Penetration of Linezolid into the Anterior Chamber (Aqueous Humor) of the Human Eye after Intravenous Administration

E. García Vázquez,^{1*} J. Mensa,¹ Y. López,² P. Díaz Couchard,³ D. Soy,⁴ J. R. Fontenla,³ M. Sarasa,² X. Carné,² and E. Montull⁵

Institut d'Infeccions i Immunologia,¹ Unitat d'Avaluació Suport i Prevenció,² Servei d'oftalmologia,³ Servei de Farmàcia,⁴ and Medical Department, Pfizer Spain,⁵ Hospital Clínic, 08036 Barcelona, Spain

Received 25 June 2003/Returned for modification 13 August 2003/Accepted 14 October 2003

We determined the linezolid concentrations in serum samples and aqueous humors (AHs) from 21 patients undergoing cataract extraction. Cataract removal was performed at various times (from 60 to 270 min) after the end of a 30-min infusion of 600 mg of linezolid. Serum samples were obtained 1 h after the end of linezolid administration to determine the maximum concentration of linezolid ($C_{\max}$); AHs and a second serum sample were taken simultaneously during the operation, and the concentrations of linezolid in AH (C_{AH}) and serum (C_s) were determined. The mean C_{AH} 1 h after linezolid administration was 4.94 $\mu\text{g/ml}$, and the mean ratio of C_{AH} to C_s ($R = C_{\text{AH}}/C_s$) was 0.43. All patients had a C_{AH} of $>2 \mu\text{g/ml}$, which was higher than the MIC at which 90% of *Staphylococcus epidermidis* strains are inhibited.

Bacterial endophthalmitis is an infection of the interior of the eye that despite appropriate therapeutic intervention frequently results in loss of vision. Thus, treatment represents a challenge to preserve vision (7).

Penetration of antibiotics into the eye is variable, as the anterior chamber and the vitreous are avascular and the latter is also isolated from systemic circulation by the blood-ocular barrier (2). Thus, systemic antibiotics do not usually enhance visual outcomes, and intravitreal administration remains a key part of the clinical management of endophthalmitis.

Linezolid is a synthetic oxazolidinone antimicrobial that binds to the ribosome and inhibits protein synthesis (6). Surveys have shown almost 100% susceptibility among staphylococci, including methicillin-resistant strains. Orally administered linezolid is virtually completely bioavailable (5). Its elimination half-life allows dosing twice per day. Maximum concentrations in plasma ($C_{\max}$) are achieved 1 to 2 h after an oral dose of the drug. The drug has low serum plasma protein binding (approximately 31%) and is freely distributed to well-perfused tissues. The volume of distribution is 40 to 50 liters.

There are some clinical data on the use of linezolid in meningitis due to *Enterococcus* sp. in humans, and a recent study using the rabbit meningitis model showed good penetration into the cerebrospinal fluid. There are no clinical data on the penetration of linezolid into the anterior chamber (aqueous humor) of the human eye.

From clinical and bacteriological data, it is evident that linezolid is effective against gram-positive bacteria. Since many of these susceptible organisms are frequently the causative agents in intraocular infections, information on the ability of linezolid to penetrate into the aqueous humor is important. This study was designed to determine the characteristics of

linezolid penetration of the aqueous humor of the noninflamed human eye.

(The abstract and preliminary results of this study were presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, September 2003, in Chicago, Illinois.)

A total of 21 patients who underwent cataract extraction during the period from December 2002 to February 2003 were included. Cataract removal was performed at various times (from 60 to 270 min) after the end of a 30-min intravenous infusion of 600 mg of linezolid (as recommended by the manufacturer). The clinical study was approved by the Institutional Review Board at Hospital Clínic.

All patients gave informed consent to take part in the study. Exclusion criteria were all other ocular diseases, previous ocular surgery, topical or systemic antibiotic treatment 1 week preoperatively, and renal function impairment (creatinine clearance of $<50 \text{ ml/min}$).

Serum samples were obtained 1 h after the end of linezolid administration. The aqueous humor sample and a second serum sample were taken simultaneously during surgery. Ocular paracentesis was performed, and 0.05 to 0.1 ml of aqueous humor was aspirated. All samples were stored immediately at -80°C until processing.

