An In Vitro Study of Ceftazidime and Vancomycin Concentrations in Various Fluid Media: Implications for Use in Treating Endophthalmitis

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Purpose. To investigate the precipitation process of a mixture of vancomycin and ceftazidime by equilibrium dialysis and determine its subsequent effect on the level of free antibiotics for treatment of endophthalmitis.

Methods. Concentrations of vancomycin and ceftazidime in an equilibrium dialysis chamber were measured during the equilibrium process by high-performance liquid chromatography. Normal saline (NS), balanced salt solution (BSS), and vitreous were used separately as the medium of dialysis.

Results. Precipitation of ceftazidime occurred at 37°C but not at room temperature and did not affect the pH of the medium. It formed precipitate on its own or when mixed with vancomycin in all the three media of NS, BSS, and vitreous. More precipitation was formed if ceftazidime was initially prepared in BSS than in NS. After 168 hours in the dialysis chambers, ceftazidime prepared in NS precipitated to 54% of that in vitreous, compared with 88% if prepared in BSS. At 48 hours, ceftazidime prepared in NS decreased from an initial concentration of 137.5 to 73.4 μg/mL in vitreous medium and to 6.3 μg/mL if prepared in BSS. Precipitation of vancomycin was negligible.

Conclusions. Based on this in vitro investigation, ceftazidime precipitates in vitreous at body temperature, regardless of the presence of vancomycin. NS is preferred to BSS as a preparation medium for antibiotics for intravitreal injection, because the extent of ceftazidime precipitation is less. However, due to precipitation, the concentration of free ceftazidime in vitreous may not be sufficiently high for antibacterial activity against most common organisms. (*Invest Ophthalmol Vis Sci.* 2002;43: 1182–1188)

Infective endophthalmitis is a potentially blinding condition and remains a serious postoperative complication of such frequently performed eye surgeries as cataract extraction.[1–3] The infection can be due to a wide variety of bacterial strains, although *Staphylococcus* species are the cause in more than 50% of the cases. Intravitreal vancomycin is considered to be the treatment of choice for Gram-positive organisms. It is nontoxic in the recommended clinical dosage and is active against almost all Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*.[4–6] To combat infection by Gram-negative organisms, a combination of intravitreal vancomycin and aminoglycosides, such as amikacin or gentamicin, have been used commonly.[5,7,8] However, there has been increasing reported occurrence of macular infarction after intravitreal injection of aminoglycosides.[7] Substitution with other antibiotics has therefore been advocated.[8–10] Ceftazidime,[9] a cephalosporin with broad-spectrum antibacterial action, is now frequently administered together with vancomycin.[11] Its antibacterial action is as effective as that of the aminoglycosides and it poses low risk for macular infarction.[6,12] Physicochemical incompatibility of vancomycin and ceftazidime is known to lead to precipitation, but this combination has been a widely accepted treatment regimen for years, without clinical drawback.[10,13] It has been thought that precipitation can be avoided by using separate syringes to inject the two antibiotics.[8]

However, a recent report described the formation of whitish microprecipitates after the two drugs were injected into the eye intravitreally through separate syringes.[14] The precipitates were presumed to be formed by an amalgamation of the compounds. So far, there is no evidence as to whether the precipitation disrupts the therapeutic effects of the antibiotics, nor is it clear whether it is a consistent event. In view of the uncertainty of the nature of the precipitate and its possible effects on the bioavailability of the antibiotics, we investigate the precipitation process of a mixture of vancomycin and ceftazidime by equilibrium dialysis.

Methods

All experiments were conducted in duplicate, and the mean values taken as results. Vitreous was obtained from cadaveric donor eyes. The standard intravitreal dosage of vancomycin (Abbott, Chicago, IL) and ceftazidime (Fortum; Glaxo Wellcome, Greenford, UK) for treatment of infective bacterial endophthalmitis was 1 and 2.2 mg respectively, prepared in 0.1 mL of 0.9% normal saline (NS; Otsuka, Guangdong, China) or balanced salt solution with glutathione (BSS Plus; Alcon, Fort Worth, TX), herein referred to as BSS.[5,6] The vitreous volume of an adult emmetropic human eye is approximately 4 mL, giving a respective empiric concentration of 0.25 and 0.55 mg/mL for vancomycin and ceftazidime, respectively, when injected into the vitreous. The actual concentrations would be different, depending on the extent of precipitation and the actual vitreous volume.

