Intravitreal penetration of teicoplanin

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Abstract

Teicoplanin is a glycopeptide antibiotic, similar to vancomycin, but safer and better tolerated. The purpose of this study was to evaluate the penetration of teicoplanin into the vitreous when administered topically and intravenously. Twenty-five patients undergoing routine vitrectomy were recruited. Twenty were given intravenous teicoplanin: five 1 h pre-operatively, five 12 h pre-operatively, five 24 h pre-operatively and five 24 h as well as 48 h pre-operatively. Five received teicoplanin drops half-hourly for the 6 h immediately preceding vitrectomy. Undiluted vitreous specimens were obtained at the beginning of each vitrectomy procedure. Teicoplanin levels were measured using a biological assay with *Staphylococcus aureus* as the indicator organism. Teicoplanin activity was detected in 8 of the 20 specimens from those patients receiving the intravenous antibiotic. Teicoplanin did not penetrate readily into the vitreous cavities in these eyes despite the blood-ocular barrier being compromised in some patients, although there was evidence of accumulation with time. No activity was detected in the vitreous of those patients who received topical teicoplanin.

Key words Endophthalmitis, Glycopeptide, *Staphylococcus*, Teicoplanin, Vancomycin, Vitrectomy

Bacterial endophthalmitis is a serious infection of the intraocular tissues that often has devastating consequences for vision and in many cases results in loss of the eye. Successful treatment is dependent on achieving an effective concentration of the appropriate antibiotic in all ocular tissues. The place of intravitreal antibiotics, usually combined with vitreous biopsy, is now well established.¹ The role of adjunctive therapy with topical and systemic antibiotics is not as clear although it is current practice.²

The major bacterial pathogens responsible for endophthalmitis following surgery are coagulase-negative staphylococci.³ These organisms have become increasingly resistant to

multiple antibiotics, with the exception of the glycopeptides.⁴ Some standard empirical regimes therefore include vancomycin administered systemically.⁵ This agent has a significant adverse effect profile, including the requirement for central venous access due to phlebitis, histamine release (Red Man Syndrome) and nephrotoxicity (especially when combined with an aminoglycoside). Therapeutic drug monitoring is therefore mandatory.⁶ In addition the topical form has a pH of 2, causing severe irritation when instilled into the eye.

Teicoplanin is an alternative glycopeptide that can be administered peripherally once daily, whose adverse effects are usually limited to hypersensitivity reactions.⁷ It has the same antibacterial spectrum as vancomycin, i.e. gram-positive bacteria including staphylococci, streptococci, enterococci and gram-positive anaerobes. The topical form has a more physiological pH (pH 7) than vancomycin. Comparative trials have shown it to have a similar efficacy to vancomycin but with fewer adverse effects.⁶

Experimental work in rabbits has established the intraocular penetration of vancomycin following intravenous and topical administration,⁸ although the only human study using subconjunctival vancomycin showed no penetration into the vitreous.⁹ Studies have been conducted on the penetration of teicoplanin administered topically, subcutaneously and subconjunctivally in rabbits,^{10,11} but no studies have been performed in humans.

The purpose of this study was to determine the penetration into the vitreous of teicoplanin when administered topically and intravenously.

Methods

Twenty-five patients (age range 18–92 years) undergoing vitrectomy for a variety of non-infectious pathologies were recruited. Approval was given by the hospital ethics committee and written informed consent obtained. Patients with a history of allergy to antibiotics or of asthma were excluded. Renal function was assessed by the measurement of serum urea and

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creatinine. Patients were recruited into five groups of five patients each. They were examined by slit lamp biomicroscopy at recruitment and the presence of intraocular inflammation, defined by the presence of either anterior chamber cells or vitreous inflammatory cells, recorded.

- Group A patients were given a single intravenous dose of 600 mg of teicoplanin 1 h pre-operatively.
- Group B patients were given a single intravenous dose of 600 mg of teicoplanin 12 h pre-operatively.
- Group C patients were given a single intravenous dose of 600 mg of teicoplanin 24 h pre-operatively.
- Group D patients were given an intravenous dose of 600 mg of teicoplanin 48 h pre-operatively and another dose 24 h pre-operatively.
- Group E patients had teicoplanin drops (2%) instilled every half hour for the 6 h preceding surgery. These patients also had cyclopentolate 1% and phenylephrine 2.5% drops instilled six times over the hour preceding surgery.