TABLE 1. Concentrations of linezolid in aqueous humor and serum

Parameters (treatment intervals)	Mean (range; SD) ($\mu\text{g/ml}$)	Mean ratio ($R = C_{\text{AH}}/C_s$) ^b (range; SD)
Mean $C_{\max}$	13.49 (10.25–18.04; 2.41)	
Mean C_{AH} (first hour after LNZ) ^a	4.94 (2.68–6.12; 1.03)	0.43 (0.23–0.52; 0.09)
Mean C_{AH} (135 to 270 min after LNZ)	5.17 (4–6.96; 0.95)	0.48 (0.34–0.66; 0.11)

^a LNZ, linezolid.

^b Serum and aqueous humor were obtained simultaneously.

* Corresponding author. Mailing address: Servicio de Infecciones, Hospital Clínic, C/ Villarroel 170, 08036 Barcelona, Spain. Phone: 00 34 93 227 55 29. Fax: 00 34 93 4514438. E-mail: egarciav@clinic.ub.es.

TABLE 2. Characteristics of patients

Patient	Sex ^a	Age (yr)	Wt (kg)	C _{max}	C _s	C _{AH}	Time (min) ^b
1	M	73	69	13.73	11.11	5.48	110
2	F	77	59	15.93	12.93	4.42	185
3	F	87	68	15.23	9.93	4.94	230
4	M	78	87	11.02	8.83	4.42	150
5	F	78	58	15.3	12.38	6.96	155
6	F	73	81	12.14	8.51	5.26	170
7	F	78	72	13.33	7.69	5.08	220
8	F	87	69	12.47	11.38	5.39	115
9	M	78	72	12.69	12.96	4.44	270
10	F	77	72	18.04	15.56	6.3	135
11	M	81	65	17.43	14.77	4.76	75
12	F	87	60	15.18	14.09	5.84	120
13	M	72	83	11.55	9.16	3.98	170
14	F	76	91	10.43	8.45	3.66	110
15	F	66	65	11.36	9.95	5.18	105
16	M	77	67	16.57	12.63	5.9	150
17	F	80	75		11.91	6.12	105
18	M	82	82	11.75	11.75	2.68	60
19	M	83	75	10.25	10.25	4.64	75
20	M	64	75		11.32	4.66	90
21	M	77	59	11.85	11.85	5.88	65

^a M, male; F, female.

^b Time after linezolid administration (when samples for C_s and C_{AH} were obtained).

Concentrations of linezolid were determined by using a rapid high-performance liquid chromatography assay, developed and validated for the quantification of the drug in human plasma at the Pharmacology Laboratory in our hospital. Samples were prepared by mixing with a solution of perchloric acid, and 100 µl of the clear supernatant was injected. The high-performance liquid chromatography analysis used a reversed-phase C₁₈ analytical column and a mobile phase consisting of an isocratic mixture of 15-mM phosphate buffer (pH 5)–acetonitrile and UV monitoring. The method was linear over the

therapeutic concentration range of 0.5 to 100 µg/ml. The quantification limit was 0.5 µg/ml in plasma for a sample size of 200 µl. The accuracy of the method ranged from 94.4 to 106.1%, and the precision values ranged from 0.88 to 6.0% for intraday precision and from 3.7 to 5.6% for the interday values. Standards were made up in serum as well as ocular fluid.

Several variables were analyzed, including the mean C_{max} and the mean concentrations in aqueous humor (C_{AH}) and serum (C_s) for samples taken simultaneously from patients who underwent surgery <135 min and 135 to 270 min following linezolid administration.

Descriptive statistical analysis (determination of means and standard deviations [SD]) was done using the SPSS version 9.0 package.

Out of 21 patients, 10 (47.6%) were men and 11 (52.4%) were women. The mean age was 78 years (range, 64 to 87 years; SD, 6.04). The mean weight of the patients was 71.65 kg (range, 58 to 91 kg; SD, 9.3). The mean concentration of creatinine in serum was 1.13 mg/dl (range, 0.9 to 1.4 mg; SD, 0.16).

The mean C_{max} was 13.49 µg/ml (range, 10.25 to 18.04 µg/ml; SD, 2.41). The mean C_{AH} at the first hour following linezolid administration was 4.94 µg/ml (range, 2.68 to 6.12 µg/ml; SD, 1.03), and the mean C_s was 11.53 µg/ml (range, 8.45 to 14.77 µg/ml; SD, 1.77). The mean ratio ($R = C_{AH}/C_s$) was 0.43 (range, 0.23 to 0.52; SD, 0.09). The mean C_{AH} at 135 to 270 min after linezolid administration was 5.17 µg/ml (range, 4 to 6.96 µg/ml; SD, 0.95), the mean C_s was 11.06 µg/ml (range, 7.69 to 15.56 µg/ml; SD, 2.57), and the mean ratio was 0.48 (range, 0.34 to 0.66; SD, 0.11). All patients had a C_{AH} of >2 µg/ml 1 h after linezolid administration and a C_{AH} of >4 µg/ml 2 h after antibiotic administration. The concentrations of linezolid in aqueous humor and serum are shown in Tables 1 and 2. Ratio versus time values are detailed in Fig. 1.