Assay of Antibiotics

Ceftazidime was assayed by high-performance liquid chromatography (HPLC)[15] and vancomycin by a fluorescence polarization immunoassay (TDx; Abbott Laboratories, Diagnostics Division, Abbott Park, IL).

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Study 1: Visual and pH Test

Standard mixture solutions of 1 mg vancomycin and 2.2 mg ceftazidime in 0.1 mL of 0.9% NS or BSS were mixed separately with 4 mL NS, BSS, or vitreous for incubation at ambient temperature or at 37°C.

Study 2: Checkerboard Analysis

Mixture samples with various concentrations of ceftazidime and vancomycin prepared in NS or BSS were incubated at 37°C in microtiter plates (Table 1) covered with paraffin foil. Aliquots were taken at 24 and 48 hours for assays by HPLC (ceftazidime) and fluorescence polarization (vancomycin) to determine the amount of free drugs.

Study 3: Control Experiment of Equilibrium Dialysis with NS as the Medium

Equilibrium dialysis studies were performed in an equilibrium dialyzer (Spectrum Medical Industries, Los Angeles, CA) with a half-cell working volume of 5.0 mL vancomycin (625 μg) and ceftazidime (1375 μg) prepared in NS. The mixtures were added to half-cell chamber A, which was separated from half-cell chamber B by a semipermeable dialysis membrane (Spectrapor; Medical Industries) with a molecular weight cutoff at 6000 to 8000. Both chambers were filled with 5 mL NS. The whole system was incubated at 37°C. Aliquots were taken from half-cell chamber B at appropriate time intervals up to 168 hours for antibiotic assays.

Study 4: Control Experiment of Equilibrium Dialysis with BSS as the Medium

The procedure was the same as that used in study 3, but with BSS as the preparation medium in both chambers.

Study 5: Equilibrium Dialysis in Vitreous

The same procedure was used as in study 3, but with vitreous as the medium in both chambers. Because the volume of available vitreous was small, an equilibrium dialysis apparatus with a half-cell chamber volume of 1 mL instead of 5 mL was used. Accordingly, 125 μg vancomycin and 275 μg ceftazidime were added to maintain the same concentrations as in previous studies. The antibiotics were prepared in NS before addition into the chambers. The experiment was repeated with the antibiotics prepared in BSS.

Results

Study 1: Visual and pH Test

Precipitate was visually detected in NS, BSS, and vitreous after incubation for 1 day at 37°C but not at ambient temperature. There was no change in the pH of 7.2 before or after precipitation.

Study 2: Checkerboard Analysis

In NS, vancomycin alone showed neither visual precipitation nor measurable decrease after 24 or 48 hours (Tables 1B–E). Ceftazidime alone decreased in concentration from 0% to 24.7%, suggesting precipitation (first column, Tables 1D, 1E). In mixtures of ceftazidime and vancomycin, there were no changes in vancomycin concentration but a progressive decrease in ceftazidime after 48 hours (median, 26.8%; range 12.0%–39.7%; Table 1E), suggesting precipitation of ceftazidime but not vancomycin. The decrease in concentration of the antibiotics was taken as the extent of precipitation.

In BSS preparation, vancomycin alone precipitated from 10.9% to 34.2% after 48 hours (median, 15.5%; first row, Table 1I). With ceftazidime alone, much more precipitation occurred in BSS than in NS. After 48 hours, the median decrease was 94.9% (range, 93.7%–95.8%; first column, Table 1I). In mixture, the extent of precipitation was similar, as if the antibiotics were on their own (Tables 1H, 1I). In both the NS and BSS mixtures, varying concentrations of vancomycin apparently did not influence ceftazidime concentration.

Study 3: Control Experiment of Equilibrium Dialysis with NS as the Medium

The vancomycin concentration in chamber B rose to approximately 45% of the original concentration in chamber A after approximately 60 hours and then reached a plateau, showing no loss to the end of the experiment at 168 hours. For ceftazidime, after an initial crossover into chamber B for the first 20 hours, there was a steady decline in concentration to approximately 20% at 168 hours, suggesting precipitation. After 168 hours, the total amount of free vancomycin in chambers A and B was 591.1 μg and of free ceftazidime, 577.0 μg, compared with the respective initial levels of 625 and 1375 μg. Accordingly, vancomycin decreased by 5.4% and ceftazidime by 58.0%. The decrease was attributed to precipitation.

