Vancomycin Concentration in the Vitreous After Intravenous and Intravitreal Administration for Postoperative Endophthalmitis

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Objectives: To measure the concentrations of vancomycin in the vitreous of patients with postoperative endophthalmitis after administration of 1 g of vancomycin hydrochloride intravenously and injection of 1 mg of vancomycin hydrochloride into the vitreous, and to determine whether these concentrations are adequate for treatment of gram-positive infections.

Methods: Patients with acute postoperative endophthalmitis were treated with intravenous administration of 1 g of vancomycin hydrochloride followed by vitrectomy and collection of vitreous samples 1 to 5 hours later. Intravitreal vancomycin and ceftazidime were given. Vitreous samples were cultured and their vancomycin concentrations assayed. Minimal inhibitory concentrations of vancomycin for the isolated vitreal pathogens, and serum and vitreous cidal activity were determined.

Results: Eighteen patients with acute postoperative endophthalmitis were studied. Fourteen vitreous samples were available after intravenous vancomycin administration, and 4 vitreous samples were available after intravitreal vancomycin administration. After intravenous injection, vitreous vancomycin concentrations ranged from 0.4 to 4.5 µg/mL. Minimal inhibitory concentrations in these samples, obtained from 10 bacterial isolates, were below the therapeutic levels for most causative organisms, including staphylococci. Vitreous cidal activity values were negative at a dilution of 1:2 in 9 of 10 patients examined. After a 1-mg intravitreal injection, vancomycin concentrations in vitreous samples obtained by a second tap from 4 patients 44 to 72 hours later were 182, 138, 58, and 25 µg/mL. In 2 patients in whom measurements were obtained, vitreous cidal activity values were 1:512 and 1:32.

Conclusion: Vitreous vancomycin concentrations for the treatment of gram-positive endophthalmitis were nontherapeutic after intravenous administration but therapeutic after intravitreal administration.


BACTERIAL endophthalmitis remains the most serious complication of cataract extraction, with a reported incidence of 0.07% to 0.08%.1,2 Because most cases are caused by gram-positive organisms,3,4 vancomycin—with broad activity against most gram-positive species—has become an agent of choice.2-7 Routine use of intravenous antibiotic drugs that were previously a mainstay of therapy8,9 has come into question as a result of findings of the Endophthalmitis Vitrectomy Study (EVS), which showed no benefit. Penetration of intravenous vancomycin into the vitreous cavity after intravenous administration is thought to be limited and variable, based in part on the severity of intraocular inflammation and resultant breakdown of the blood ocular barriers. Although animal data are available,10,11 to our knowledge the concentration of intravenously administered vancomycin in the infected vitreous of patients with postoperative endophthalmitis has not been reported.

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This study measured vancomycin concentrations in the vitreous after its intravenous and intravitreal administration, and determined whether such concentrations are adequate for the treatment of representative organisms that cause gram-positive endophthalmitis in humans.

RESULTS

Of 18 patients enrolled in the study, endophthalmitis was diagnosed in 15 of them 3 to 9 days after cataract surgery, in 2 of them 12 to 14 days after surgery, and in 1 of them 1 year after surgery. Fifteen vitreous samples were taken for vancomycin assay 1 to 5 hours after intrave-
PATIENTS AND METHODS

Patients referred to the Department of Ophthalmology, Meir General Hospital, Sapir Medical Center, Kfar-Saba, Israel, between August 1, 1995, and December 31, 1996, for acute endophthalmitis that developed after cataract extraction were enrolled in this prospective study. Cataract surgery had been performed in 1 of 7 surgical centers, including the Sapir Medical Center. Prior informed consent was obtained from all participants.

