Oxacillin for bacterial endophthalmitis: subconjunctival, intravenous, both, or neither?

Michael Barza, Anne Kane, and Jules Baum

We compared the intraocular concentrations of oxacillin given by continuous intravenous infusion, subconjunctival injection, or combined therapy in a rabbit model of Staphylococcus aureus endophthalmitis. At equilibrium during intravenous infusion, concentrations in the aqueous humor, cornea, and choroid-retina were 25% to 30% of the serum level; in contrast, vitreous levels were only 2% of the serum concentration. Subconjunctival injection produced extremely high levels in the cornea and aqueous and moderate concentrations in the choroid-retina; vitreous penetration remained poor (<1 μg/ml). Combined therapy offered little advantage in terms of concentrations in the aqueous or cornea and had a modest effect on levels in the choroid-retina. Vitreous concentrations showed a striking relation to serum levels with all regimens, including subconjunctival ones; although this could have been fortuitous, it suggests an important role for the hematogenous route in this model. Only those modes of delivery producing serum concentrations greater than 50 μg/ml consistently resulted in vitreous levels greater than 0.4 μg/ml. The optimal therapy of bacterial endophthalmitis may require direct intravitreal injection of antibiotic.

Key words: oxacillin, ocular penetration, vitreous, subconjunctival, antibiotic, endophthalmitis, intravenous

Bacterial endophthalmitis continues to have a guarded prognosis for the salvage of useful vision despite the use of periocular injections together with systemic antibiotics. Although many factors, including delay in institution of therapy, may account for the failures, an obvious consideration is the possibility that the antibiotics are not reaching the major focus of infection in sufficient quantity.

In the present paper, we examine the ocular penetration of oxacillin, a commonly used antistaphylococcal drug, after high-dose intravenous administration, subconjunctival injection, or both routes simultaneously. In a separate paper, we report our results when a similar study was attempted with gentamicin.

Materials and methods

All studies were performed in Dutch belted (pigmented) rabbits, weighing approximately 2 kg. Bilateral endophthalmitis was induced in all eyes by the intravitreal injection of 500 cfu of Staphylococcus aureus 209P. After 48 hr, when the red reflex was no longer evident, antibiotic administration was begun. Six to 10 eyes were studied at each time interval with each route.

Intravenous oxacillin. Oxacillin (Bristol Laboratories) was administered as a continuous infusion...
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Fig. 1. Mean and S.E. of oxacillin concentrations in ocular sites during continuous intravenous infusion of 75 mg/kg/hr. The stippled area encompasses mean and S.E. of serum levels.

Fig. 2. Mean concentrations in ocular sites and serum after the termination of continuous infusion of oxacillin, 75 mg/kg/hr, for 6 hr. Arrowheads indicate that levels in choroid-retina were undetectable (<1.0 μg/ml) by 9 hr and in vitreous (<0.6 μg/ml) by 7 hr.

Fig. 3. Mean oxacillin concentrations in ocular sites and serum after 6 hr of continuous infusion at 40 or 75 mg/kg/hr (bars on left), 60 min of continuous infusion after subconjunctival injection of 100 mg (center bar), or 60 min after combined therapy (bars on right). Note the difference in vertical scales. See text for details of sites of sampling of cornea and choroid-retina and for identification of asterisks.

at a rate of 75 or 40 mg/kg/hr through the marginal ear vein with a Harvard pump. Rabbits were sacrificed at intervals 2, 4, 6, and 12 hr after the onset of therapy. In a separate group the infusion was stopped after 6 hr (efflux study), and animals were sacrificed at 0.5, 1, and 3 hr after termination of antibiotic administration. Blood was drawn for measurement of serum levels of antibiotic immediately before sacrifice. Both eyes were removed, and samples of aqueous, vitreous, cornea (central and peripheral), iris, sclera, anterior choroid-retina (anterior to the equator of the globe), and posterior choroid-retina (posterior to the equator) were obtained. The central cornea sample was a disc of 8 mm; the peripheral sample was the remaining corneal ring to within 1 mm of the limbus. Aqueous and vitreous humors and serum were assayed by a standard agar-diffusion bioassay using Bacillus subtilis as the test organism. Tissue samples were assayed by the collagenase-digest
Table I. Levels of oxacillin (μg/ml or μg/gm) in serum, ocular tissues, and fluids after 6 hr intravenous infusion alone, subconjunctival injection alone, or combined therapy

