N-formimidoyl thienamycin (MK-787) is a new β-lactam with potent activity against both aerobic and anaerobic gram-positive and gram-negative bacteria. Its spectrum and activity suggest it may be useful in treatment of complicated intraocular infections. Its ocular penetration was studied in New Zealand white rabbits immediately before and after the third dose of 40 mg/kg administered intravenously at q6h intervals. Plasma, aqueous humor, and vitreous humor were obtained by direct aspiration, and antibiotic levels were assayed using an agar well diffusion method. MK-787 penetrated uninfamed intraocular fluids, including vitreous humor, although vitreous concentrations achieved (0.1-0.2 μg/ml) were significantly lower than the mean peak plasma (15 μg/ml) and aqueous concentrations (7 μg/ml). Nevertheless, the intraocular levels attained approached or exceeded the MIC90 for most sensitive organisms including some gram-negative bacilli important in bacterial endophthalmitis. When administered in combination with the renal enzyme inhibitor MK-791, plasma and aqueous concentrations of MK-787 were markedly potentiated, although vitreous concentrations were minimally affected. The potential usefulness of MK-787 in conjuction with MK-791 in the infected eye should be examined further in an animal model of bacterial endophthalmitis. Invest Ophthalmol Vis Sci 24:1147-1149, 1983

Materials and Methods. Study animals: Groups of New Zealand white female rabbits weighing 2-3 kg were studied. Each rabbit was adapted in individual cages for 48 hrs prior to experimentation. Anesthesia was attained by intramuscular injection of ketamine hydrochloride (100 mg/ml) admixed with acepromazine maleate (25 mg/ml) in a proportion of 10 ml to 1 ml, each animal requiring approximately 1 ml per injection. Animals were administered either MK-787 alone or in combination with the enzyme inhibitor MK-791 at 6-hr intervals by intravenous bolus infusion through the anterior marginal ear veins. Immediately before, and at 0.5, 1, 2, 4, and 6 h after the third dose of antibiotic, samples were obtained by direct aspiration from the anterior chamber, vitreous cavity, and the anterior marginal ear veins. Approximately 2.5 ml of plasma, 0.2 ml of aqueous humor, and 0.5-0.8 ml of vitreous humor could be obtained per animal at each sampling. Aqueous and vitreous humor were aspirated only once per eye for each animal. No bloody samples were accepted for analysis. All samples were immediately stabilized in a 50% (vol/vol) ethylene glycol: 1 M morpholinoethane-sulfonate buffer, pH 6.0 (MES) in equal proportions (vol/vol), quick frozen in dry ice and acetone, and stored at –80°C until ready for assay. Animals were killed by intracardiac injection of sodium pentobarbital.

Antibiotic preparations: N-formimidoyl thienamycin (MK-787) powder (Merck Sharp & Dohme Research Laboratories, Rahway, NJ) was dissolved in sterile normal saline and injected via an anterior marginal ear vein at the dosage of 40 mg/kg by bolus infusion. Antibiotic solutions containing either MK-
alone or with MK-787/MK-791 yielded identical re-
tained at 80°C. The completely dissolved MK-787/
buffer. Repeated measurements using spiked samples
bioassay of MK-787. Therefore, standards for both
ocular fluids and plasma were prepared in MES
formimidoyl thienamycin (MK-787) after third q6h
dosage at 40 mg/kg administered intravenously
without renal enzyme inhibitor (MK-791)

<table>
<thead>
<tr>
<th>No. of samples</th>
<th>Time (hrs)</th>
<th>Pre</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>5</td>
<td>0</td>
<td>15.12</td>
<td>1.98</td>
<td>0.28</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>± 1.31</td>
<td>± 0.14</td>
<td>± 0.04</td>
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</tr>
<tr>
<td>Aqueous</td>
<td>5</td>
<td>0</td>
<td>3.10</td>
<td>6.96</td>
<td>0.25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>± 0.34</td>
<td>± 1.70</td>
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</tr>
<tr>
<td>Vitreous</td>
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<td>0.17</td>
<td>0.15</td>
<td>0.06</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>± 0.03</td>
<td>± 0.06</td>
<td>± 0.03</td>
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</tr>
</tbody>
</table>

Table 1. Concentrations (mean ± SE, µg/ml) of N-
formimidoyl thienamycin (MK-787) after third q6h
dosage at 40 mg/kg administered intravenously
without renal enzyme inhibitor (MK-791)

Pharmacokinetic determinations: The concentra-
tions of MK-787 in plasma and ocular fluids mea-
sured after the third intravenous dose were fitted to
a regression line by the method of least mean squares.
The half-life (t½) of this agent in plasma or ocular fluids was calculated by dividing ln2 by the elimi-
nation constant k, where k = 2.3 × the slope of the
regression line. The area-under-the concentration vs
time curve (AUC) for plasma and aqueous as well as
vitreous humor were obtained by successive trape-
zoidal approximation for time = 0 to time = ∞.