Immediately after confirmation of the diagnosis, all patients except 1 were administered 1 g of vancomycin hydrochloride intravenously for 20 minutes. One to 5 hours later, each patient who received vancomycin was taken to the operating room. An anterior chamber maintainer was inserted, and vitreous tap was performed through a pars plana sclerotomy using a vitrectomy probe. A 1-mL tuberculin syringe was connected to the suction tube, and vitreous material was drawn directly into the syringe using the vitrectomy cutter and manual suction. The vitrectomy cutter was then removed, and the residual vitreous material was drawn into the syringe from the dead space of the tubing. Balanced salt solution was injected through the anterior chamber maintainer only after vitreous biopsy, and either core or complete vitrectomy was performed. The vitreous specimens were submitted for microbiologic cultures and determination of vancomycin concentrations. Bacterial isolates were identified according to conventional microbiologic techniques, and the minimal inhibitory concentration (MIC) of vancomycin for each isolate was determined. Vitreous cidal activity (VCA) against the specific pathogen was determined with an inoculum of 5 × 10⁵ microorganisms in microplate dishes during a 24-hour period. A venous blood sample was drawn at the same time, and the serum was separated. Vancomycin concentrations in the serum and vitreous samples were determined by fluorescence polarization immunoassay (TDX; Abbott Laboratories, North Chicago, Ill). Serum cidal activity was determined according to National Committee for Clinical Laboratory Standards criteria using 5 × 10⁵ CFU/mL at 35°C and confirmed by colony count after incubation for 24 hours. Cidal activity was determined as the concentration that killed 99.9% of the inoculum. Four patients in whom no clinical improvement was noted after 2 to 3 days of therapy underwent another vitreous tap and intravitreal vancomycin and ceftazidime administration.

Statistical analysis was done by one-way analysis of variance using a statistical software program (SPSS-6 for Windows; SPSS Inc, Chicago, Ill).

Eleven isolates were available for vancomycin MIC determinations. In 9 patients, levels of vancomycin in the vitreous specimens after intravenous injection and MICs for the corresponding isolate were available. Vancomycin vitreal concentration was higher than the MIC of the isolated pathogen in 5 of these patients, and lower in 4. Vitreous cidal activity was positive at a dilution of 1:32 in only 1 patient. In the remaining 8 patients, the VCA was negative at a dilution of 1:2. This suggests that vancomycin levels in vitreous specimens were too low to confer bactericidal activity in most patients, even though in some, the actual concentration of vancomycin exceeded the MIC. Serum vancomycin levels 1 to 5 hours after intravenous administration were available in 11 patients and ranged from 8.94 to 28.42 µg/mL (mean, 13.23 µg/mL). The differences in serum drug level at various time intervals were not statistically significant (Table 3 and Figure 2). Serum cidal activity values were available in 7 patients; serum samples were bactericidal at a dilution of 1:4 in 3 patients, 1:8 in 2, and 1:32 in 1. In 1 patient, serum vancomycin level was available 44 hours after intravenous administration and was 3.11 µg/mL, but the serum cidal activity was negative at a dilution of 1:2 (Table 1, patient 17).

In 4 patients (Table 4), vitreal vancomycin levels were available for measurement 2 to 3 days after intravitreal administration of 1 mg of vancomycin hydrochloride. Mean vancomycin concentration was 100.84 ± 72.01 µg/mL (range, 25.05-182.36 µg/mL), which was significantly higher than those measured after intravenous administration (P < .001). Microbiologic cultures of the 4 vitreous specimens taken after intravitreal vancomycin administration were negative. In 2 of these patients (6 and 17), VCA values toward the initially isolated organism were also measured 2 to 3 days after the initial intravitreal vancomycin administration and were positive at dilutions of 1:512 and 1:32. This result is significantly better than that obtained before intravitreal administration.
of vancomycin, ie, after its intravenous administration alone (P = .01 by χ2 analysis).

Results of the EVS3 show that the final visual outcome in patients with endophthalmitis was better than previously described. This is probably attributed to the current management of endophthalmitis—using immediate intravitreal antibiotic agents, with or without vitrectomy.15,16 One conclusion of the EVS was that, based on clinical experience, there is no advantage conferred by intravenous administration of antibiotic agents. Results of several studies17-20 demonstrate low or marginal vitreous levels of antibiotic drugs after intravenous, intramuscular, or oral administration in animal models and in humans. Results of other studies21,22 demonstrate that inflammation significantly increases the ability of cefal-
zolin sodium and ceftazidime to penetrate the vitreous cavity. This study provides laboratory evidence supporting clinical evidence of the EVS.

Gram-positive bacteria are the most frequent cause of postoperative endophthalmitis and were recently reported to be responsible for 94.2% of all cases of confirmed bacterial endophthalmitis. In that study, vancomycin was the only antibiotic drug to which all the gram-positive pathogens were sensitive. Vancomycin was not administered to the subgroup of patients receiving intravenous antibiotic drugs in the EVS because its penetration into the vitreous after intravenous administration is thought to be poor. An earlier study detected no vancomycin in vitreous specimens from either healthy or chemically inflamed eyes after intravenous injection. In a recent study using an animal model, vancomycin levels in vitreous specimens after intravenous injection exceeded the MIC for the gram-positive pathogens usually responsible for endophthalmitis. In another animal study, the efficacy of vancomycin and amikacin sulfate used to prevent experimental staphylococcal endophthalmitis was studied. No significant differences were found between patients treated with antibiotic drugs and saline-treated controls. Many ophthalmologists are reluctant to withhold systemic antibiotic drug therapy, including vancomycin, in severe, vision-threatening infection, and some even recommend starting intravenous vancomycin treatment before a microbiologic diagnosis is established. We are aware of no clinical studies in which vancomycin concentrations in the infected vitreous of patients with postoperative endophthalmitis have been measured after intravenous administration of the antibiotic agent.

