Comparison of Intravitreal Ceftazidime and Meropenem in Treatment of Experimental Pseudomonal Posttraumatic Endophthalmitis in a Rabbit Model

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ABSTRACT

We developed an experimental animal model of posttraumatic pseudomonal endophthalmitis in rabbits to compare the relative efficacy of intravitreal ceftazidime and 3 doses of meropenem.

A penetrating eye injury was made in the right eyes of 40 rabbits and 0.1 mL of 10^4 colony-forming units (cfu/mL) of *Pseudomonas aeruginosa* ATCC 27853 was injected into the midvitreous body the rabbits. Most animals showed the first signs of endophthalmitis 4 to 5 hours after the inoculation. The animals were examined clinically at 2, 4, 12, and 22 hours after surgery using slit-lamp biomicroscopy and indirect ophthalmoscopy.

Rabbits were divided into 5 treatment groups of 8 rabbits; Group 1 received 0.1 mL intravitreal ceftazidime injection (22.5g/L); Group 2, 0.1 mL intravitreal injection of meropenem (0.5g/L); Group 3, 0.1 mL intravitreal injection of meropenem (1g/L); Group 4, 0.1 mL intravitreal injection of meropenem (2g/L); and Group 5, 0.1 mL intravitreal injection of normal saline. At 2 and 24 hours post treatment, two 100 µL vitreous samples were taken for high performance liquid chromatography analysis and colony counting in the culture.

Vitreous levels of ceftazidime were above the 3 doses of meropenem at 2 hours post treatment. At 2 hours post treatment, there was no significant difference between the 3 different doses of meropenem ($P< 0.01$). There was no significant difference between vitreous levels of ceftazidime and the 3 doses of

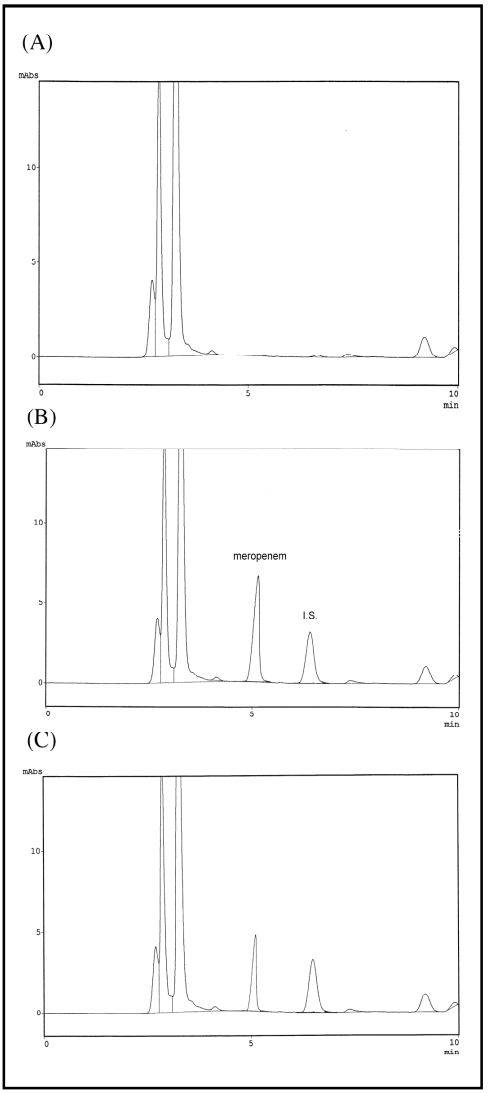

Figure 1. (A) Chromatograms obtained after direct injection of a drug-free aqueous humor sample, (B) meropenem and internal standard added aqueous humor sample, and (C) the aqueous humor sample from a rabbit after 2 hours of intravitreal administration of meropenem with UV detection at 298 nm.

meropenem at 24 hours (P>0.05). Culture results showed no difference between treatment with ceftazidime and 3 doses of meropenem. Clinical and bacteriological examinations revealed significantly less inflammation in rabbits treated with ceftazidime and meropenem than saline control groups. Intravitreal antibiotic treatment both with ceftazidime and meropenem appears effective.

