EXTENDED REPORT

Pharmacokinetics of vancomycin following intracameral bolus injection in patients undergoing phacoemulsification cataract surgery

Conor C Murphy, Steven Nicholson, Say Aun Quah, Mark Batterbury, Timothy Neal, Stephen B Kaye

Br J Ophthalmol 2007;91:1350–1353. doi: 10.1136/bjo.2006.112060

See end of article for authors' affiliations

Correspondence to: Mr S B Kaye, St Paul's Eye Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK; Stephen.kaye@rlbuht.nhs.uk

Accepted 16 March 2007

Published Online First

27 March 2007

Aim: To determine the elimination kinetics of intracameral vancomycin administered as a bolus injection at the end of phacoemulsification cataract surgery.

Methods: Vancomycin 1 mg/0.1 ml saline solution was administered to 19 patients by intracameral bolus injection at the end of routine cataract surgery. The aqueous concentration of vancomycin was determined in nine patients 1 minute after administration and in 10 patients 18–24 hours postoperatively. Aqueous samples were obtained by inserting a Rycroft cannula into the anterior chamber via the side port incision. Fluorescence polarisation immunoassay was used to calculate the aqueous vancomycin concentration.

Results: The median (interquartile range) vancomycin concentration was 5458 (4756–6389) mg/l at 1 minute and 40.6 (25.9–47.1) mg/l 18 to 24 hours (median 19 hours) postoperatively. The vancomycin concentration exceeded the minimum inhibitory concentration (MIC) of endophthalmitis-causing gram-positive bacteria by a factor of 4 for up to 26 hours postoperatively. No adverse event or reaction was noted.

Conclusion: Following bolus intracameral injection at the end of cataract surgery the concentration of vancomycin in the anterior chamber vastly exceeds its MIC for at least 24 hours but is predicted to fall below the MIC after 33 hours.

Postoperative endophthalmitis is a rare but potentially blinding complication of intraocular surgery. Population-based studies in the USA and Australia have reported an incidence rate of approximately 0.2% following cataract surgery,^{1,2} although it is recognised that the incidence rate varies widely in different locations and is influenced by the use of prophylactic measures.³ In a recent multi-centred randomised controlled trial in Europe, a five-times lower incidence of endophthalmitis was reported in patients who received a prophylactic bolus injection of intracameral cefuroxime at the end of phacoemulsification cataract surgery compared with those who did not.⁴ This is the only randomised controlled trial to date to demonstrate unequivocally the efficacy of prophylactic antibiotics for reducing the incidence of postoperative endophthalmitis and the findings support the routine use of intracameral antimicrobial therapy in cataract surgery.

Gram-positive bacteria are the predominant cause of postoperative endophthalmitis and accounted for 94% of 420 culture-positive cases in the endophthalmitis vitrectomy study.⁵ Vancomycin is a bactericidal antibiotic with 100% coverage of gram-positive endophthalmitis-causing organisms.^{6,7} Based on its spectrum of activity and the reported isolation of cephalosporin-resistant enterococci from vitreous biopsies in 25% of cases of postoperative endophthalmitis in a recent study from Sweden,⁸ we have adopted as standard practice in our department the administration of vancomycin 1 mg in 0.1 ml saline 0.9% as a bolus intracameral injection at the end of cataract surgery.

The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent that prevents visible growth of bacteria after an 18-hour or 24-hour period of incubation in vitro.⁹ The MIC of vancomycin for gram-positive endophthalmitis-causing pathogens is 4 mg/l or less and in most cases is in the range of 0.5 to 1.0 mg/l.^{6,7} The aim of this study was to measure the concentration of vancomycin in the anterior chamber in the early postoperative period to determine

if the MIC of vancomycin is exceeded during the period that is most critical to the development of endophthalmitis.

MATERIALS AND METHODS

Twenty patients undergoing routine phacoemulsification cataract surgery with posterior chamber intraocular lens implantation were recruited for this study. Inclusion criteria were routine uncomplicated cataract surgery and age over 18 years. Exclusion criteria were ocular disease other than cataract, previous intraocular surgery, perioperative complications, diabetes mellitus, poor vision in the fellow eye and a history of vancomycin allergy. As the final step in the surgery, a bolus of vancomycin 1 mg in 0.1 ml 0.9% saline solution was injected into the centre of the anterior chamber using a Rycroft cannula (BD Visitech, Waltham, MA, USA) on a 1 ml syringe inserted through the side port incision. The precise time of the vancomycin injection was recorded.