Results of our study demonstrate erratic penetration by a single dose of intravenous vancomycin in eyes with endophthalmitis, confirming that intravenous therapy with vancomycin cannot be relied on as a sole mode of therapy in patients with postoperative endophthalmitis of which the suspected causative pathogens are gram-positive cocci.

The therapeutic level of an antibiotic agent depends on its MIC for a specific microorganism and on its concentration at the site of infection. The therapeutic adequacy of antibiotic drug concentrations in the serum and vitreous specimens can be confirmed by measurement of serum cidal activity or VCA. In this study, the MIC of vancomycin toward S. epidermidis—the most common causal agent of gram-positive endophthalmitis after cataract extraction—was 1.9 µg/mL, and the MIC of other isolated bacteria was 0.5 to 3.0 µg/mL. Vancomycin levels in serum samples of all patients after intravenous injection were, as expected, much higher than the MICs. Serum cidal activity was positive at a dilution of 1:4 to 1:32, confirming that vancomycin had reached an adequate therapeutic level in the serum samples. In contrast, vancomycin levels in the vitreous specimens of the same patients were higher than the MICs for S. epidermidis (1.9 µg/mL) in only 6 of 14 patients. Even when the vancomycin level in the vitreous specimen was higher than the MIC of the specific pathogen, the VCA was sufficient high (1:32) in only 1 patient. Vitreous vancomycin levels were higher 4 to 5 hours after intravenous injection than after 3 hours or less (Figure 1). It is, therefore, possible that after multiple doses of intravenous vancomycin, vitreal vancomycin levels might be higher than those attained by a single intravenous dose, and perhaps even be therapeutic. The apparent paradox of adequate vitreal vancomycin concentrations, together with low VCA, could possibly be explained in terms of the binding of vancomycin to proteins present in the inflamed vitreous. Such binding might diminish the antibacterial activity of this drug, but the bound vancomycin might nevertheless be recognized as free vancomycin in an assay based on chemical detection rather than on microbiology. In this study, determination of the vitreous levels was not delayed for more than 5 hours after administration of the drug because it was considered unethical to place the patient at risk by delaying surgery. In 4 patients, it became necessary to perform a second vitrectomy and intravitreal injection (Table 4); thus, intravitreal vancomycin levels could be measured 2 to 3 days after a single injection. Vitreal vancomycin levels in these 4 patients were up to 100 times higher than after intravenous injection alone, and the VCA was present at dilutions of between 1:32 and 1:514. This finding is in accordance with an experimental study in rabbit eyes that demonstrated high levels of vitreous vancomycin 48 hours after its intravitreal injection.

In conclusion, intravitreal concentration of vancomycin, the most effective antibiotic drug for treating gram-positive endophthalmitis, usually does not reach therapeutic concentrations after intravenous administration of a single dose. Therefore, intravenous injection of vancomycin cannot replace its intravitreal administration. Administration of a single intravitreal vancomycin dose maintains high and effective vitreous levels for at least 3 days. Therefore, in postoperative endophthalmitis caused by gram-positive cocci, the addition of intravenous vancomycin administration is probably not indicated.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time After Surgery, d</th>
<th>Time After Intravitreal Vancomycin Administration, h</th>
<th>Vitreal Vancomycin Level, µg/mL</th>
<th>Organism From First Vitrectomy</th>
<th>MIC, µg/mL</th>
<th>Cidal Activity</th>
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<tr>
<td>6</td>
<td>3</td>
<td>72</td>
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<td>137.85</td>
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<td>NA</td>
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<tr>
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<td>9</td>
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<td>58.11</td>
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<td>&gt;1:2</td>
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<tr>
<td>18</td>
<td>12</td>
<td>72</td>
<td>25.05</td>
<td>Negative</td>
<td>NA</td>
<td>...</td>
</tr>
</tbody>
</table>

* MIC indicates minimal inhibitory concentration; NA, not available; and ellipses, not relevant. Vancomycin administered as vancomycin hydrochloride.
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REFERENCES


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