Study 4: Control Experiment of Equilibrium Dialysis with BSS as the Medium

Vancomycin concentration in chamber B increased in the first 60 hours as in study 3. For ceftazidime, after an initial crossover into chamber B in the first 10 hours, there was a steady decrease by more than 90% after 120 hours. After 168 hours, the total amounts of free vancomycin in chambers A and B were 549.4 μg and of free ceftazidime, 244.2 μg, compared with the respective initial levels of 625 and 1375 μg. Decreases of 12.1% vancomycin and 82.0% ceftazidime occurred—again, attributable to precipitation.

Study 5: Equilibrium Dialysis in Vitreous

First, the antibiotics were prepared in NS before addition into chamber A with vitreous as the medium in cell chambers A and B. The vancomycin concentration in chamber B increased to slightly more than 50% of the original concentration in chamber A after approximately 70 hours. For ceftazidime, after an initial crossover into chamber B in the first 10 hours, there was a decrease in concentration by more than 80% after 120 hours (Fig. 1A). After 168 hours, the total amount of free vancomycin in chambers A and B was 137.9 μg and of ceftazidime, 127.2 μg, compared with the respective initial levels of 125 and 275 μg, suggesting no loss of vancomycin but a 54% decrease in ceftazidime. At 48 hours, the concentration of free ceftazidime in the dialysis chambers B was 73.4 μg/mL (Fig. 1B).

In another experiment with the antibiotics prepared in BSS, the vancomycin concentration in chamber B again increased to slightly more than 50% of the original concentration in chamber A after approximately 70 hours. For ceftazidime, after an initial crossover into chamber B within the first 10 hours, there was a decrease in concentration by more than 90% after 40 hours (Fig. 2A). At the end of 168 hours, the total amount of free vancomycin in chambers A and B was 135.6 μg and of ceftazidime 34.5 μg, against the respective initial additions of 125 μg and 275 μg, suggesting no loss of vancomycin but approximately 88% loss of ceftazidime. At 48 hours, the concentration of free ceftazidime in dialysis chamber B was 6.3 μg/mL (Fig. 2B).

Discussion

In the clinical setting, the observation of ceftazidime precipitates is infrequently reported.[14] This may be related to a poor view of the fundus in the presence of infective endophthalmitis, with corneal edema, inflammatory debris, intraocular lens opacities and/or vitreitis. The alkaline pH due to the presence

TABLE 1. Checkerboard Study Showing the Change with Time in Concentrations of Ceftazidime and Vancomycin in Normal Saline and Balanced Salt Solution

A. Initial concentrations

0/0	0/250	0/125	0/62.5	0/31.25
550/0	550/250	550/125	550/62.5	550/31.25
275/0	275/250	275/125	275/62.5	275/31.25
137.5/0	137.5/250	137.5/125	137.5/62.5	137.5/31.25
68.75/0	68.75/250	68.75/125	68.75/62.5	68.75/31.25

B. Concentrations in NS at 24 hours

0/0	**0/280.4**	**0/142.6**	**0/68.23**	**0/36.37**
432.91/0	398.73/241.2	434.81/122.9	444.3/64.98	374.05/34.22
222.15/0	225.95/272.7	222.15/129.5	224.05/66.28	235.44/35.66
121.52/0	119.62/264.1	105.53/132.2	110.13/65.67	117.72/36.01
56.96/0	53.16/271	56.96/139.7	62.66/65.47	64.56/35.04

C. Concentrations in NS at 48 hours

0/0	0/295.5	0/144	0/66.05	0/35.28
413.92/0	349.37/236.7	387.34/136.6	383.54/64.01	400.63/34.01
209.21/0	177.63/227.6	205.26/132.1	165.79/63.11	197.37/32.8
112.5/0	153.95/372	100.66/140.8	102.63/62.74	120.39/31.34
75/0	57.24/285.1	59.21/146.6	55.26/62.87	76.97/33.98