INTRODUCTION

Endophthalmitis complicating penetrating ocular injury generally has a worse visual prognosis than does postsurgical endophthalmitis. It is now agreed that the most effective route of antibiotic administration for the treatment of endophthalmitis is intravitreal injection.[1-4]

Endophthalmitis is caused by gram-positive bacteria, gram-negative bacteria, and anaerobic organisms.[5-9] Gram-negative bacteria are more prevalent. Among gram-negative bacteria causing endophthalmitis *Pseudomonas aeruginosa* was the most isolated pathogen and can disrupt the vision much despite intravitreal antibiotic treatment and vitrectomy. The virulence of *P. aeruginosa* is believed to be multifactorial including toxin-mediated effects, antiphagocytic properties, and beta-lactamase production. These properties can result in severe infections, which are often resistant to treatment.[7,10]

Ceftazidime is a third-generation cephalosporin with broad spectrum activity and particularly good coverage of gram-negative bacteria. Furthermore, its antipseuodomonal activity gives it an advantage over other third-generation cephalosporins.[7,11,12,13]

Meropenem is a carbapenem antibiotic with a broad antibacterial spectrum of activity. Its main route of elimination is through the kidneys, with 63% of the drug excreted unchanged in the urine.[14] Following intravenous administration to rats and dogs, radioactive material was very rapidly and widely distributed in the tissues, with highest levels detected in the kidney and other highly perfused organs. Concentration in all tissues decreased rapidly with time.[15]

In this study, we developed an experimental animal model of posttraumatic pseudomonal endophthalmitis in rabbits to compare the relative efficacy of intravitreal ceftazidime and 3 doses of meropenem. Vitreous fluid concentration was determined by high performance liquid cromatography (HPLC) and colony counting in the culture after intravenous ceftazidime and 3 doses mereponem, and compared with control groups.

MATERIAL AND METHODS

Natural History Pilot Study

A pilot study was performed to develop a reproducible model of posttraumatic endophthalmitis. Forty New Zealand White rabbits, weighing 2.5 to 3 kg were used in this study. All animals were treated according to the provisions of the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. Forty rabbits were anesthetized with intramuscular injection of a 50:50 mixture of ketamine hydrochloride (30 mg/kg) and xylazine hydrochloride (10 mg/kg). To further reduce discomfort, the eyes were anesthetized using 1 to 2 drops of oxybuprocaine (Benoxinate).

In the right eyes of 40 rabbits, a penetrating eye injury was made, by a modified method described by Alfaro et al.[9] After a 360˚ peritomy, a number 11 blade was used to made a 7-mm laceration 2.5 mm posterior to the limbus. Prolapsing vitreous was excised and the wound closed with interrupted 6-0 vicryl sutures, using a microsurgical technique. The vitreous cavity was then inoculated with 0.1mL of 10^4 colony-forming units (cfu/mL) of *P. aeruginosa* ATCC 27853 into the midvitreous body. Pupils were dilated with cyclopentolate 1% and phenylephrine 10%.

A moderately severe posttraumatic endophthalmitis developed in animals that received an inoculum of *P. aeruginosa* after eye injury. The first signs of endophthalmitis were visible in most animals 4 to 5 hours after the inoculation of *P. aeruginosa* ATCC 27853.

The animals were examined clinically at 2, 4, 12, and 22 hours after surgery using slit-lamp biomicroscopy and indirect ophthalmoscopy. Inflammation in the anterior chamber was graded using the conventional 1+ to 4+ grading scale. Inflammation of the vitreous cavity was assessed and graded in the standardized manner described by Ozturk et al,[1] 0 = vitreous clear; 1 = mild vitreal haze, good red reflex; 2 = moderate vitreous haze, partial red reflex; and 3 = total opacification of vitreous cavity, no red color in spectrum.

At each examination, animals were assessed 4 times, and an average of the 4 observations was used as the final grade.

After this pilot study, 40 other rabbits were used to determine the effect of ceftazidime and meropenem on the development of posttraumatic endophthalmitis.

Treatment of Experimental Pseudomanal Endophthalmitis

After 14 hours animals were divided into 5 treatment groups. We adjusted the 3 different doses of meropenem based on antibiotic concentrations, which were given into the vitreous, since endophthalmitis treatment should be at least 10 folds higher than MIC. We chose this amount because of proven studies with ceftazidime.[11,12,13]

Eight animals received 0.1 mL intravitreal injection of ceftazidime (22.5g/L), 8 animals received 0.1 mL intravitreal injection of meropenem (0.5g/L), 8 animals received 0.1 mL intravitreal injection of meropenem (1g/L), 8 animals received 0.1 mL intravitreal injection of meropenem (2g/L), and 8 animals received 0.1 mL intravitreal injection of normal saline.

