

Azlocillin concentrations in human aqueous humor after intravenous and subconjunctival administration

W. Behrens-Baumann¹ and R. Ansorg²

¹ Department of Ophthalmology, ² Department of Microbiology, University of Göttingen, Federal Republic of Germany

Abstract. Twenty-nine patients received either 4 g intravenous infusion or 100 mg subconjunctival application of azlocillin 1–12 h before cataract extraction. After intravenous application the mean aqueous humor concentration of azlocillin was 4.4 µg/ml after 3 h. The subconjunctival dose produced a mean aqueous humor concentration of 78 µg/ml and 3.4 µg/ml after 3 and 12 h, respectively. These levels are above the minimum inhibitory concentration of azlocillin for sensitive organisms.

Introduction

Azlocillin is an acylureido-penicillin (6-D-2-[2-oxoimidazolidin-1-carboxamido]-2-phenyl-acetamido-penicillanic acid), newly introduced in the United States and used in Europe since 1977 in general medicine. This drug has a broad spectrum of activity, including *Pseudomonas aeruginosa* in particular. Serum concentrations 1 h after infusion of 2 g reach mean levels of 60 µg/ml. The half-life is 1.0–1.2 h and the protein binding is approximately 30% (Knothe and Dette 1980; Lode et al. 1980).

Aqueous humor penetration of azlocillin has so far only been studied in the rabbit (Mester et al. 1978). We report on azlocillin concentration in human aqueous humor after intravenous and subconjunctival administration.

Subjects and methods

We selected 31 patients (11 males, 20 females) who came for cataract extraction and who had not received any antibiotics during two weeks prior to surgery. Patients with renal or hepatic diseases and with allergic response in their history were excluded.

Systemic application. We obtained 10 ml venous blood for control. An intravenous infusion of 4 g azlocillin¹ was then administered for a period of 30 min. The time between the end of the infusion and the anterior chamber puncture was different: 1 h (four patients), 2 h (three patients), 3 h (five patients) and 12 h (four patients). Immediately before the

operation began, 0.05–0.1 ml aqueous humor was obtained with a 27-gauge cannula. At the same time a second sample of venous blood was taken. The specimens of aqueous humor and blood serum were frozen at -70°C until assayed.

Subconjunctival route. In these groups 100 mg azlocillin (1 ml) was applied subconjunctivally into the temporal lower fornix. Aqueous humor was obtained after 1 h (three patients), 2 h (three patients), 3 h (three patients) and 12 h (four patients). Two more patients received 50 mg azlocillin (0.5 ml) subconjunctivally 12 h before taking aqueous humor samples.

Antibiotic assays. Determination of the antibiotic concentrations was performed by the large-plate assay (Bennet et al. 1960) using 1.5% Noble agar (Difco) with 1% casein peptone (E. Merck, FRG) and *Bacillus subtilis* ATCC 6051 as the test organism. Concentrations for the serum and aqueous humor standards were made in pooled human serum and 0.85% NaCl, respectively.

Results

The decrease of serum concentration of azlocillin after intravenous application is demonstrated in Fig. 1. The mean levels were 40 µg/ml and under 0.8 µg/ml after 3 and 12 h, respectively. The mean levels of azlocillin in the aqueous humor (Fig. 2) had an equal level of 4–5 µg/ml after 1–3 h, respectively, and fell under 0.8 µg/ml after 12 h. The concentration of azlocillin in the aqueous humor of the patients

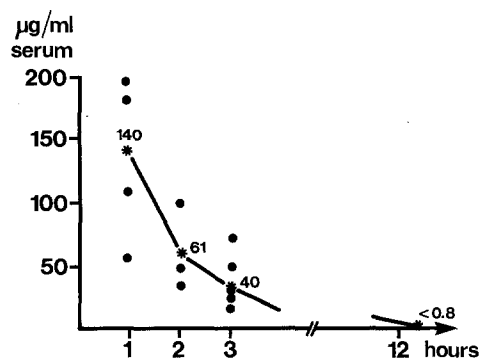


Fig. 1. Azlocillin levels in serum after intravenous infusion of 4 g. ● measurements; * mean value