D. Percentage decrease in concentrations in NS at 24 hours

0/0	0/0*	0/0*	0/0*	0/0*
21.3/0	27.5/3.5	20.9/1.7	19.2/0*	32.0/0*
19.2/0	17.8/0*	19.2/0*	18.5/0*	14.4/0*
11.6/0	13.0/0*	25.4/0*	19.9/0*	14.4/0*
17.1/0	22.7/0*	17.8/0*	8.6/0*	6.0/0*

E. Percentage decrease in concentrations in NS at 48 hours

0/0	0/0*	0/0*	0/0*	0/0*
24.7/0	36.5/5.3	29.6/0*	30.3/0*	27.2/0*
23.9/0	35.4/9.0	25.4/0*	39.7/0*	28.2/0*
18.2/0	12.0/0*	26.8/0*	25.4/0*	12.4/0*
0/0*	16.7/0*	13.9/0*	19.6/0*	0/0*

F. Concentrations in BSS at 24 hours

0/0	0/238.1	0/111.1	0/52.84	0/29.39
64.47/0	76.97/223.9	75/106.2	74.34/52.93	74.34/29.46
30.92/0	34.21/223.3	35.53/101.1	32.89/52.26	30.92/28.73
14.28/0	17.11/227.5	16.45/110.8	16.05/52.98	17.37/29.69
8.29/0	9.21/232.5	8.82/119.6	10.13/52.17	9.21/29.39

TABLE 1 (*continued*). Checkerboard Study Showing the Change with Time in Concentrations of Ceftazidime and Vancomycin in Normal Saline and Balanced Salt Solution

G. Concentrations in BSS at 48 hours

0/0	0/222.8	0/82.2	0/50.58	0/27.56
22.84/0	23.21/206.6	22.29/114.3	25.24/48.83	22.29/26.58
13.82/0	13.03/233.0	13.24/110.4	13.16/49.58	13.42/27.3
7.11/0	7.5/226.8	7.37/88.9	7.24/50.44	7.11/27.73
4.34/0	3.68235.2	3.62/111.9	3.49/51.09	3.68/27.64

H. Percentage decrease in concentrations in BSS at 24 hours

0/0	0/4.5	0/11.1	0/15.4	0/6.0
88.3/0	86.0/10.4	86.4/15.0	86.5/15.3	86.5/5.73
94.3/0	87.6/10.7	87.0/19.1	88.0/16.4	88.8/8.1
89.6/0	87.6/9.0	88.0/11.3	88.3/15.2	87.4/5.0
87.9/0	86.8/7.0	87.2/4.3	85.3/16.5	86.6/6.0

I. Percentage decrease in concentrations in BSS at 48 hours

0/0	0/10.9	0/34.2	0/19.1	0/11.8
95.8/0	95.8/17.4	95.9/8.6	95.4/21.9	95.9/11.8
95.0/0	95.3/6.8	95.1/11.7	95.2/20.7	95.1/15.0
94.8/0	94.5/9.3	94.6/28.9	94.7/19.3	94.8/12.6
93.7/0	94.65.9	94.7/10.5	94.9/18.3	94.6/11.6

Each box in each section of the table signifies a well in a microtiter plate. To determine how the two antibiotics ceftazidine and vancomycin interact at different concentrations, various amounts (in milligrams per liter) of ceftazidime and vancomycin were mixed in each well (**A**), with normal saline or with balanced salt solution, and incubated at 37°C. The contents of each well were aliquoted after 24 h and 48 hours for assay of concentration and percentage decrease in concentration of antibiotics. Data in sections (**B**), (**C**), (**F**), and (**G**) show the measurable concentrations in milligrams per liter and in (**D**), (**E**), (**H**), and (**I**) the percentage decrease in concentrations of ceftazidime/vancomycin in the two media at the 24- and 48-hour measurement time points.

* No measurable loss.

of sodium carbonate in the ceftazidime formulation may lead to precipitation of the antibiotic.[13] However, precipitation has been reported in formulation free of sodium carbonate.[9] In our study, the pH of the vitreous did not change with the addition of the two antibiotics, and it remained unchanged when ceftazidime precipitated. We also found ceftazidime precipitation to be temperature dependent, occurring at 37°C but not at ambient temperature. Moreover, we showed that vancomycin did not precipitate in NS, BSS, or vitreous. Ceftazidime precipitated regardless of the presence of vancomycin, and it precipitated more extensively if it was initially prepared in BSS rather than NS, even though the volume was small, suggesting the effective enhancing precipitation effects of mineral materials in the BSS. Precipitation was faster when the ceftazidime preparation was added to vitreous or BSS than to NS, most likely due to the presence of potassium ions, calcium ions, glutathione, and other reducing and oxidizing agents. In the presence of intravitreal inflammatory debris and endotoxin in endophthalmitis, the extent of precipitation may even be greater and faster, which may account for the shorter half-life of ceftazidime in inflamed eyes when compared with that in control eyes.[16]