Table 1. Histopathological Grading of Endophthalmitis

Anatomic Structure	Grade	Histopathological Finding
Cornea	0	Normal
	1	Partial-thickness infiltration
	2	Segmental full-thickness infiltration
	3	Total full-thickness infiltration
Anterior chamber	0	Normal
	1	Partially filled with fibrin without infiltrate
	2	Partially filled with fibrin and infiltrate
	3	Completely filled with infiltrate
Vitreus	0	Clear
	1	Inflammatory cells without focal abscess
	2	Partially filled with abscess of infiltrate
	3	Completely filled with infiltrate
Retina	0	Normal
	1	Partially infiltrated
	2	Totally infiltrated and partially necrotic, normal retina
	3	Complete necrosis of all retinal layers

Two samples of 100 µL were taken 2 and 24 hours after injection of ceftazidime and three doses meropenem. One of them was frozen at -20˚C until analysis for high-pressure liquid chromatography analysis and the other 100 µL was used for colony counting in the culture.

Control animals that received mereponem in the vitreous cavity developed signs of inflammation.

Vitreous Culture

From each treatment and control group, 100 µL vitreal samples were obtained and cultured on blood and chocolate culture mediums using standard culture techniques. After 18 hours incubation at 35˚C, colony counting was performed and recorded.

Histopathological Examination

Twenty four hours after inoculation, the rabbits were killed with an overdose of sodium pentobarbital and the right eye of each animal was enucleated and fixed with a 10% formalin solution to await histopathologic examination. Following routine tissue processing, 2 microscopic sections (through the largest dimension demonstrating all the anatomical structures) were prepared and stained with hematoxylene and eosin. The sections were examined under light microscope (Leica, DMLS) and graded by a blinded pathologist according to the scheme developed by Alfaro et al[10] (Table 1). Clinical and histopathologic scores were analyzed with the Wilcoxon rank sum test (P<0.5).

Reagent and Chemicals

Ceftazidime and Meropenem Assay

Meropenem and ceftazidime were kindly supplied by Zeneca (Istanbul, Turkey) and I.E.Ulugay (Istanbul, Turkey), respectively. Analytical-grade potassium dihydrogen orthophospate and hydrochloric acid and HPLC-grade methanol were purchased from Merck (Darmstadt, Germany). The water was doubly distilled. The filters (0.45 µm, 13 mm for mobile phase filtration, 0.2 µm,

4 mm for sample filtration) were purchased from Waters (Milford, Mass).

Instrumentation

The HPLC analysis was carried out on a system consisted of an LC-10AT solvent-delivery system equipped with an injection valve with a 20 µL loop (Shimadzu, Tokyo, Japan). Integration and system parameter were controlled by CBM-10A software system (Shimadzu). Separation was performed on an Inertsil ODS C18 column (5 µm, 250 mm x 4.6 mm) fitted with a guard column (20 mmX3.9mm, Waters) packed with the same material. The column eluates were monitored by a Shimadzu SPD 10A UV-Visible detector at 298 nm for meropenem and 256 nm for ceftazidime. The mobile phase consisted of a mixture of phosphate buffer pH 4.0-methanol (80:20, v/v). The flow-rate was 1.0 mL/min. All assays were performed at 25˚C. An oven was used for relevant temperature.

Mobile Phase

The mobile phase consisted of a mixture of methanol-phosphate buffer pH 4.0 (20:80, v/v, for meropenem assay, 15:85, v/v, for ceftazidime assay). The phosphate buffer pH 4.0 was prepared by dissolving 1.361 g of potassium dihydrogen orthophosphate in 75 mL of water. The pH was adjusted to 4.0 with 0.1 M hydrochloric acid and the volume was made up to 100 mL with water.

The mobile phase was filtered through a millipore membrane filter and deaerated with helium gas. The samples were eluted isocratically at a mobile phase flow-rate 1.0 mL/min for meropenem, 0.8 mL/min for ceftazidime.

Preparation of Standard Solutions

Stock solutions of meropenem and ceftazidime were prepared by dissolving an accurately weighed amount of drugs in water (1 mg/mL). These solutions were diluted with water to make standard solutions of 10 µg/ml. The standard solutions of meropenem in rabbit vitreous samples were prepared by spiking vitreous samples with the appropriate volume of stock solution, creating final meropenem vitreous sample concentrations of 0.1, 0.25, 0.50, 1, 2, and 5 µg/ml. The standard solutions of ceftazidime in rabbit vitreous samples were prepared similarly, creating final ceftazidime vitreous sample concentrations of 0.25, 0.50, 1, 1.25, 2.5, and 5 µg/mL.