The patients were divided equally into two groups based on the timing of aqueous humour sampling for vancomycin concentration measurement. Patients in group 1 underwent aqueous sampling 1 minute after intracameral vancomycin injection. A Rycroft cannula attached to an insulin syringe was inserted through the side port incision and at least 0.04 ml aqueous humour was aspirated. Patients in group 2 underwent anterior chamber paracentesis when they returned for review the following day approximately 20 hours postoperatively. After instilling topical proxymetacaine anaesthetic 0.5%, povidone-iodine 5% was painted on the periocular skin and instilled into the conjunctival fornix. A speculum was placed between the eyelids and the patient was positioned at the slit-lamp microscope. A Rycroft cannula attached to an insulin syringe was inserted into the anterior chamber through the side port incision and 0.04 ml aqueous humour was aspirated with the help of an assistant. Postoperatively patients in both groups

Abbreviation: MIC, minimum inhibitory concentration

received betamethasone 0.1% and chloramphenicol 0.5% eye drops four times daily for four weeks. All patients were reviewed 1 week postoperatively. Local ethics committee approval for this study was obtained and informed consent given by all participants.

All samples were stored in sterile Eppendorf tubes at -70°C until analysis of vancomycin levels. All samples were analysed simultaneously using a competitive binding fluorescence polarisation immunoassay (Abbott TDx; Abbott Diagnostics, Maidenhead, Berkshire, UK).¹⁰ As sample volumes were small and expected values for patients in group 1 were greater than the highest calibrator on the assay (100 mg/l), all samples were diluted with buffer (Abbott Diagnostics, Maidenhead, Berkshire, UK) prior to the assay. The assay value was multiplied by the dilution factor to obtain the final sample concentration. The vancomycin was prepared for intracameral injection in the hospital pharmacy as follows: unpreserved vancomycin 500 mg powder was reconstituted with 10 ml sterile water for injections. The resulting 10 ml solution was diluted with 40 ml sodium chloride 0.9% to give a final concentration of 10 mg/ml vancomycin. This was then filtered into 1 ml syringes to a volume of 0.5 ml and 0.1 ml (1 mg) of this was administered intracamerally.

Analysis

A simple exponential decay model was used, that is, $C(t) = C_0 e^{-Kt}$ where K is the proportionality constant of decay. The mean and median vancomycin concentration together with the 95% upper (UCL) and lower (LCL) confidence intervals at the two time points were used to construct the concentration decay models.

RESULTS

Twelve of the 20 patients were women and the mean age (range) of the group was 71 (46–87) years. One of the samples taken 1 minute following vancomycin injection was insufficient for analysis, so that aqueous samples in nine patients in group 1 and 10 patients in group 2 were available for analysis. Table 1 shows the axial length of the eye, timing of aqueous sampling following vancomycin injection and the aqueous vancomycin concentration recorded. There was no correlation between axial length and vancomycin concentration in either group. There were no adverse effects of aqueous sampling or intracameral vancomycin injection detected. The mean and median (interquartile range) vancomycin concentrations were 5385 mg/l and 5458 (4756–6389) mg/l at 1 minute and 41.1 mg/l and 40.6 (25.9–47.1) mg/l 18 to 24 hours (median 19 hours) postoperatively. The mean (95% LCL, 95% UCL) concentration at 1 minute and 23 hours (using the concentrations measured between 22 and 24 hours) were 5385.2 mg/l (4386.9, 6383.54) and 41.1 mg/l (31.8, 50.4), respectively. These values were then used to determine K (table 2). A predicted plot of the vancomycin concentration against time with the respective 95% LCL and UCL is shown in fig 1.

The concentration of vancomycin in the anterior chamber exceeded the MIC for gram-positive organisms on average by a factor of 10 approximately 20 hours after administration. Based on established MIC values of 2–4 mg/l for gram-positive microorganisms,^{6–7} the aqueous vancomycin concentration exceeded the MIC by between 6 and 12 times in all samples in group 2, with the exception of one sample in which the MIC was exceeded by 2–4 times. Assuming a simple monoexponential decay, the concentration (C) of vancomycin at time t was approximated using the data in Table 2 by the function $C(t) = C_0 e^{-Kt}$. The half-life of vancomycin is then approximately 3.27 hours ($0.69/K$). Using the lower 95% band, the MIC of vancomycin would then be reached 32–33 hours after

intracameral injection (representing a vancomycin concentration of 3.73–4.62 mg/l). Levels of four times higher than a MIC of 4 mg/l would be present until 26 hours (16.72 mg/l, 95% LCL) post-surgery.