During pars plana vitrectomy, BSS is more suitable for intravitreal irrigation than NS because it contains the appropriate bicarbonate, pH, and ions necessary for the maintenance of normal retinal electrical activity.[17] It is also preferred over NS for use in anterior segment surgery, because it contains glutathione, which is necessary for maintenance of endothelial cell adenosine triphosphatase and for protection against free radical damage and oxidative stress.[18] However, in the current study we showed that ceftazidime was much more prone to precipitation in BSS than in NS. If ceftazidime has to be administered intravitreally for the treatment of endophthalmitis, NS should be preferred over BSS to avoid formation of precipitates. However, this is impossible when intravitreal antibiotics were given at the end of pars plana vitrectomy, which is routinely performed today with the continuous infusion of BSS.

We have shown that when ceftazidime was initially prepared in BSS, 6.3 μg/mL free drug remained at 48 hours in a volume of vitreous humor of 4 mL approximating that of an emmetropic eye. Such concentration is still higher than the minimal inhibitory concentration at 50% (MIC_{50}) of ceftazidime against common Gram-negative bacteria commonly identified in our hospital (Table 2),[19] but it is close to that of *Acinetobacter* spp., *Pseudomonas aeruginosa*, and other nonfermenters. In addition, it is lower than the 90% minimal inhibitory concentration (MIC_{90}) against *Enterobacter, Citrobacter,* and *Acinetobacter* spp. and other nonfermenters. When ceftazidime was initially prepared in NS before injection, the extent of precipitation was less and the amount of free ceftazidime available was approximately 73.4 μg/mL at 48 hours. The resultant concentration should be higher, but still less than the respective MIC_{90} of these organisms. Such concentrations would not be considered adequate to treat vision-threatening infections. Moreover, the antibiotic concentration may be even lower in large, myopic eyes with more vitreous volume than normal, or in the presence of aphakia or pseu-