Ceftazidime was used as internal standard for meropenem assay. Similarly, meropenem was used as internal standard for ceftazidime assay. The internal standard solutions were prepared by dissolving 1 mg substance in 10 mL of water.

The stock solutions were stored at 4˚C and were stable for a month.

Sample Preparation for HPLC System

Vitreous samples of 50 µL were transferred to the vial and mixed with 10 µL internal standard and diluted with 100 µL of water. The vials were capped and the contents were mixed by vortex mixer. After filtration, 20 µL of the solution was injected onto the HPLC system.

Determination of Standard Curve and Assay Validation

The peak-area ratio of meropenem and ceftazidime to internal standard versus drug concentrations were plotted at the calibration curves, and the equations of the line were determined using least-square method. Assay reproducibilities were determined at 2 different concentrations (0.5 and 2 µg/mL for meropenem, 1 and 2.5 µg/mL for ceftazidime) within one day and on 6 consecutive days.

Results and Discussion

Figure 1 shows chromatograms

obtained after direct injection of a drug-free vitreous samples (1A), meropenem and internal standard added vitreous sample (1B) and the vitreous sample from a rabbit after 2 hours of intravitreal administration of meropenem (1C) with UV detection at 298 nm.

There was not any interfering peak in the blank vitreous sample chromatogram. The retention times of mereponem and internal standard (ceftazidime) were 5.1 and 6.3 minutes respectively, for the assay of meropenem.

The calibration curve was obtained by linear regression analysis of the peak-area ratios of meropenem to internal standard versus the concentration. The concentration range was 0.1 to 5 µg/mL (y = 0.684 □ + 0.0028; r = 0.9997) and internal standard was added at 5 µg for each 1 mL of assay. The mean recoveries (±SD) from vitreous samples were 101.58 (±3.0%) and 102.23 (±3.8%) at 0.5 and 2 µg/mL of meropenem (n=6), respectively. The within-day and day-to-day reproducibilities were determined for samples containing 0.5 and 2 µg/mL of meropenem (n=6). The relative standard deviations (RSD) and relative mean errors (RME) were between 1.31 to 4.21 % and 0.58 to 4.33 %, respectively.

For the assay of ceftazidime, the retention times of ceftazidime and internal standard (meropenem) were 13.7 and 9.7 minutes respectively. The concentration ranges for the calibration curve were 0.25 to 10 µg/mL (y = 0.3002 □ + 0.0042; r = 0.9995) and an internal standard was added at 4 µg/mL to each sample. The mean recoveries (±SD) from vitreous samples were 101.37 (± 2.7%) and 103.83 (±2.8%) at 1 and 2.5 µg/mL of ceftazidime (n=6), respectively. The within-day and day-to-day reproducibilities were determined for samples containing 1 and 2.5 µg/mL of ceftazidime (n=6). The relative standard deviations (RSD) and relative mean errors (RME) were between 0.95 to 4.66 % and 0.44 to 3.98 %, respectively.

RESULTS

Natural History Pilot Study

A moderately severe posttraumatic endophthalmitis developed in approximately all of animals. Most animals showed the first signs of endophthalmitis 4 to 5 hours after the inoculation of *P. aeruginosa* ATCC 27853. Slit-lamp examination and indirect ophthalmoscopy, at 2, 4, 12 and 22 hours after surgery and inoculation, revealed only scant vitreous hemorrhage at the scleral laceration site. This was characterized by vitritis and retinitis.

Eye examination with the biomicroscope showed corneal edema in 10 (25%) rabbits at 2 hours and 14 (35%) rabbits at 4 hours post surgery. Examination of the anterior chamber showed 2+ cells, but hypopyon did not develop. Indirect ophthalmoscopy of clear corneas showed grade 2 to 3 vitreous reaction, which developed first at the site of inoculation. Over the ensuing examination, inflammation in the anterior chamber remained mild to moderate, ranging from 1+ to 2+, but the vitreous inflammation became increasingly severe over the ensuing 14 hours. This was visible peripherally through the vitreous haze. Corneal edema, hypopyon, and dense vitreous abscess were noted at 14 hours.

