Comparison of efficiency of intravitreal ceftazidime and intravitreal cefepime in the treatment of experimental *Pseudomonas aeruginosa* endophthalmitis

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In this study, we evaluated the efficiency of cefepime in the treatment of experimental *Pseudomonas aeruginosa* endophthalmitis. We compared the findings with the standard dose of ceftazidime (1 mg/0.1 ml). Thirty-six New-Zealand White rabbits were divided into 6 equal groups and were treated with different methods (Group 1 = sham, Group 2 = 0.5 mg/0.1 ml cefepime, Group 3 = 1 mg/0.1 ml cefepime, Group 4 = 2 mg/0.1 ml cefepime, Group 5 = 1 mg/0.1 ml ceftazidime, Group 6 = control). The eyes of rabbits in each group were examined clinically on 1st, 3rd, and 6th day of the experiment. At 6th day, 0.1 ml vitreous humor aspirates were obtained and plated for quantification on the blood agar and the results were expressed as colony-forming unit/ml. Subsequently, the eyeballs were enucleated and the histopathological evaluation was performed. Our findings denoted beneficial effects of cefepime in treatment groups (especially, in Groups 3 and 4). Intravitreal cefepime may be an alternative drug in the treatment of *P. aeruginosa* endophthalmitis.

Key words: Cefepime, ceftazidime, endophthalmitis, *Pseudomonas aeruginosa*

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A majority of the episodes of endophthalmitis caused by gram-negative bacteria are due to *Pseudomonas aeruginosa* and members of Enterobacteriaceae.[1] *P. aeruginosa* endophthalmitis is typically a rapidly progressive, sight-threatening condition that demands immediate therapeutic intervention.[2] The ability of P. aeruginosa to survive on minimal nutritional requirements and to tolerate a variety of physical conditions has allowed this organism to persist in both community and hospital settings.[3]

The aim of this study was to compare the efficiency of standard dose intra-vitreal ceftazidime and different doses of intra-vitreal cefepime in the treatment of experimental *P. aeruginosa* endophthalmitis.

Materials and Methods

All the animal-related procedures were complied with The Association for Research in Vision and Opthamology (ARVO) Statement for the use of animals in ophthalmic and vision research. The study was approved by Fırat University Animal Care and Use Committee. *P. aeruginosa* American Type Culture Collection 27853 was used to generate endophthalmitis. Thirty-six healthy New-Zealand White rabbits weighing 2500-3000 g were divided into 6 equal groups. The right eyes of rabbits in Group 1 to Group 5 received 2×10^4 colony-forming unit (CFU)/0.1 ml intravitreal injections of *P. aeruginosa* suspension. Group 6 was used as control and received intravitreal 0.1 ml sterile physiological saline. Rabbits in Group 2 to Group 5 were treated with intravitreal antibiotics (Group 2 = 0.5 mg/0.1 ml cefepime, Group 3 = 1 mg/0.1 ml cefepime, Group 4 = 2 mg/0.1 ml cefepime, Group 5 = 1 mg/0.1 ml ceftazidime). No treatment was given to rabbits in Group 1. The antibiotics were injected into the vitreous cavity by using a 30-gauge needle attached to a tuberculin syringe. The eyes of rabbits in each group were examined clinically on 1st, 3rd, and 6th day of the experiment. Severity of endophthalmitis was graded clinically by using a scoring system that previously reported by Pleyer *et al*.[4] At 6th day, 0.1 ml vitreous humor aspirates were obtained and plated for quantification on blood agar and the results were expressed as CFU/ml. Subsequently, the eyeballs

were enucleated and the histopathological evaluation was performed. Histopathological findings were scored with a scale that previously described by Meredith and associates.[5]

Statistical analysis was performed with the SPSS version 15 to determine the differences between the three treatment groups. The Wilcoxon test, Mann-Whitney U test, and Kruskal-Wallis test were used in the statistical analysis as indicated. *P* values smaller than 0.05 were considered statistically significant.