<table>
<thead>
<tr>
<th></th>
<th>IV 40 mg/kg/hr</th>
<th>IV 75 mg/kg/hr</th>
<th>IV 40 mg/kg/hr + s/c 100 mg OS</th>
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<tbody>
<tr>
<td></td>
<td>15 min*</td>
<td></td>
<td>60 min*</td>
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<tr>
<td></td>
<td>Injected eye</td>
<td>Contra-lateral eye</td>
<td>Injected eye</td>
</tr>
<tr>
<td>Cornea</td>
<td>Both eyes</td>
<td>Both eyes</td>
<td>Both eyes</td>
</tr>
<tr>
<td>Superior</td>
<td>12.9 ± 2.3 (p)</td>
<td>39.1 ± 7.0 (p)</td>
<td>38.50 ± 9.46</td>
</tr>
<tr>
<td>Inferotemporal</td>
<td>6.6 ± 1.0 (c)</td>
<td>22.1 ± 3.8 (c)</td>
<td>1096 ± 419</td>
</tr>
<tr>
<td>Inferonasal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Iris</td>
<td>Superior</td>
<td>8.8 ± 1.5</td>
<td>29.6 ± 4.2</td>
</tr>
<tr>
<td>Inferior</td>
<td>8.5 ± 1.5</td>
<td>27.3 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Choroid-Retina</td>
<td>Anterior</td>
<td>7.9 ± 1.5</td>
<td>26.8 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>8.6 ± 1.5</td>
<td>31.3 ± 4.8</td>
</tr>
<tr>
<td>Aqueous</td>
<td>10.3 ± 1.0</td>
<td>33.8 ± 5.2</td>
<td>218 ± 68</td>
</tr>
<tr>
<td>Vitreous</td>
<td>0.4 ± 0.2</td>
<td>1.9 ± 0.4</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>Serum (at time of sacrifice)</td>
<td>32.4 ± 11.1</td>
<td>117 ± 22</td>
<td>78.1 ± 8.8</td>
</tr>
</tbody>
</table>

s/c = subconjunctival; IV = intravenous; each value is the mean ± S.E. of 6 to 10 eyes.
*Time of sacrifice after s/c injection.
†For animals receiving intravenous infusion alone, the cornea samples were peripheral (p) and central (c) rather than superior, inferonasal, and inferotemporal.

bioassay method; however, in order to detect the low concentrations after the infusion was discontinued, the trephine-disk bioassay was used in the efflux study group.

Subconjunctival oxacillin. Oxacillin (100 mg) was injected in the left eye 2 to 3 mm from the superior corneoscleral limbus. Animals were sacrificed 15 and 60 min later. Tissues and fluids were assayed in the same manner as described above except that iris was divided into superior and inferior halves and cornea was divided into inferonasal, and inferotemporal thirds. Only the injected eye was studied.

Combined delivery. After the sixth hour of continuous intravenous infusion of oxacillin, either 75 or 40 mg/kg/hr, 100 mg of antibiotic was injected subconjunctivally into the left eye, and the infusion was continued. Rabbits were sacrificed 15 or 60 min following the subconjunctival injection. Ocular tissues and fluids were studied in the same manner as that described for the subconjunctival route alone; both the injected and the contralateral eyes were examined.

Results

Intravenous oxacillin. The time course of antibiotic levels in serum, aqueous, cornea (central), and choroid-retina (posterior) during the continuous infusion of oxacillin, 75 mg/kg/hr, are shown in Fig. 1. Penetration into the anterior segment (central cornea, aqueous humor) occurred more slowly than into the highly vascular choroid-retina as shown by the values at 2 hr; however, by 6 hr, the concentrations in the three sites were similar. Intraocular levels reached a plateau after 6 hr of continuous infusion; the slight rise in vitreous levels between 6 and 12 hr was not statistically significant (unpaired t test).

