Docetaxel Secretion in Tears

Association With Lacrimal Drainage Obstruction

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Objective: To test the hypothesis that docetaxel may be secreted in tears after intravenous infusion.

Design: Prospective pilot trial.

Patients and Methods: Tear fluid was collected from 4 patients receiving docetaxel weekly and 2 patients receiving docetaxel every 3 weeks as a single agent for the treatment of metastatic breast cancer. Tear samples were collected once prior to and again within 30 minutes following the end of the 1-hour docetaxel infusion. A blood sample was also obtained after infusion. The tear and plasma samples were analyzed for drug content using high-performance liquid chromatography and tandem mass spectrometry.

Results: Docetaxel was found in the tear samples collected from all 6 patients.

Conclusion: The secretion of docetaxel in tears may be a mechanism for canalicular inflammation and tear drainage obstruction, which are known to occur as an adverse effect of the drug.

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OCETAXEL (Taxotere; Aventis, Bridgewater, NJ) is an effective anti-neoplastic agent that is widely used for the treatment of metastatic or locally advanced breast cancer.1,2 We have previously reported that stenosis of the canaliculi and blockage of the nasolacrimal ducts are common adverse effects of the weekly administration of docetaxel.3-5 In this study, we sought to test the hypothesis that docetaxel may be secreted in tears. The secretion of docetaxel in tears would suggest that closure of the lacrimal drainage apparatus may be due in part to its direct contact with the drug.

TEAR SAMPLE COLLECTION TIMES

Docetaxel was administered intravenously to each patient in 1-hour infusions. During the first infusion of docetaxel, 2 samples of tear fluid were collected from each patient: one sample immediately before infusion to serve as a baseline or control sample, and another sample within 30 minutes after the end of infusion. A 5-ml blood sample was also obtained within 30 minutes after the end of infusion.

TEAR SAMPLE COLLECTION METHOD

To anesthetize the conjunctival surface, a drop of topical proparacaine hydrochloride was placed in each eye. Polyester rods (Filtrona Richmond, Inc, Richmond, Va) were placed in the inferior lateral conjunctival fornix (Figure). For each sample, 2 polyester rods were used (1 in each eyelid) to collect the volume of tears required for analysis. During sampling, care was taken to avoid irritating the ocular surface and eyelid margin. No agent other than ambient light was used to stimulate tear production. Collection time was limited to 1 to 2 minutes or until 50 µL of tears was obtained, whichever occurred first. Tear collection was monitored...
by direct visualization of the wetting of the rods’ polyester substrate. After sampling, the rods were suspended in a microcentrifuge tube that contained a shortened micropipette tip and were frozen at −70°C. Tear fluid was subsequently recovered using centrifugation at 13,200g at 4°C for 10 to 15 minutes. The volume collected from each rod was measured; tear volumes typically ranged from 15 to 30 µL.

ANALYSIS OF DRUG CONCENTRATIONS IN TEAR AND SERUM SAMPLES

Docetaxel concentrations in the tear and serum samples were determined by direct injection of the tears or extracted plasma into a tandem mass spectrometer (Ultima Quattro LC/MS/MS; Micromass, Beverly, Mass) equipped with a binary high-performance liquid chromatography system (Agilent 1100; Agilent Technologies, Wilmington, Del). Docetaxel was identified and quantified using negative-ion electrospray mass spectrometry in multiple-reaction monitoring mode with the transition ion (806.5 → 54.4 [mass/charge], or parent > major product). Chromatographic conditions included a rapid methanol gradient (10mM ammonium acetate; pH level, 8.5) starting at 20% methanol and ending at 95% methanol within 5 minutes. The flow rate was 250 µL/min, and the column temperature was 45°C. The chromatographic separation of docetaxel from background noise was accomplished using an analytical column (3 µm; 2 × 100 mm; Xterra C18; Waters, Milford, Mass). The lower limit of quantitation for docetaxel in the tandem mass spectrometer was 10 ng.

Docetaxel was measured in plasma using solid-phase extraction. After the extraction cartridges (C2; Varian, Palo Alto, Calif) were prepared according to the manufacturer’s instructions, 1 mL of plasma was passed through them. The cartridges were then washed with 2 mL of an 0.01M ammonium acetate solution (pH level, 5.0) followed by 2 mL of a methanol/0.01M ammonium acetate buffer (pH level, 5.0) in a 20:80 vol/vol mixture. The drug was eluted from the columns with 300 µL of 100% methanol. A 25-µL aliquot of the resulting extract was injected directly into the tandem mass spectrometer.