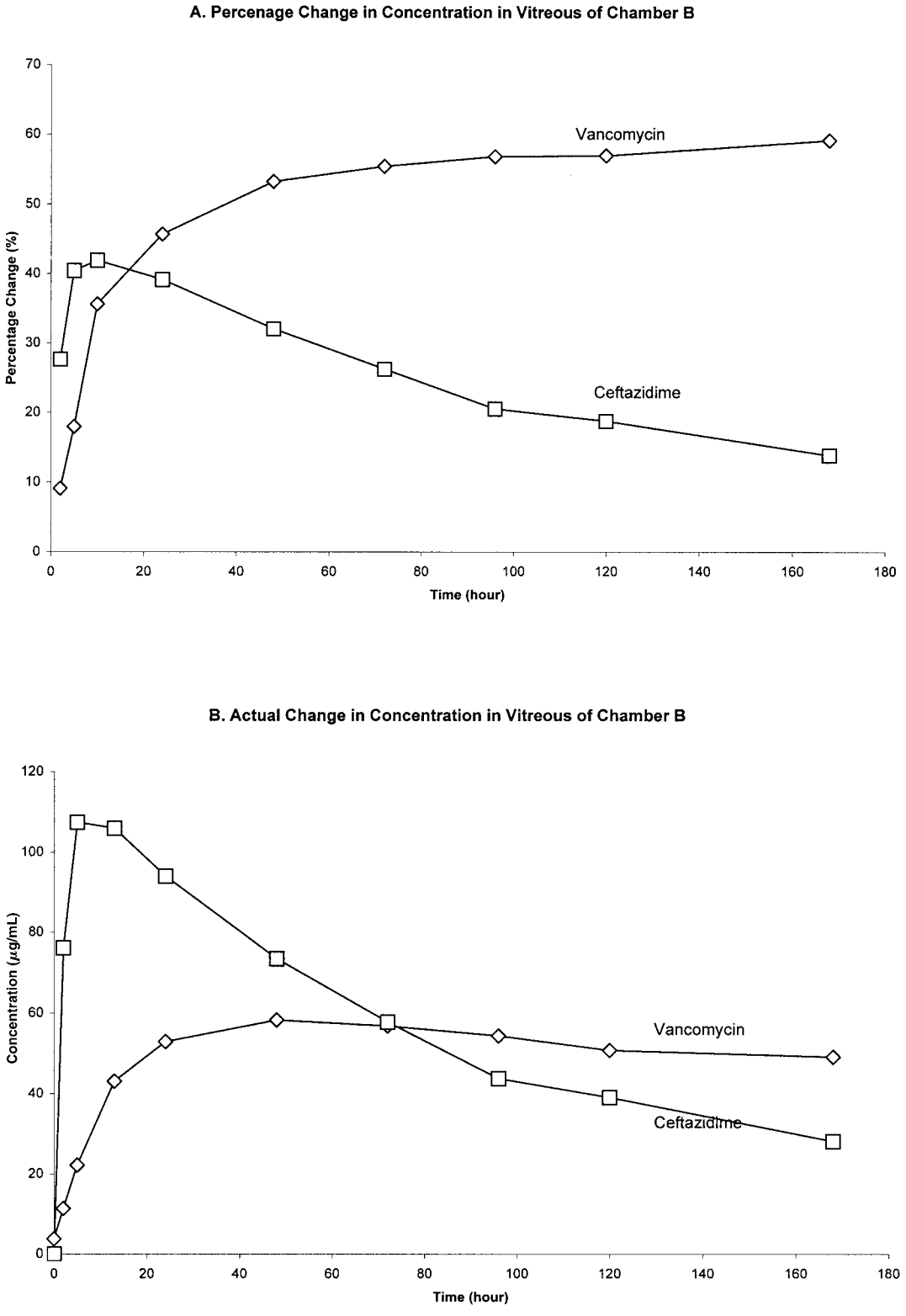

FIGURE 1. Equilibrium dialysis in vitreous medium with vancomycin and ceftazidime initially prepared in NS. Percentage (**A**) and actual (**B**) changes in concentration are shown.

dophakia which hastens the elimination of intravitreal drugs such as ceftazidime.[16] Nonetheless, the microbiologic spectrum and susceptibility of postoperative endophthalmitis are different among the United States and European and Asian countries.[3,20,21] Resistance to ceftazidime among Gram-negative organisms up to 39% of cases has been reported in India.[21]

Our experimental findings, based on an equilibrium dialysis system, may not be a perfect representation of what actually happens during clinical treatment of endophthalmitis. We used vitreous from cadaveric eyes, which have different solubility parameters, such as pH and electrolyte concentrations, compared with vitreous in infected eyes. The activities of metabolic