DISCUSSION

The results of this study confirm that the concentration of vancomycin in the anterior chamber following intracameral bolus injection into the pseudophakic eye exceeds the MIC for gram-positive organisms by a factor of four 26 hours after administration and is estimated to remain above the MIC for approximately 32 hours. As the first 24 to 48 hours after phacoemulsification is the most critical period for the development of endophthalmitis, it would appear that bolus intracameral vancomycin may be of clinical value in preventing endophthalmitis for at least the first 32 hours post-surgery.

Aqueous vancomycin concentrations were determined using a fluorescence polarisation immunoassay (Abbott TDx). This assay is designed for routine therapeutic drug monitoring and is the most common assay used by laboratories contributing to the National UK quality assurance scheme. In a comparative study of commercially available assays the Abbott TDx was in the statistical group with the highest precision for four out of the five drugs tested including vancomycin.¹⁰

The addition of vancomycin to the infusion solution at a dose of 20 mg/l during phacoemulsification has been a popular method of endophthalmitis prophylaxis since 1991, when Gills reported an endophthalmitis rate of only one in 10 000 cases using vancomycin alone and no endophthalmitis out of 25 000 cases using a combination of vancomycin and gentamicin in the irrigation solution.¹¹ No significant difference in aqueous contamination at the end of cataract surgery has, however, been found in two separate studies comparing patients who received vancomycin in the infusion with those who did not.^{6–12} Intracameral vancomycin concentration after delivery in the infusion fluid at a dose of 20 mg/l falls below the MIC in less than 5 hours⁶ and vancomycin at this dose does not inhibit the growth of most bacteria when exposed for a period of 140 minutes in vitro.¹³

Ferro and colleagues found a 47% decrease in aqueous vancomycin concentration within 2 hours of completing phacoemulsification surgery using vancomycin 20 mg/l in the infusion, indicating an elimination half-life of approximately 2 hours early in the postoperative period,⁶ a finding that has been verified by Mendivil *et al.*¹⁴ In the present study, the half-life of vancomycin in the anterior chamber was estimated to be approximately 3 hours 16 minutes. The concentration of a drug in the anterior chamber depends on the initial concentration, the volume of distribution and its elimination half-life. The volume of the anterior chamber is approximately 0.3 ml in the phakic eye and probably increases to around 0.5 ml in the pseudophakic eye.¹⁵ The half-life of a drug in the anterior chamber may be affected by a variety of factors, although published data pertaining to these are limited. Intracameral drugs are predominantly eliminated across the trabecular meshwork⁹ and it is plausible that this may be affected by molecular weight and reversible molecular binding in the anterior chamber, for example, to soluble aqueous proteins and iris melanin. Protein binding in the serum is in the range of 10% to 50% for vancomycin and this has a profound impact on its pharmacokinetics.¹⁶ Absorption by the cornea, iris and ciliary body might also affect the intracameral concentration, especially if it is later re-released into the anterior chamber, as has been demonstrated for intracameral cyclosporin in a rabbit model.¹⁷ The most important factor determining aqueous drug concentration after intracameral injection is the rate of aqueous turnover, which is estimated to be 1.5% per minute or half the

Figure 1 The concentration of vancomycin in the anterior chamber following a bolus injection of 0.1 ml of 1 mg/l at the end of cataract surgery. Semilogarithmic plot of the predicted vancomycin concentration modelled on the measured concentrations at 1 minute and 18 to 24 hours postoperatively using a monoexponential decay (central line). Upper (UCL) and lower (LCL) 95% confidence intervals (broken lines).

anterior chamber volume every 46 minutes.¹⁵ That the measured half-life of intracameral vancomycin exceeds this raises the possibility that a degree of binding occurs in the anterior chamber, thus delaying its elimination, although this remains speculative. It is important to note that our predicted model assumes a monoexponential decay and even with 95% bands, the predicted values are based on only two time points. In order to improve the accuracy of the model, it will be necessary to sample the vancomycin concentrations at a number of time points, particularly beyond the 48-hour time period. Until this has been done very little reliability can be placed on the calculated half-life and predictive value of the above model, beyond 24 hours postoperatively.