None of the patients developed infection after surgery.

FIG. 1. Ratio of C_{AH} to C_s ($R = C_{AH}/C_s$) versus time for linezolid.

Infectious agents generally gain access to the eye as a consequence of intraocular surgery (60%) or following a penetrating injury of the globe (8). Postoperative endophthalmitis occurs most frequently following cataract removal, as this is the most common ocular intervention. The incidence of postoperative endophthalmitis after this procedure is about 0.1% and ranges between 0.05 and 0.37% following other types of intraocular surgery (3).

The etiologic agents of acute postoperative endophthalmitis are microorganisms of the eyelid skin and preocular tear film. Coagulase-negative staphylococci are responsible for about 70% of post-cataract surgery infections, followed by *Staphylococcus aureus* and other gram-positive microorganisms. Enterococci are prevalent, and infection is characterized by its severity (9). Posttraumatic endophthalmitis is usually caused by *Bacillus cereus* or staphylococci (1) (4). All these bacteria are susceptible to linezolid.

The results of our study demonstrate that microbiologically significant levels of linezolid can rapidly be achieved in the aqueous humor of the noninflamed human eye after intravenous administration of 600 mg. Two hours after administration of the antibiotic, the levels obtained were higher than the MIC at which 90% of *Staphylococcus epidermidis* strains are inhibited.

Further studies should be done with the posterior chamber, because if this rapid and high penetration of linezolid into the eye is confirmed, it could be highly useful in the systemic treatment of endophthalmitis and might make the local administration of antibiotics into the eye unnecessary. The easy administration of linezolid (intravenous or oral, as the pharmacokinetic is similar) makes early treatment possible when

diagnosis is not yet confirmed and direct injection of antibiotics into the eye might not be a first choice. Early treatment of endophthalmitis is mandatory to avoid visual impairment, and therefore, high levels of the antibiotic in the eye early after antibiotic administration are meaningful. According to our results, it appears that the C_{AH} is still increasing in late determinations (270 min after linezolid administration) and that equilibrium is still not reached. Therefore, for further studies, sampling at much later time points (e.g., 8 and 12 h) should be considered, as linezolid is a time-dependent antibiotic.

REFERENCES

1. Affeldt, J. C., H. W. Flynn, Jr., R. K. Forster, S. Mandelbaum, J. G. Clarkson, and G. D. Jarus. 1987. Microbial endophthalmitis resulting from ocular trauma. *Ophthalmology* **94**:407–413.
2. Axelrod, J. L., R. M. Klein, R. L. Bergen, and M. Z. Sheikh. 1985. Human vitreous levels of selected antistaphylococcal antibiotics. *Am. J. Ophthalmol.* **100**:570–575.
3. Callegan, M. C., M. Engelbert, D. W. Parke II, B. D. Jetty, and M. S. Gilmore. 2002. Bacterial endophthalmitis: epidemiology, therapeutics, and bacterium-host interactions. *Clin. Microbiol. Rev.* **15**:111–124.
4. Duch-Samper, A. M., J. L. Menezo, and M. Hurtado-Sarrio. 1997. Endophthalmitis following penetrating eye injuries. *Acta Ophthalmol. Scand.* **75**:104–106.
5. Eliopoulos, G. M. 2003. Quinupristin-dalfopristin and linezolid: evidence and opinion. *Clin. Infect. Dis.* **36**:473–481.
6. Moellering, R. C. 2003. Linezolid: the first oxazolidinone antimicrobial. *Ann. Intern. Med.* **138**:135–142.
7. O'Brien, T. P. 2000. Endophthalmitis. In G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), *Principles and practice of infectious diseases*, 5th ed. Churchill Livingstone, New York, N.Y.
8. Somani, S., A. Grinbaum, and A. R. Slomovic. 1997. Postoperative endophthalmitis: incidence, predisposing surgery, clinical course and outcome. *Can. J. Ophthalmol.* **32**:303–310.
9. Speaker, M. G., F. A. Milch, M. K. Shah, W. Eisner, and B. N. Kreiswirth. 1991. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. *Ophthalmology* **98**:639–650.