Results

The mean and the standard deviation of clinical scores in 1st, 3rd and 6th day after inoculation in groups are presented in Table 1. In 3rd day, there was no clinical difference between Group 1 and Group 2, but in 6th day a marked decline was noted in the clinical inflammatory findings in all treatment groups when compared with Group 1.

Mean and standard deviation of CFU/ml values in groups are given in Table 1. Group 1 had significantly more CFU/ml when compared with the treatment groups. There was no statistically significant differences in mean CFU/ml values between treatment groups (Group 2 to Group 5), but the mean CFU/ml values of eyes in these groups and in Group 1 were significantly higher when compared with uninfected controls.

The mean and the standard deviation of the histopathological scores in groups are presented in Table 1. Histopathological examination in Group 1 and in Group 2 denoted severe inflammation in the vitreous cavity and total destruction of the retinal architecture [Figs. 1-3]. Histopathological findings were similar in Group 3, 4, and 5 [Fig. 4].

Discussion

Available data suggest that the cefepime may have advantages over ceftazidime owing to a broader spectrum of activity and reduced potential for development of bacterial resistance.[6] Compared with ceftazidime, cefepime has enhanced activity *in vitro* against Gram positive bacteria, including meticillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae*.[7] Cefepime has better activity against gram-negative bacteria that produce extended spectrum β-lactamase and has broadened antipseudomonal activity than the ceftazidime.[6] Jay and Shockley delineated the dose-and time-dependent retinal toxicity of cefepime using electroretinography in pigmented rabbit eyes. Electroretinographic patterns at 1st and 2nd weeks indicated a toxic response to 20 mg of cefepime. B-waves were normal at 1st and 2nd weeks for rabbits receiving doses of 0.5 mg

Table 1: The mean and the standard deviation of clinical, histopathological and culture (CFU/ml) results in groups

Groups	Clinical results			Histopathological results	Culture results
	1st day	3rd day	6th day		
Group 1	10.16±0.7	10.83±0.4	11.50±0.5	15.66±1.0	$1\times10^{8}\pm2\times10^{8}$
Group 2	8.33±2.3	9.16±2.2	7.00±2.7[a]	10.40±5.0	$4\times10^{4}\pm5\times10^{4}$[c]
Group 3	7.83±2.9	8.00±2.6[a]	4.83±2.7[a]	6.66±3.8[b]	$3\times10^{3}\pm4\times10^{3}$[c]
Group 4	8.00±2.6	7.16±2.1[a]	4.00±2.2[a]	7.50±4.2[b]	$2\times10^{3}\pm3\times10^{3}$[c]
Group 5	9.50±1.8	7.83±2.3[a]	4.50±2.1[a]	6.66±4.3[b]	$3\times10^{3}\pm5\times10^{3}$[c]
Group 6	0.00±0.0[a]	0.00±0.0[a]	0.00±0.0[a]	0.00±0.0[b]	No growth[c]

CFU: Colony-forming unit, [a]Clinically significant when compared with Group 1 (*P*<0.05), [b]Histopathologically significant when compared with Group 1 (*P*<0.05), [c]Microbiological culture result is statistically significant when compared with Group 1 (*P*<0.05)

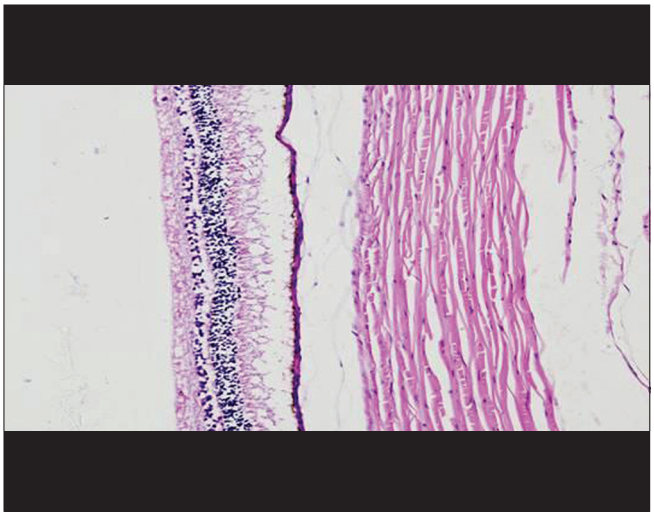

Figure 1: The view of normal retinal architecture in Group 6 (control group) (H and E, ×100)