Fourteen rabbits (35%) were grade 0, 10 rabbits (25%) were grade 1, 13 rabbits (32.5%) were grade 2, and 3 rabbits (7.5%) were grade 3 according to the evaluation of the vitreous results at hours 2 and 4.

By 14 hours, visualization of the posterior pole was obscured in all rabbits.

All of the animals receiving 3 doses of intravitreal ceftazidime, 90% devel-

Table 2. Histopathological Grading Scores

Rabbit	Cornea					Anterior Chamber					Vitreous					Retina					Detachment					Periorbital inflammation				
	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V	I	II	III	IV	V
1	1	1	2	1	0	2	2	2	2	0	2	2	2	2	0	2	1	2	1	0	+	-	+	+	+	+	-	+	+	+
2	1	0	1	1	0	2	2	1	1	0	2	2	1	1	0	2	2	2	2	0	+	+	+	+	+	+	+	+	+	+
3	1	1	2	1	0	1	2	2	1	0	0	2	3	3	0	0	2	3	2	0	+	-	+	+	+	-	+	+	+	+
4	1	1	1	1	0	2	2	2	2	0	2	2	3	3	0	2	1	3	2	0	+	-	+	+	+	-	+	+	+	+
5	1	1	0	1	0	1	2	0	2	0	1	2	0	2	0	2	3	1	2	0	+	+	+	+	+	+	+	-	-	+
6	1	1	1	1	0	2	2	0	2	0	2	1	1	3	0	2	2	1	2	0	+	+	+	+	+	+	+	+	+	+
7	1	1	2	2	0	2	1	1	3	0	3	2	2	3	0	2	2	2	2	0	+	+	+	+	+	+	+	+	+	+
8	1	1	1	0	0	2	2	0	0	0	2	2	1	1	0	3	2	1	2	0	+	+	+	+	+	+	+	+	+	+

Table 3. Total Scores of Histopathologic Examinations

Rabbit no.	1	2	3	4	5	6	7	8	AIS*
Group I	7	7	2	7	5	7	8	8	6.37
Group II	6	6	7	6	8	6	6	7	6.5
Group III	8	5	10	9	1	3	7	3	5.75
Group IV	6	5	7	8	7	8	10	3	6.63
Group V	0	0	0	0	0	0	0	0	0

*AIS indicates average inflammatory score

Table 4. Statistical Analysis of the Second Hour Effects of the Antibiotics

Groups	N	Median	Standard Deviation	Standard Error
1. Antibiotic	8	1.3717	0.3484	0.1317
2. Antibiotic	8	0.1363	0.2513	0.0961
3. Antibiotic	7	0.08153	0.0709	0.0289
4. Antibiotic	8	0.2103	0.1853	0.0700
Total	31	0.4495	0.5722	0.1101

oped grade 2 vitritis, characterized by blurring of the raphe; in one of these rabbits, the vitritis progressed to grade 3 disease on the last day of examination. Vitreous reaction was concentrated in the area of intravitreous inoculum. All control animals developed grade 2 disease 24 hours after inoculation, which progressed to grade 3 disease, characterized by total obscuration of the fundus.

Funduscopic examinations of the right eye were performed in each experimental animal using slit-lamp examination and indirect ophthalmoscopy, 18 hours after surgery and inoculation. Indirect examination could not be done in one eye because of hypopyon and in a second eye that demonstrated severe corneal opacification. Anterior segment findings in eyes treated with intravitreal antibiotics were minimal. All saline control eyes revealed severe anterior chamber opacification and a dense vitritis, which obscured the retina. In cases where posterior segment examination was possible, most eyes demonstrated varying degrees of vitreal and retinal inflammation.

Eyes treated with ceftazidime and meropenem closely resembled eyes in

Table 5. ANOVA Results of the Second Hour Effects of the Antibiotics

	Mean of fum square	Standard Deviation	Mean of square	F	Sig.
Intergroups valve	7.173	3	2.391	41.08	.000
In the group	1.338	23	0.0582		
Total	8.511	26			

Table 6. Statistics of the 24 Hour Effects of the Antibiotics

Groups	N	Median	Standard Deviation	Standard
1. Antibiotic	4	0.7925	0.0475	0.0335
2. Antibiotic	6	0.6790	0.6922	0.3461
3. Antibiotic	7	0.1792	0.1795	0.0803
4. Antibiotic	8	0.6254	0.2434	0.0861
Total	25	0.5368	0.4012	0.0920

Table 7. ANOVA Results of the 24 hour Effects of the Antibiotics

	Mean of fum square	Standard Deviation	Mean of square	F	Sig.
Intergroups value	0.914	3	0.305	2.304	.118
In the group	1.984	15	0.132		
Total	2.897	18			

the untreated natural history and saline control groups, demonstrating severe vitreal haze with no red reflex.