Results. The intracoar and plasma concentra-
tions of MK-787 attained without and with co-ad-
ministration of the renal enzyme inhibitor MK-791
are shown in Tables 1 and Table 2, respectively. A
mean peak plasma concentration of 15.12 µg/ml
without, and 20.4 µg/ml with, co-administration of
MK-791 were observed at 30 min after infusion of
the third dose. Without MK-791, the plasma half-life
was 0.27 hr, and the AUC value was 9.45 µg hr/ml.
With co-administration of MK-791, the plasma half-
life was 0.45 hr, and the AUC value was 14.2 µg hr/
ml. Mean plasma concentrations of MK-787 admin-
istered with MK-791 were significantly higher than
corresponding concentrations without MK-791 at 0.5
and 1 hr after infusion (P < 0.05, Student's t-test)
(Table 2).

The mean peak aqueous concentrations of MK-
787 in these animals were 6.96 µg/ml without co-
administration of MK-791, and 8.66 µg/ml with co-
administration of MK-791, and in both instances,
mean peak aqueous concentrations were delayed un-
til 1 hr after drug administration, confirming a barrier
in intraocular penetration. Mean aqueous concentra-
tions of MK-787 co-administered with MK-791 were
significantly higher than corresponding concentra-
tions without MK-791 at 0.5 and 2 hrs after infusion
(P < 0.05) (Table 2). Based on the ratio of aqueous
AUC to serum AUC (X100), the penetration of MK-
787 into aqueous humor was estimated at 76%, both
when administered alone, and when co-administered
with MK-791.

Vitreous penetration by MK-787 in the normal
rabbit was relatively poor and was not significantly

Table 2. Concentrations (mean ± SE, µg/ml) of N-formimidoyl thienamycin (MK-787) after third q6h
dosage at 40 mg/kg co-administered intravenously with renal enzyme inhibitor (MK-791)

<table>
<thead>
<tr>
<th>No. of samples</th>
<th>Time (hrs)</th>
<th>Pre</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>5</td>
<td>0</td>
<td>20.40</td>
<td>1.90*</td>
<td>3.66</td>
<td>0.43*</td>
<td>0.76</td>
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<tr>
<td>Aqueous</td>
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<td>4.82</td>
<td>0.38*</td>
<td>8.66</td>
<td>2.01</td>
<td>1.22</td>
</tr>
<tr>
<td>Vitreous</td>
<td>5</td>
<td>0</td>
<td>0.30</td>
<td>0.13</td>
<td>0.13</td>
<td>0.03</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Significantly higher than levels achieved without renal enzyme inhibitor (P < 0.05, Student's t-test).
affected by co-administration with MK-791 (2.9% and 2.3%, respectively). Nevertheless, mean concentrations of 0.1–0.3 μg/ml was attained. MK-787 was cleared from all compartments at 4 hrs postinfusion without the enzyme inhibitor and at 6 hrs postinfusion when co-administered with MK-791.

Discussion. Although the intraocular penetration of MK-787 is comparable to other β-lactams and is relatively poor in vitreous humor even after co-administration with MK-791, the concentrations obtained in the uninflamed eye, coupled with the exquisite activity of this antibiotic, make its use in the management of endophthalmitis potentially important. In the present study, mean vitreous concentrations attained (0.1–0.3 μg/ml) exceeded or approached the MIC90 (minimal antibiotic concentration inhibiting 90% of strains) for most sensitive bacteria including Staphylococcus aureus (0.1 μg/ml), Staphylococcus epidermidis (0.2 μg/ml), Streptococcus pyogenes (0.1 μg/ml), Streptococcus pneumoniae (0.01 μg/ml), Hemophilus influenzae (0.1 μg/ml), and Escherichia coli (0.1 μg/ml). Other gram-negative bacilli potentially important in bacterial endophthalmitis such as Pseudomonas aeruginosa (MIC90 12.5 μg/ml), Serratia marcescens (6.3 μg/ml), and Proteus mirabilis (1.6 μg/ml) are much less susceptible. It is conceivable, however, that intraocular penetration of MK-787 in the inflamed eye may be considerably higher. As shown by Barza, inflammatory mediators in the inflamed eye may lower the blood retinal barrier and allow for greater antibiotic penetration.

Co-administration of the renal enzyme inhibitor MK-791, known to have no antibiotic effect by itself, resulted in higher and more prolonged plasma and aqueous levels of MK-787. This most likely reflects the greater systemic bioavailability, as evidenced by the increased plasma half-life of MK-787 due to inhibition of renal metabolism and inactivation of the drug by MK-791. Our data do not suggest presence of the inactivating dipeptidase enzyme within intraocular compartments, but do suggest that the renal metabolism of MK-787 in the rabbit may be similar to that reported in chimpanzees and man.

The observation that MK-787 penetrates uninflamed intraocular fluids at levels above the MIC90 for most sensitive bacteria, and that its intraocular concentrations may be further augmented by the co-administration of MK-791, strongly suggest its clinical potential for the treatment of bacterial endophthalmitis. Further studies of the clinical efficacy of this new β-lactam in experimental infective endophthalmitis are clearly indicated.

Key words: endophthalmitis, ocular pharmacokinetics, N-formimidoyl thienamycin, dipeptidase inhibitor, MK-787, MK-791, vitreous humor, aqueous humor

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