Specimens of undiluted vitreous were obtained at the beginning of each vitrectomy procedure. A standard 20 gauge three-port vitrectomy was performed with the infusion port in the infero-temporal quadrant. Care was taken that the infusion was not switched on at this stage. After checking that the infusion cannula was in the correct position, a second sclerotomy was made in the upper temporal quadrant. The vitreous cutter was introduced into the eye (the system must not be primed with fluid previously) and a biopsy of the vitreous gel made under microscopy. At the same time, an indenter was applied on the globe at the equator in the upper nasal quadrant to maintain intraocular pressure. Using this bi-manual technique a specimen of vitreous was removed. Vitreous cutter aspiration was then switched off by a three-way tap along its tubing. The cutting was continued without suction to ensure the cutting port was free from vitreous gel. The cutter was then removed, the ocular infusion was switched on and the indentation released commensurate with the gradual elevation to normal intraocular pressure as the intraocular infusion began. A scleral plug was introduced at the sclerotomy site. The vitreous in the tubing was collected into a 2 ml syringe. This technique avoids hypotony and undesirable vitreous traction.

In those cases where intravenous teicoplanin had been administered a serum specimen was obtained during vitrectomy. All specimens were stored at -70 °C until assays were performed.

Teicoplanin was assayed using a large plate biological assay by the agar diffusion method with the Oxford *Staphylococcus aureus* as the indicator organism (10^5 cfu/ml) poured onto Antibiotic Medium no. 2 (Merck) adjusted to pH 5.6.¹² For serum samples, working standards over the range 2–64 mg/l were prepared in pooled human sera (Sigma). For vitreal samples the working standards were prepared in phosphate buffer over the range 0.25–8 mg/l. The accuracy of the reference standards was confirmed by a

reference laboratory. The zone sizes were read by Vernier callipers and the results calculated by the method of Perkins.¹³ The sensitivity of the assay was 0.5 mg/l in both serum and vitreous. The coefficients of variation were 6.1% and 10.7% for high and low serum controls and 6.7% and 11.5% for high and low vitreous controls, respectively.

Results

Teicoplanin was only detectable in 8 of the 20 vitreous samples as follows:

- Group A (600 mg i.v. 1 h pre-operatively): Detectable in one of five specimens; 0.5 mg/l.
- Group B (600 mg i.v. 12 h pre-operatively): Detectable in one of five specimens; 0.5 mg/l.
- Group C (600 mg i.v. 24 h pre-operatively): Detectable in two of five specimens; 0.5 and 0.9 mg/l.
- Group D (600 mg i.v. 24 and 48 h pre-operatively): Detectable in four of five specimens; 0.5, 0.8, 1.1 and 1.8 mg/l.

Teicoplanin was present in all serum samples in the following concentrations:

- Group A (600 mg i.v. 1 h pre-operatively): Mean 34.4 mg/l (range 26–40, SD 4.9).
- Group B (600 mg i.v. 12 h pre-operatively): Mean 6.2 mg/l (range 5.0–7.0, SD 0.7).
- Group C (600 mg i.v. 24 h pre-operatively): Mean 4.6 mg/l (range 3.3–7.1, SD 1.5).
- Group D (600 mg i.v. 24 and 48 h pre-operatively): Mean 6.7 mg/l (range 3.2–9.5, SD 2.1).

There was no significant relationship between the magnitude of serum and vitreous levels of teicoplanin (Pearson correlation coefficient = -0.29, $p>0.2$; Table 1). There were 4 cases in which significant ocular inflammation was recorded pre-operatively (Table 1). Renal function as assessed by serum urea and electrolytes was within normal limits in each case.

Teicoplanin was not detectable in any of the vitreous specimens following its topical administration (Table 2).

Discussion

The place of systemic therapy in endophthalmitis is controversial because studies have consistently shown poor intravitreal penetration. However, these studies have either been in animal models or in human volunteers without evidence of inflammation.² We have shown in this study the poor initial penetration of teicoplanin following intravenous administration, although there does appear to be intravitreal accumulation of the agent with time. An initial loading dose of 400 mg (approximately 6 mg/kg) with a subsequent daily maintenance dose of 400 mg or 200 mg⁷ is the usual regime in clinical practice. Thus those subjects given intravenous teicoplanin in this study appear to have received an adequate dose of the drug. Despite this the levels of teicoplanin achieved in the