The Table shows the patient characteristics, dose intensity of docetaxel, and concentrations of the drug in tear and plasma samples collected after drug administration. Although docetaxel was not present in any of the baseline (control) samples of tears, it was found in the tear samples collected from all 6 patients after injection of the drug. The concentrations of docetaxel were 1.4 to 7 times (mean, 4.5 times) higher in plasma than in tears.

**Table**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Race</th>
<th>Dose Intensity (mg/m²)/Total Dose (mg)</th>
<th>Docetaxel Concentration in Tears, ng/mL</th>
<th>Docetaxel Concentration in Plasma, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>Hispanic</td>
<td>35/58</td>
<td>435</td>
<td>1.28</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>Hispanic</td>
<td>35/83</td>
<td>294</td>
<td>2.08</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>Asian American</td>
<td>75/123</td>
<td>833</td>
<td>1.20</td>
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<tr>
<td>4</td>
<td>55</td>
<td>White</td>
<td>75/131</td>
<td>477</td>
<td>1.62</td>
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<tr>
<td>5</td>
<td>54</td>
<td>White</td>
<td>35/67</td>
<td>170</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>African American</td>
<td>35/71</td>
<td>116</td>
<td>0.74</td>
</tr>
</tbody>
</table>

The detection of docetaxel in tears collected from all 6 patients after its injection supports our hypothesis that the ocular surface irritation and fibrosis of the tear drainage ducts seen following treatment with this drug may be partly due to direct contact between the drug and both the conjunctival surface and mucosal lining of the tear drainage apparatus.

The concentrations of several drugs, including valproic acid, acetaminophen, lithium, phenobarbital, carbamazepine, and methotrexate, have been previously quantitated in tears. Transfer of the free non–protein-bound fraction from plasma to tears can be expected only with drugs that are not ionized and that have sufficient lipid solubility. Previous studies have demonstrated that concentrations of drugs in tears are proportionate to the concentration of free drug in plasma. Tears seem to have a relatively constant protein content (0.6-0.8 g/dL), and the passage of small molecules with low binding properties to plasma proteins via secretion into the tears is fairly unimpeded. Docetaxel is water insoluble and seems to readily cross physiologic barriers. The drug strongly binds to plasma proteins, with an in vitro plasma binding rate of 93% to 94% regardless of the drug concentration. In our study, the concentration of docetaxel in the plasma of all 6 patients was several times higher than the concentration of the drug in tears from these patients. These findings suggest that only a small fraction of the administered dose of docetaxel (ie, the unbound portion) has access to the tear film.

The method of tear collection in our study was simple and did not cause ocular adverse effects. In most cases, ambient light was an adequate stimulus for tear produc-
tion. Previous studies have used several methods for the collection of tear samples, including the use of glass micropipettes, Schirmer paper strips, and the polyester rods used in our study. We prefer to use polyester rods because they are easy to handle and do not seem to cause discomfort to the patients.

Various alternative methods for the detection of drugs in tear samples have also been proposed, including gas chromatography coupled with mass spectrometry and high-performance liquid chromatography. A high-performance liquid chromatograph in combination with a tandem mass spectrometer permits the precise determination of compounds through measurement of their exact molecular weight and through production of a fragmentation pattern unique to the compound being analyzed. Detection limits at the level of picograms or lower are possible. We chose our method because it gives reproducible results and because a volume of tears as small as 50 µL was adequate for the detection and quantitation of docetaxel.

The aim of our study was to determine whether docetaxel is secreted in tears. We did not attempt to examine the pharmacokinetics of drug secretion in tears owing to the small number of patients and to concerns that ocular adverse effects could result from repeated tear collection within a short interval after infusion of the drug. However, docetaxel concentrations in tears might be higher if measured at longer intervals after administration. Raines et al demonstrated that the concentration of azithromycin in tears is highest 24 hours after administration, a sampling time much later than that used in our study. Also, azithromycin concentrations in tears may remain high even after the drug is cleared from the plasma. Thus, future studies of docetaxel should be designed so that tear samples are collected at various intervals after its administration to determine when the maximum concentration is achieved and how long the drug remains in tears.

As stated in our previous articles on this topic, the best way to prevent irreversible damage to the tear drainage apparatus during docetaxel treatment is to provide close monitoring by an ophthalmologist and specific evaluation of the nasolacrimal ducts using probing and irrigation. These measures will allow for the early identification of anatomic narrowing of the canaliculi and nasolacrimal ducts as well as early stenting of the ducts to prevent their complete closure during continued treatment with docetaxel.

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REFERENCES