethorphan to dextrorphan between individuals and concomitant medications. The highest trough dextromethorphan levels achieved in this study were 145 and 189 ng/ml (0.5 and 0.7 μM) by patients 10 and 9, respectively; neither of these individuals reported significant adverse effects. Higher concentrations of dextromethorphan, approximately 10–30 μM, are required to reduce NMDA receptor-mediated injury in cortical cell cultures. However, in rat, brain dextromethorphan concentrations are observed to be 10–35 times higher than serum concentrations. The possibility that dextromethorphan may become a useful therapeutic agent for stroke remains open. Additional studies to evaluate the safety and tolerance of higher doses of dextromethorphan will be required.

References


KEY WORDS • cerebrovascular disorders • dextromethorphan • neuroprotection
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