Table 1. Patients receiving intravenous teicoplanin

Patient no.	Diagnosis	Time of injection (hours pre-op.)	Serum teicoplanin (mg/l)	Vitreous teicoplanin (mg/l)	Ocular inflammation
1	Intravitreal nuclear fragment	1	32	0.5	Yes
2	Intravitreal nuclear fragment	1	40	<0.5	Yes
3	Retinal detachment	1	37	<0.5	No
4	Macular pucker	1	37	<0.5	No
5	Macular pucker	1	26	<0.5	No
6	RD following perforating injury	12	5.9	0.5	No
7	Pseudophakic RD	12	7.0	<0.5	No
8	IOFB	12	6.7	<0.5	No
9	Macular hole	12	6.3	<0.5	No
10	Aphakic RD	12	5.0	<0.5	No
11	Pseudophakic RD	24	3.4	0.9	No
12	Macular pucker	24	7.1	0.5	No
13	Pseudophakic RD	24	3.7	<0.5	Yes
14	Retinal detachment	24	5.6	<0.5	No
15	Retinal detachment	24	3.3	<0.5	No
16	PVR	48 + 24	3.2	1.8	Yes
17	Diabetic retinopathy	48 + 24	8.1	1.1	No
18	Diabetic retinopathy	48 + 24	6.3	0.8	No
19	Pseudophakic RD	48 + 24	9.5	0.5	No
20	Retinal detachment	48 + 24	6.6	<0.5	No

IOFB, intraocular foreign body; PVR, proliferative vitreoretinopathy; RD, retinal detachment.

vitreous do not exceed the MIC₉₀ for coagulase-negative staphylococci (2–4 mg/l).¹⁴ At 48 h (after two doses) the vitreous teicoplanin levels are approaching the MICs of the following bacteria, all of which have a worse prognosis than coagulase-negative staphylococci:³ *Staphylococcus aureus* (MIC₉₀ = 0.5–1.0 mg/l),¹⁴ *Streptococcus* spp. except group D (MIC₉₀ = 0.2 mg/l),¹⁴ *Propionibacterium acnes* (median MIC = 0.4 mg/l)¹⁵ and *Clostridium difficile* (MIC range 0.1–0.5 mg/l).¹⁶

There are no published studies on the penetration of teicoplanin into the vitreous following intravenous administration in human or animal subjects. Pryor *et al.*⁸ investigated the penetration of vancomycin in normal and chemically inflamed rabbit eyes following intravenous administration; vancomycin was detected in the aqueous for up to 4 h following injection but vitreous levels remained undetectable despite high serum concentrations. It is of note that in some of the cases in the present study the blood–ocular barrier was compromised by ocular inflammation, although the small number (4) prevents attempts to correlate the presence of inflammation with increased penetration of teicoplanin. In endophthalmitis the blood–ocular barrier is likely to be severely compromised and this may enhance penetration of the antibiotic.

Table 2. Patients receiving topical teicoplanin

Patient no.	Diagnosis	Vitreous teicoplanin (mg/l)
21	PVR	<0.5
22	Macular pucker	<0.5
23	Intravitreal nuclear fragment	<0.5
24	RD following resection of MM	<0.5
25	Macular pucker	<0.5

MM, malignant melanoma; PVR, proliferative vitreoretinopathy; RD, retinal detachment.

No teicoplanin was detected in the vitreous following topical administration. Carney *et al.*¹¹ investigated the intraocular penetration of teicoplanin in normal rabbit eyes following topical and subconjunctival administration. Teicoplanin drops 5% were instilled every 5 min for 2 h. The animals were then killed 30 min, 1 h or 2 h later. Measurable teicoplanin levels were present only in the vitreous of 2 of the 3 rabbits killed 30 min after cessation of administration of the drops. Our regimen of half-hourly 2% teicoplanin did not achieve measurable levels of the antibiotic. Further work has been reported in rabbits using subcutaneous and subconjunctival vancomycin and teicoplanin, but again no intravitreal activity was detected.¹⁰ Barza *et al.*⁹ also reported the absence of intravitreal penetration of vancomycin following subconjunctival administration.

We chose to study the penetration of teicoplanin as it has similar antibacterial activity to vancomycin (which is used empirically in the treatment of endophthalmitis by some practitioners) but has less toxicity. The most important therapeutic manoeuvre in endophthalmitis, however, is the early intravitreal injection of broad-spectrum antibiotics. There is evidence that in animal models intravitreal vancomycin persists at supra-inhibitory levels for 38 h.¹⁷ Our study shows that the intravitreal levels of teicoplanin following intravenous administration are initially undetectable, although there is evidence that this agent does penetrate the vitreous and accumulates with time. This contrasts with the lack of evidence for any intravitreal penetration of systemically administered vancomycin in humans.

