Oral Pilocarpine Hydrochloride for the Treatment of Refractory Xerostomia Associated With Chronic Graft-Versus-Host Disease

To the Editor:

Chronic graft-versus-host disease (GVHD) occurs in 20% to 40% of long-term survivors of allogeneic bone marrow transplantation. The overall clinical picture resembles scleroderma with involvement of the skin, liver, eyes, mouth, upper respiratory tract, and esophagus. Oral chronic GVHD causes lichenoid stomatitis and sialadenitis with sialodochitis, resulting in decreased or absent salivary IgA and inorganic phosphate secretion; decreased salivary flow rates; and increased concentrations of salivary sodium, albumin, and IgG. Xerostomia because of decreased salivary flow results in oral pain, discomfort, caries, repeated infections, and difficulty in eating and speaking, and is a major cause of morbidity in patients with chronic GVHD. The xerostomia is often persistent despite systemic immunosuppression and improvement of GVHD elsewhere. Artificial saliva relieves the symptoms to a limited extent, and its acceptability is low.

Pilocarpine hydrochloride is a parasympathomimetic agent with predominantly muscarinic activity that stimulates secretion of mucin, proteins, glycoproteins, and electrolytes in the saliva. Oral administration of pilocarpine has been shown to improve saliva production and relieve the symptoms of postirradiation xerostomia in patients with head and neck cancer. We have treated five patients with xerostomia caused by chronic GVHD with the ophthalmic preparation of pilocarpine administered orally at the dose of 5 mg three times a day. Oral GVHD was diagnosed on the basis of the typical clinical findings of mucosal atrophy, erythema, or lichenoid mucosal lesions and pain. Four patients had received total body irradiation as part of the conditioning regimen for the allograft, but none had noticed xerostomia before the onset of chronic GVHD.

All patients had found artificial saliva to be unsatisfactory in relieving their symptoms. Previous or concomitant immunosuppressive therapy was unsuccessful in relieving xerostomia in all patients and included cyclosporine, corticosteroids, azathioprine, thalidomide, and psoralen-UV irradiation in various combinations. The intensity of concomitant immunosuppression was either unchanged or decreased during pilocarpine therapy.

As shown in Table 1, four of five patients noticed significant improvement in salivary flow and relief of symptoms. Furthermore, increased salivation had a beneficial effect on the oral mucosa and dental hygiene. The time for benefit to be noticed (7 to 45 days) and the time to maximum benefit (7 to 186 days) were widely variable. Patients no. 1, 4, and 5 had xerophthalmia as well, but improvement was noticed only by patient no. 1.

Adverse effects were infrequent, transient, and acceptable and led to discontinuation of the drug in only one patient (patient no. 1). The drug was stopped electively in patient no. 2, a heavy smoker.

Table 1. Response to Pilocarpine in Patients With Xerostomia Caused by Chronic GVHD

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Grade of Xerostomia</th>
<th>Response</th>
<th>Time to Response (d)</th>
<th>Time to Maximum Response (d)</th>
<th>Duration of Therapy (d)</th>
<th>Adverse Effects</th>
<th>Reason for Stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe</td>
<td>Excellent</td>
<td>45</td>
<td>95</td>
<td>111</td>
<td>Wheezing</td>
<td>Wheezing</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>Chest infection</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Excellent</td>
<td>7</td>
<td>186</td>
<td>242+</td>
<td>Sweating</td>
<td>Abdominal cramps</td>
</tr>
<tr>
<td>4</td>
<td>Moderate</td>
<td>Moderate</td>
<td>28</td>
<td>55</td>
<td>173+</td>
<td>Sweating</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>Excellent</td>
<td>7</td>
<td>7</td>
<td>143+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
when he developed dyspnea (but no wheezing) during an upper respiratory tract infection.

After noticing a marked improvement in her symptoms, patient no. 5 stopped pilocarpine on her own to see if the improvement was a coincidence and became severely symptomatic once again. The benefits were reproducible on restarting pilocarpine. Three patients are on continuous pilocarpine with persistent benefit. We plan to stop the drug when the oral cavity has been asymptomatic and normal on examination for 2 to 3 months.

We conclude that oral pilocarpine is beneficial in relieving symptoms of refractory xerostomia associated with chronic GVHD and is more acceptable than saliva substitutes. Unless significant adverse effects are encountered, the drug should be continued for 6 to 8 weeks before failure to respond is concluded.

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REFERENCES
Oral pilocarpine hydrochloride for the treatment of refractory xerostomia associated with chronic graft-versus-host disease [letter]

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