Offprint requests to: Dr. W. Behrens-Baumann, Department of Ophthalmology, Robert-Koch-Str. 40, D-3400 Göttingen, Federal Republic of Germany

¹ Securopen (Bayer-Pharmaceuticals, Leverkusen, FRG)

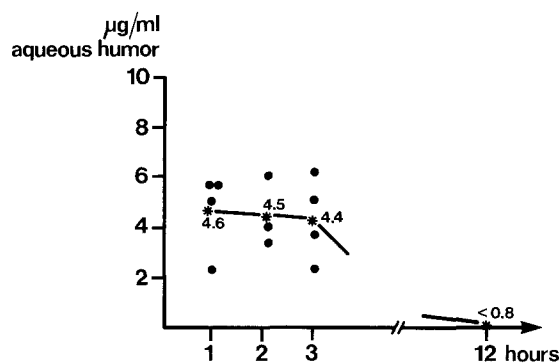


Fig. 2. Azlocillin levels in human aqueous humor after a 4 g intravenous infusion. • measurements; * mean value

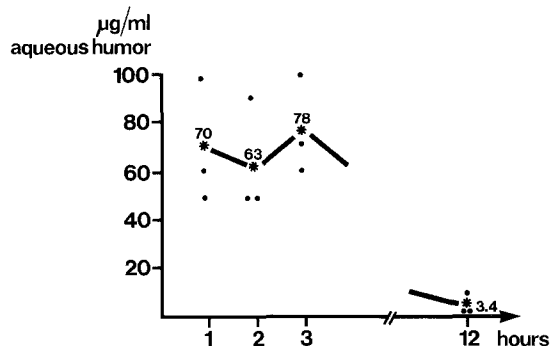


Fig. 3. Azlocillin levels in human aqueous humor after a 100 mg subconjunctival application. • measurements; * mean value

who received the 100-mg dose subconjunctivally (Fig. 3) was much higher, averaging 78 µg/ml and 3.4 µg/ml after 3 h and after 12 h, respectively. After subconjunctival application of 50 mg azlocillin, the level in the aqueous humor was under 0.8 µg/ml after 12 h. No azlocillin was found in the serum after subconjunctival administration.

Discussion

The prognosis in bacterial endophthalmitis as far as vision is concerned, is poor. Immediate administration of high doses of antibiotics by systemic and local routes is necessary. In such cases an antibiotic with a broad spectrum and a good ocular penetration is desired. In the non-inflamed eyes of patients undergoing cataract extractions, intravenous doses of 4 g azlocillin produced a mean aqueous humor level of 4.4 µg/ml after 3 h. No azlocillin was demonstrable after 12 h. Whereas the serum concentration of azlocillin decreased rather quickly in the first 3 h, the aqueous

humour level remained constant during this period. This low outflow of azlocillin is therapeutically desirable.

After subconjunctival application of 100 mg azlocillin, the mean aqueous humor levels were 78 µg/ml and 3.4 µg/ml after 3 and 12 h, respectively. This 12 h concentration is above the minimum inhibitory concentration of sensitive organisms. The subconjunctival route is therefore superior to the intravenous application. This was supported for other antibiotics, too (Furgiuele 1964; Records and Ellis 1964; Utermann et al. 1977; Petounis et al. 1978; Papapanos et al. 1979).

The good aqueous humor penetration of azlocillin could be expected to be even more effective in inflamed eyes. No adverse reactions and no post-operative endophthalmitis occurred in these series.

In bacterial infections of the anterior segment of the eye a daily subconjunctival application of 100 mg azlocillin may be sufficient. However, additional intravenous infusion in bacterial endophthalmitis is recommended.

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