Levels in aqueous, choroid-retina, and cornea at equilibrium were about 25% to 30% of the steady-state serum concentration. The most striking barrier to penetration was noted in the vitreous; levels in that site were only 2% to 3% of serum concentrations.

Efflux of antibiotic following termination of the infusion was rapid (Fig. 2); the terminal half-life could be roughly estimated as about 1 hr in aqueous and choroid-retina and slightly over 2 hr in the cornea. Vitreous levels also declined very rapidly.
**Table I** shows the concentrations of oxacillin in all ocular sites after 6 hr of continuous infusion at rates of 75 and 40 mg/kg/hr. In addition to the points noted above, the data in the table show the following. (1) Levels in peripheral cornea were about twice those in central cornea. (2) Anterior and posterior choroid–retina were very similar to each other and to iris in the content of oxacillin. (3) At the lower dose of oxacillin (40 mg/kg/hr), serum and intraocular levels were all about one third as high as at the higher dose.

**Subconjunctival oxacillin.** The concentrations of antibiotic 15 and 60 min after injection of 100 mg of oxacillin are shown in Table I. The levels of antibiotic in the cornea varied according to the distance from the site of injection but were at least 800 μg/gm. In contrast to the results with systemic injection, oxacillin levels in the aqueous humor were lower than in the cornea. Concentrations in the anterior choroid–retina were much higher than those in the posterior choroid–retina, a phenomenon which did not occur with intravenous infusions. Vitreous concentrations ranged from 0.6 to 0.8 μg/ml.

The most striking differences between the 15 and 60 min values were noted in choroid-retina, which showed a marked decline, and aqueous humor, which exhibited a striking increase in concentrations. Serum levels decreased from 41 to 21 μg/ml, and vitreous concentrations declined slightly during this interval.

**Combined routes.** The results of combined therapy are shown in Table I. In order to facilitate comparisons, the 60 min values for subconjunctival or combined-route therapy and the 6 hr values for intravenous administration are shown graphically in Fig. 3. The sites of lowest concentration in each tissue are depicted on the assumption that these are of greatest concern to the clinician. Accordingly, central cornea is displayed in groups receiving intravenous infusion, and inferotemporal cornea for those given subconjunctival or combined therapy. The values for choroid-retina are for the posterior segment.

As shown in Fig. 3, oxacillin levels in the aqueous and cornea were strikingly higher with subconjunctival or combined therapy than with intravenous injection alone. Levels in the choroid-retina were higher with subconjunctival than with intravenous administration, but the most striking concentrations...
were reached with combined therapy. As expected, the 15 min values were somewhat higher in choroid-retina and somewhat lower in the aqueous than the corresponding 60 min values in animals receiving combined therapy (Table I).

Concentrations in the vitreous were very closely related to those in the serum in each group (Fig. 3); they were generally about 2% of the serum level. The contralateral eye in animals treated by combined routes was somewhat lower than the injected eye (Table I and Fig. 3, asterisks within the bars); this suggests that the subconjunctival route exerted some effect on vitreous penetration independent of its contribution via the systemic circulation.

Vitreous concentrations were frequently undetectable (less than 0.6 to 0.8 μg/ml) in animals given subconjunctival or low-dose intravenous oxacillin alone. To calculate the means shown in Table I and Fig. 3, undetectable concentrations were arbitrarily taken as one-half the minimal detectable value. With this approach, vitreous levels with high-dose intravenous administration were significantly higher than those with subconjunctival or low-dose therapy (p < 0.02 by unpaired t test) but not different from the results of combined-route therapy. When median vitreous levels were computed, the values were very similar to the mean concentrations.

Discussion

A major objective of this investigation was to examine the merits of the common clinical practice of administering systemic together with periocular antibiotic for the therapy of serious intraocular infections. In order to avoid the problem of attempting to study two dynamic processes simultaneously, we “froze” one, the systemic route, by examining it under steady-state conditions. This was accomplished by continuous infusion of oxacillin for 6 hr. At least two gradients were evident between the serum and ocular sites: one between the serum and aqueous, cornea, and choroid-retina and the other between the serum and vitreous. The former achieved concentrations which were about 25% to 30% of those in the serum, the latter about 2%. These relations were similar at the two intravenous dosages of oxacillin.