The half-life of intracameral gentamicin is reportedly 51 minutes and is even less for cefuroxime, the concentration of which has been shown to decrease by a factor of four from a

Table 1 Axial length, timing of aqueous sampling and aqueous vancomycin concentration recorded

Patient number	Axial length (mm)	Time sample taken (hh:mm)	Vancomycin concentration (mg/l)
1	22.83	0:01	5476
2	22.17	0:01	5458
3	22.63	0:01	3658
4	22.93	0:01	7453
5	23.03	0:01	6691
6	22.17	0:01	6389
7	20.08	0:01	4896
8	22.91	0:01	3690
9	23.56	0:01	4756
Median (interquartile range)	22.83 (22.17–22.93)	0:01 (0:01–0:01)	5458 (4756–6389)
10	22.5	17:30	26.6
11	23.31	19:10	9
12	23.32	22:30	46.8
13	22.45	23:45	40.9
14	23.52	21:45	55.6
15	22.51	22:00	25.6
16	25.09	19:00	40.3
17	22.05	19:15	47.2
18	23.41	17:30	24
19	24.13	19:20	48.3
Median (interquartile range)	23.32 (22.50–23.50)	19:20 (19:00–22:00)	40.6 (25.90–47.10)

Table 2 Vancomycin concentration (mg/l) and coefficient (K) of decay

	1 minute	23 hours	K
Mean	5385.22	41.09	–0.212
95% LCL	4386.91	31.79	–0.214
95% UCL	6383.54	50.38	–0.211

median of 2742 mg/l to 756 mg/l in the first hour after a bolus injection of 1 mg in 0.1 saline 0.9%.^{18–19} There are, however, no reports to our knowledge on the aqueous concentration of cefuroxime 18 to 20 hours after intracameral administration to compare with our results. Table 3 summarises published reports of antibiotic half-lives in the anterior chamber following intracameral delivery.

Vancomycin is a bactericidal antibiotic that inhibits bacterial cell wall synthesis by interfering with peptidoglycan synthesis. In a recent in vitro study, Libre *et al* found that vancomycin was bacteriostatic for the first 6 hours and only became bactericidal after 8 hours, a finding that is consistent with a mechanism of action that blocks cell wall synthesis.^{21–22} This may also explain why vancomycin in the irrigating infusion has been shown to have no significant effect on aqueous contamination after cataract surgery as the aqueous concentration drops below the MIC within 5 hours and therefore well before bactericidal activity has been achieved.^{6–12} Vancomycin has a slower kill-time curve than the β -lactam antibiotics, which also act by inhibiting bacterial cell wall synthesis and include the penicillins and cephalosporins.²³ However, the prolonged high concentration of vancomycin in the anterior chamber demonstrated in this study following bolus injection might allow effective bacterial killing to be achieved, especially as its bactericidal activity is greater during the logarithmic bacterial growth phase than during the stationary growth phase.²⁴ The low rate of endophthalmitis compared with the reported rate of aqueous contamination (3–43%) suggests that only rarely does infection overwhelm the innate defences of the eye.^{25–26}

The possibility of increasing antimicrobial resistance with the prophylactic use of intracameral vancomycin or cefuroxime is a controversial issue and has been reviewed in detail by Gordon.²⁷ As the eye is a relatively closed compartment and elimination of intracameral vancomycin is very unlikely to lead to significant systemic levels, it is highly unlikely that its use will promote drug resistance and to our knowledge there is no evidence to suggest otherwise. The risk of corneal endothelial damage and

Table 3 Summary of published reports of the half-life of antibiotics following intracameral delivery

Drug	Method of intracameral delivery	T _{1/2} (hours)	Reference
Vancomycin	Bolus injection	3.27	Current report
Vancomycin	Added to irrigating infusion	<2	7
Vancomycin	Added to irrigating infusion	<2	14
Gentamicin	Added to irrigating infusion	<2	7
Gentamicin	Added to irrigating infusion	0.85	18
Cefuroxime	Bolus injection	<1	19
Amikacin (rabbit)*	Bolus injection	0.58	20
Chloramphenicol (rabbit)*	Bolus injection	0.69	20

*Data derived from phakic rabbits. T_{1/2}, half-life.

retinal toxicity with bolus intracameral injections of vancomycin has not been studied to date. Cystoid macular oedema associated with vancomycin in the irrigating solution has, however, been reported in 20% of patients receiving intracameral vancomycin compared with 0% of control patients in a prospective randomised double-blind study.²⁸ This possible adverse effect warrants further investigation. Considering the high and sustained concentration of intracameral vancomycin resulting from a dose of 1 mg/0.1 ml in the present study, it is possible that lower and potentially safer doses could be as effective at preventing endophthalmitis. Finally, as dosage errors are a definite risk, we recommend that all vancomycin is prepared for bolus intracameral injection in the hospital pharmacy and not the operating theatre.

In conclusion, this study demonstrates that the aqueous concentration of vancomycin following intracameral bolus injection at the end of cataract surgery is on average four times the MIC for the main endophthalmitis-causing micro-organisms 26 hours postoperatively, and is predicted to fall below the MIC after 33 hours.