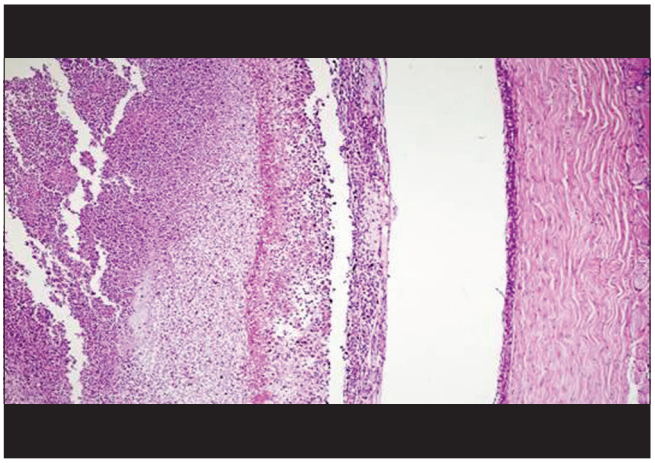

Figure 2: Severe exudation and abscess formation in the vitreous cavity, dense inflammation in retina and total destruction of the retinal architecture and total retinal detachment is seen in one eye in Group 1 (untreated infected group) (H and E, ×100)

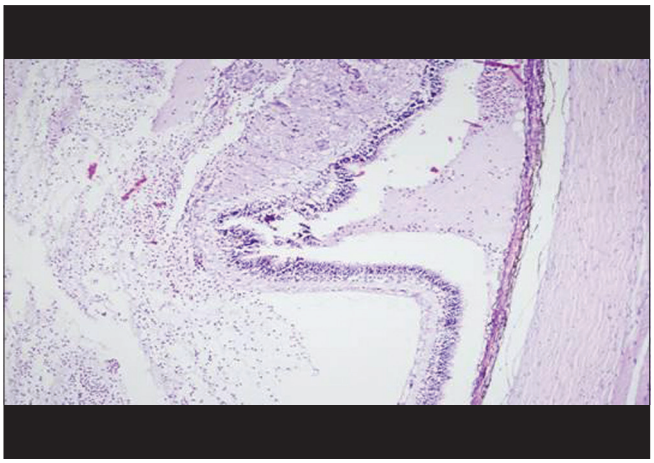

Figure 3: Abscess formation in the vitreous cavity, dense inflammation in retina and diffuse retinal necrosis and retinal detachment is seen in an eye in Group 2 (0.5 mg/ml cefepime) (H and E, ×100)

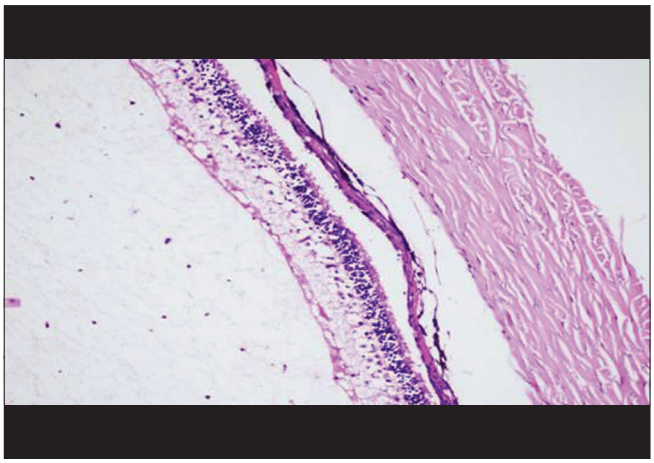

Figure 4: Preservation of retinal architecture, minimal neutrophil infiltration, and minimal exudation in vitreous cavity is seen in one eye in Group 3 (1 mg/ml cefepime) (H and E, ×100)