Histopathological Examination

Histopathological examination revealed different degrees of inflammatory infiltration of the anatomical structures of the eyes, predominantly by polymorphonuclear leucocytes, in the study group. The anterior chambers were filled with the infiltrate in most of the cases and the vascularization of the iris was prominent. Vitreous abscesses were seen in almost all eyes. Detachment of the retinal layers, subretinal inflammatory infiltration, necrosis, and architectural loss were observed in some of the cases (Tables 2 and 3).

Statistical Analysis

One-way Anova analysis of variance test was used for comparison of the drug concentrations among groups at each sampling time, at 2 and 24 hours (Tables 4, 5, 6, and 7).

Treatment Group

Vitreous levels of ceftazidime and meropenem were found above MIC90 of *P. aeruginosa* at hours 2 and 24. In the vitreous sample of control group, the bacteria count was $10^{7\text{-}8}$ cfu/mL.

Vitreous levels of ceftazidime were above the 3 doses of meropenem at hour 2. At the hour 2, there was no significant difference between the 3 different doses of meropenem (F= 41.08, $P<$ 0.01). There was no significant difference between vitreous levels of ceftazidime and the 3 doses of meropenem at 24 hours (F= 2,304, $P>0.05$). Culture results showed no difference between treatment with ceftazidime and 3 doses of meropenem. Clinical and bacteriological examinations revealed signifi-

cantly less inflammation in rabbits treated with ceftazidime and meropenem than saline control groups.

DISCUSSION

Ceftazidime has been proven to be efficacious in laboratory and animal studies. A recent study reported that ceftazidime produced no detectable damage to the primate eye with intravitreous doses of 2.25 mg.[11,12,13]

Ceftazidime using intravenous, intravitreal, and subconjonctival routes against endophthalmitis with either gram-positive or gram-negative organisms has been studied extensively. The intravitreal route and gram-negative organisms, particularly *P. aeruginosa*, were found the most effective among them.[16,17,18]

In the Axelrod et al[19] study, 2 g ceftazidime was given intravenously to 25 patients before cataract surgery. The peak vitreous sample level was found equivalent to or slightly higher than the MIC_{90} for *P. aeruginosa.* In the Schauersberger et al[20] study, 2 g meropenem was given intavenously to patients undergoing cataract surgery, afterwards vitreous levels were measured. The results were over MIC_{90} both for gram-positive and gram-negative bacteria, including *P. aeruginosa* and *Enterobacteriaceae*.

Intravitreal aminoglycoside antibiotics have been considered the drugs of choice for gram-negative endophthalmitis, including that caused by *P. aeruginosa*. Current controversy exists, however, over the routine use of intraocular aminoglycosides for treating endophthalmitis because of the potential retinal toxic effects of these agents. Other agents with more favorable toxicity profiles such as ceftazidime, imipenem, cefazolin, and fluoroquinolone antibiotics have been suggested as alternatives to aminoglycosides for intraocular injection.[5,7,9-13,21]

In the Alfaro et al[10] study, intravitreal antibiotic treatment with imipenem or amikacin appears to limit intraocular inflammation and retinal tissue damage when given early in the course of posttraumatic pseudomonal endophthalmitis. Results with ceftazidime are less conclusive in this study.

In our study, we found no major difference reflected in either the culture or treatment results. It is clear that advancement in the treatment of endophthalmitis has not yet reached an endpoint, and further experimental studies of intravitreal antibiotic efficacy and clinical trials are necessary. Imipenem appears to be a promising nontoxic alternative to aminoglycosides in the treatment of gram-negative endophthalmitis**.** In the literature, there were studies using imipenem for the treatment of endophthalmitis.

In our study, the comparison of treatment results of ceftazidime and 3 doses of meropenem were not statistically different.

CONCLUSION

With regard to its broad spectrum, high antibacterial activity, and good penetration in to ocular fluids, meropenem seems to be an alternative to currently used systemic drugs. Its usefulness in perioperative prophlaxis, as initial therapy after perforating or penetrating injuries, or in the therapy of bacterial endophthalmitis has yet to be proved.

Intravitreal antibiotic treatment both with ceftazidime and meropenem appears effective.

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