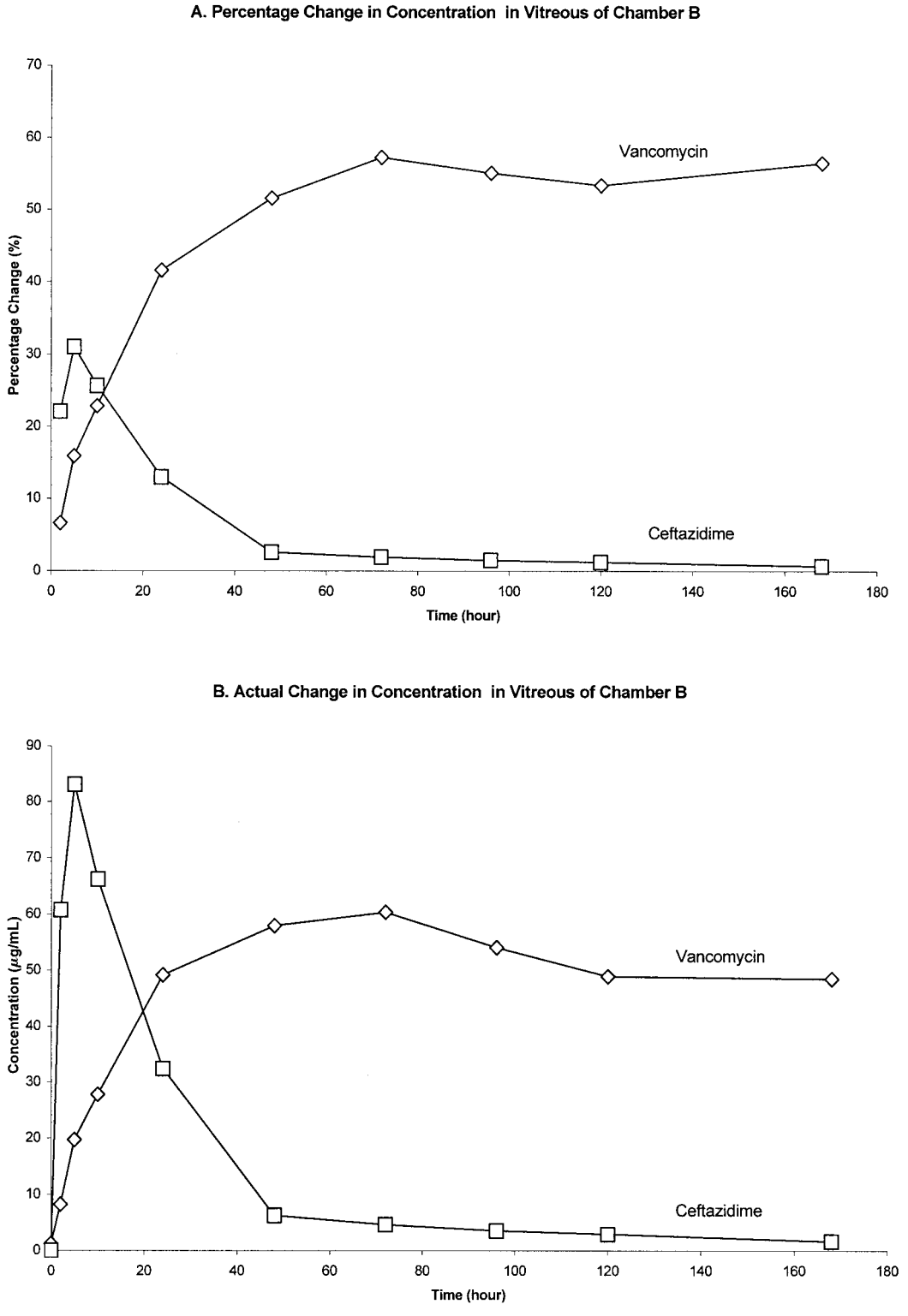

FIGURE 2. Equilibrium dialysis in vitreous medium with vancomycin and ceftazidime initially prepared in BSS. Percentage (**A**) and actual (**B**) changes in concentration are shown.

enzymes were also different. Such discrepancies in experimental and physiological conditions pose a limitation in extrapolating our in vitro collected data to in vivo clinical applications. However, based on our and other available data,[8,10,13,14] we suggest that ceftazidime not be used as the first-line treatment for infective endophthalmitis until further studies have validated its safety and efficacy. For the time being, the use of amikacin, as recommended by the Endophthalmitis Vitrectomy Study, is advisable.[5]

In summary, this in vitro study showed ceftazidime precipitation regardless of the presence of vancomycin at body temperature. NS is preferable to BSS in preparing the antibiotics for intravitreal injection in lessening the extent of ceftazidime precipitation. However, the concentration of free ceftazidime

TABLE 2. Minimal Inhibitory Concentration of Ceftazidime against Common Gram-Negative Bacteria Isolated from the Bloodstream in a Teaching Hospital

Bacterial Species	MIC_{50}	MIC_{90}
Escherichia coli	0.12	0.5
Klebsiella spp.	0.12	0.5
Indole-positive *Proteus* spp.	0.06	8
Proteus mirabilis	≤0.06	0.06
Enterobacter, Citrobacter	0.25	128
Acinetobacter spp.	4	128
Pseudomonas aeruginosa	1	4
Other nonfermenters	2	128

Data are expressed as micrograms per milliliter.

in vitreous may not be sufficiently high for antibacterial action against most common organisms. We are looking into such precipitation properties of other potent anti-Gram-negative antibiotics with broad-spectrum antibacterial action including fluoroquinolone and meropenem. Investigation of whether precipitation affects the free concentrations of these antibiotics and, possibly their efficacy and clinical usefulness, is in progress using a similar experimental model.

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