We have demonstrated that inadequate vitreous levels of teicoplanin are achieved by intravenous injection alone and, therefore, that intravitreal injection is essential to achieve sufficient concentrations of antibiotic quickly. There may be a role for systemic administration of teicoplanin to augment intravitreal injection once

sensitivities on the *Aspergillus* isolated at this time were identical to those from the previous culture. After cataract extraction a retrocorneal membrane adjacent to the corneal section developed over a 2 week period and the pupil became almost completely secluded with the development of a thick cyclitic membrane. Progression of fungus infection was assumed and an intravitreal injection of amphotericin 5 µg together with amphotericin 750 µg subconjunctivally over the staphyloma was carried out on 9 April. A course of 23 daily injections of subconjunctival amphotericin starting on 18 April followed. The oral steroids were tailed off during this period and the intraocular inflammation almost completely resolved. By 23 May the intraocular inflammation had completely resolved. To provide a view of the posterior segment, the cyclitic membrane was removed surgically on 23 May and iris, vitreous and scleral biopsies were taken. No *Aspergillus* was cultured from the multiple biopsies that were taken. Histological examination of the divided specimens, however, showed the presence of fungal hyphae in all iris and scleral specimens. Therapy with oral itraconazole 200 mg twice a day was continued for another month together with topical steroids and the eye remained quiet with light perception afterwards.

Discussion

These case reports demonstrate the problems that may be encountered in the management of fungal scleritis. These include the difficulty of diagnosing mycotic infections, the choice of antifungal therapy, the difficulty of eliminating mycotic scleritis by medical therapy alone, and determining the technique and timing of surgical measures.

Scleritis is most frequently an aseptic, immune-mediated inflammation that can occasionally be initiated by surgical trauma.^{1,12,13} Infectious scleritis after surgery should be suspected when there is no history of autoimmune disease and when the disease characteristics are atypical of immune-mediated scleral inflammation. Signs that were indicative of an infection in the reported cases include suture abscess, hypopyon, endophthalmitis and scleral necrosis without episcleral non-perfusion. Negative microbiology findings from swabs or scrapings are – as in fungal keratitis¹⁴ – a frequent finding and do not exclude an infection, since the organisms may be present only in the deep stroma. The diagnosis of *Aspergillus* infection was established in all three cases only after scleral biopsy. We recommend, therefore, as with bacterial keratitis,¹⁵ that in cases of progressive scleritis when infection is suspected, scleral tissue should be taken and divided for histopathological diagnosis and further microbiological investigations. The presence of mycotic elements on histological examination alone, without fungal growth in the cultured tissue, however, does not allow conclusions on their viability. Fungal elements may persist in the sclera after successful medical treatment, as shown by case 3.

The management of patients with scleromycosis remains difficult despite the availability of new antifungal agents. There are no clear guidelines for the selection and administration of antifungal antibiotics since scleromycosis is extremely rare and *in vitro* sensitivity data are of only limited value.¹⁶ Topical and systemic antibiotic therapy is recommended for infectious scleritis. Until recently, amphotericin B was the drug of choice for systemic *Aspergillus* infection.¹⁶ More recently itraconazole has become an alternative to amphotericin B for this indication.¹⁷ Successful management solely by medical therapy was reported by Carlson *et al.*⁸ in one patient with *Aspergillus* scleritis following cataract surgery. These authors attributed the successful outcome to the use of oral itraconazole. Although itraconazole may have an enhanced efficacy and cause fewer problems with toxicity in comparison with amphotericin B,¹⁷ reliable control of mycotic scleritis by medical therapy alone is not the rule. In our cases 1 and 2 scleral inflammation was progressive and the formation of a necrotic area was observed while the patients were on oral itraconazole (200 mg/day) and intensive topical antifungal medication.

Surgical methods are important means of controlling fungal scleritis. They should be considered in cases unresponsive to medical treatment. It has to be borne in mind, however, that massive inflammatory reactions may occur after initiation of medical therapy (as in case 3). These may represent an immunological response to fungal cell death rather than actual disease progression ('Herxheimer type' of reaction).^{18,19} Surgical interventions may consist of conjunctival resection with cryotherapy to the immediate surrounding sclera or lamellar or full-thickness procedures to excise the involved sclera with subsequent graft, or both,^{20,21} Surgical excision with subsequent grafting has the advantage over cryotherapy in that tissue for diagnosis is provided and the treated area is more clearly defined. The efficacy of the different surgical procedures in the management of fungal scleritis still needs to be clarified. This small case series demonstrates that, in selected cases, surgical intervention improves the outcome of this potentially devastating disorder.

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