to 10 mg. Pharmacokinetic analysis after single intra-vitreal injection of 1 mg of cefepime disclosed the following vitreous fluid levels (μg/ml): 645 at O h, 431 at 8 h, 235 at 24 h, and 23 at 72 h. Peak aqueous humor levels (56 μg/ml) were observed at 8 h after injection.[8]

The evaluation of clinical results in this study demonstrated that in 3rd day after inoculation there was no difference between Group 1 and Group 2, but in 6th day, a marked decline was noted in the clinical inflammatory findings in all treatment groups when compared with Group 1. These findings suggest that 0.5 mg/0.1 ml intravitreal cefepime was not sufficient to clinically control the *P. aeruginosa* endophthalmitis. Bacterial culture results showed us there was no statistically significant difference in mean CFUs/ml values between the treatment groups, but in Group 4 (2 mg/0.1 ml cefepime) the mean CFU/ml value was the least. Histopathological examination in Group 1 and in Group 2 denoted severe exudation and abscess formation in the vitreous cavity, dense inflammation in the retina and total destruction of the retinal architecture and partial or total retinal detachment. These results imply that 0.5 mg/0.1 ml cefepime was not satisfactory for preserving of normal retinal architecture.

In summary, intravitreal cefepime may be an alternative drug in the treatment of *P. aeruginosa* endophthalmitis. Clinical and the histopathological results in our study indicate that 0.5 mg/ml cefepime is not satisfactory in the treatment of *P. aeruginosa* endophthalmitis. Intra-vitreal 1 mg/0.1 ml cefepime is as effective as intra-vitreal 1 mg/0.1 ml ceftazidime. Although increasing the intra-vitreal cefepime dose beyond 1 mg/0.1 ml provides additional benefits, this is not statistically significant. Hypothetically, taking into consideration the broad spectrum and lower resistance rates of cefepime, it may be an alternative drug in the treatment of endophthalmitis caused by other bacteria. Further, *in vivo* and *in vitro* studies need to be carried out to more accurately assess this subject.

References

1. Satpathy G, Patnayak D, Titiyal JS, Nayak N, Tandon R, Sharma N, *et al*. Post-operative endophthalmitis: Antibiogram and genetic relatedness between *Pseudomonas aeruginosa* isolates from patients and phacoemulsifiers. Indian J Med Res 2010;131:571-7.
2. Chen KJ, Sun MH, Lai CC, Wu WC, Chen TL, Kuo YH, *et al*. Endophthalmitis caused by *Pseudomonas aeruginosa* in Taiwan. Retina 2011;31:1193-8.
3. Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: Clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 2009;22:582-610.
4. Pleyer U, Mondino BJ, Adamu SA, Pitchekian-Halabi H, Engstrom RE, Glasgow BJ. Immune response to Staphylococcus epidermidis-induced endophthalmitis in a rabbit model. Invest Ophthalmol Vis Sci 1992;33:2650-63.
5. Meredith TA, Trabelsi A, Miller MJ, Aguilar E, Wilson LA. Spontaneous sterilization in experimental Staphylococcus epidermidis endophthalmitis. Invest Ophthalmol Vis Sci 1990;31:181-6.
6. Roberts JA, Webb SA, Lipman J. Cefepime versus ceftazidime: Considerations for empirical use in critically ill patients. Int J Antimicrob Agents 2007;29:117-28.
7. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: A systematic review and meta-analysis. Lancet Infect Dis 2007;7:338-48.
8. Jay WM, Shockley RK. Toxicity and pharmacokinetics of cefepime (BMY-28142) following intravitreal injection in pigmented rabbit eyes. J Ocul Pharmacol 1988;4:345-9.

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