The possibility that the aqueous humor might be a major source of the antibiotic in the cornea was suggested by the persistent gradient between these sites. However, the fact that peripheral cornea contained twice the concentration of oxacillin as did central cornea suggests that the hematogenous route is more important than the aqueous, or the tears, in bringing oxacillin to the peripheral cornea with systemic administration.

The higher intravenous dosage (75 mg/kg/hr) was used in order to produce consistently readable levels of antibiotic in the vitreous; the lower dose was studied in order to simulate clinical usage more closely, at least in terms of the quantities that might be administered over prolonged periods. The remarkably poor penetration of the vitreous even at the higher dosage was noteworthy, though not surprising.8–11

It is usual in treating patients to administer intermittent rather than continuous infusions. Thus it was of interest to study the rate of falloff of intraocular concentrations after termination of the infusion. Levels of oxacillin declined rapidly in all sites; the half-life was about 1 hr for most loci but about 2 hr for cornea. This suggests that even frequent repetition of intravenous boluses is unlikely to result in substantial accumulation of intraocular antibiotic.

Subconjunctival injection resulted in very high concentrations of oxacillin in the anterior segment of the eye and moderately high levels in the choroid-retina. Tissue concentrations were highest near the site of injection as has been reported previously with subconjunctival administration.12, 13 Most striking was the fact that vitreous levels were less than 1 μg/ml 15 and 60 min after injection. This finding is not peculiar to oxacillin but occurs with methicillin and cefazolin as well (unpublished data; manuscript in preparation).

Combined therapy added little to the very high levels produced by subconjunctival injection in the cornea and aqueous humor.
Choroid-retina showed an additive effect of the two routes, an observation which may be of importance in the treatment of bacterial endophthalmitis. However, concentrations in this site were exceedingly high with subconjunctival injection alone. Concentrations in the vitreous were about 2% of the serum level with each route or combination of routes (Fig. 3). This marked parallelism between the two sites suggests that the systemic circulation may be a major portal of entry of oxacillin into the inflamed vitreous even with periocular injections. A similar phenomenon has been noted with gentamicin in this model. However, it is also possible that this apparent relation is a spurious one, reflecting simultaneous but independent passage of oxacillin into the vitreous and into the systemic circulation; it would thus be fortuitous that the levels in the vitreous were 2% of the serum level with subconjunctival injection. This would not be expected to occur in humans, in whom the much greater body: eye ratio of volumes should produce negligible serum levels after a comparable subconjunctival injection. In any event, there appears to be some direct contribution of the subconjunctival route as evidenced by the fact that oxacillin levels in the vitreous of the contralateral eye were about one half as great as those in the injected eye (Table I and Fig. 3).

The addition of low-dose intravenous therapy to subconjunctival administration of oxacillin produced vitreous concentrations which were somewhat higher than those with subconjunctival injection alone (p < 0.1 at 60 min); however, as noted above, it is possible that this is simply a manifestation of the higher serum levels which resulted. Even with combined therapy at the highest intravenous dosage, vitreous concentrations were only about 3 μg/ml. At the lower intravenous dosage (40 mg/kg/hr), which would be more clinically applicable, vitreous levels with combined therapy were only about 1 μg/ml. The median inhibitory concentration of oxacillin for strains of *S. aureus* is approximately 0.4 μg/ml. Although we did not study the antibacterial activity of infected vitreous humor, it may well be that the efficacy of oxacillin is reduced in this milieu by such factors as protein binding. Thus the administration of intravenous and concomitant subconjunctival therapy would appear to provide very little, if any, therapeutic margin in the treatment of staphylococcal endophthalmitis in the rabbit.

These findings, if applicable to humans, suggest that intravitreal injections should be strongly considered for the treatment of bacterial endophthalmitis. If periocular injections are to be used in therapy of this disease, it is difficult to quarrel with the concomitant use of systemic drug for whatever slight benefit it may afford, especially in the intervals between periocular injections.

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