Authors' affiliations

Conor C Murphy, Steven Nicholson, Say Aun Quah, Mark Batterbury, Stephen B Kaye, St Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, UK

Timothy Neal, Department of Medical Microbiology, Royal Liverpool University Hospital, UK

Competing interests: None.

REFERENCES

- Morlet NM, Li J, Semmens J, *et al.* The Endophthalmitis Population Study of Western Australia (EPSWA): first report. *Br J Ophthalmol* 2003;**87**:574–6.
- West ES, Behrens A, McDonnell PJ, *et al.* The incidence of endophthalmitis after cataract surgery among the U.S. medicare population increased between 1994 and 2001. *Ophthalmology* 2005;**112**:1388–94.
- Taban M, Behrens A, Newcomb RL, *et al.* Acute endophthalmitis after cataract surgery. *Arch Ophthalmol* 2005;**123**:613–20.
- Barry P, Seal DV, Gettinby G, *et al.* ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: preliminary report of principal results from a European multicenter study. *J Cataract Refract Surg* 2006;**32**:407–10.
- Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy study: a randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. *Arch Ophthalmol* 1995;**113**:1479–96.
- Ferro JF, de-Pablos M, Lograno MJ, *et al.* Postoperative contamination after using vancomycin and gentamicin during phacoemulsification. *Arch Ophthalmol* 1997;**115**:165–70.
- Pflugfelder SC, Hernandez E, Fliesler SJ, *et al.* Intravitreal vancomycin: retinal toxicity, clearance, and interaction with gentamicin. *Arch Ophthalmol* 1987;**105**:831–7.
- Wejde G, Montan P, Lundstrom M, *et al.* Endophthalmitis following cataract surgery in Sweden: national prospective survey 1999–2001. *Acta Ophthalmol Scand* 2005;**83**:7–10.
- Meredith TA. Antibiotics and antifungals. In: Zimmerman TJ, eds. *Textbook of ocular pharmacology*. Philadelphia: Lippincott-Raven Publishers, 1997:363–85.
- Wilson J, Davis A, Tobin C. Evaluation of commercial assays for vancomycin and aminoglycosides in serum: a comparison of accuracy and precision based on external quality assessment. *J Antib Chemo* 2003;**52**:78–82.
- Gills JP. Filters and antibiotics in irrigating solution for cataract surgery. *J Cataract Refract Surg* 1991;**17**:385.
- Feys J, Salvanet-Bouccara A, Emond JP, *et al.* Vancomycin prophylaxis and intraocular contamination during cataract surgery. *J Cataract Refract Surg* 1997;**23**:894–7.
- Gritz DC, Cevallos AV, Smolin G, *et al.* Antibiotic supplementation of intraocular irrigation solutions; an in vitro model of antibacterial action. *Ophthalmology* 1996;**103**:1204–8.
- Mendivil AS, Mendivil MP. The effect of topical povidone-iodine, intraocular vancomycin, or both on aqueous humor cultures at the time of cataract surgery. *Am J Ophthalmol* 2001;**131**:293–300.
- Schoenwald RD. Ocular pharmacokinetics. In: Zimmerman TJ, ed. *Textbook of ocular pharmacology*. Philadelphia: Lippincott-Raven Publishers, 1997:119–38.
- Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis* 2006;**42**:S35–39.
- Oh C, Saville BA, Cheng Y, *et al.* A compartment model for the ocular pharmacokinetics of cyclosporine in rabbits. *Pharm Res* 1995;**12**:433–7.
- Lehmann OJ, Thompson JP, White LO, *et al.* Half-life of intracameral gentamicin after phacoemulsification. *J Cataract Refract Surg* 1997;**23**:883–8.
- Montan PG, Wejde G, Setterquist H, *et al.* Prophylactic intracameral cefuroxime: evaluation of safety and kinetics in cataract surgery. *J Cataract Refract Surg* 2002;**28**:982–7.
- Mayers M, Rush D, Madu A, *et al.* Pharmacokinetics of amikacin and chloramphenicol in the aqueous humor of rabbits. *Antimicrob Agents Chemother* 1991;**35**:1791–8.
- Libre P, Della-Latta P, Chin N. Intracameral antibiotic agents for endophthalmitis prophylaxis: a pharmacokinetic model. *J Cataract Refract Surg* 2003;**29**:1791–4.
- Kodjikian L, Burillon C, Garweg JG. Intracameral vancomycin and endophthalmitis prophylaxis. *J Cataract Refract Surg* 2004;**30**:2030.
- Small PM, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob Agents Chemother* 1990;**34**:1227–31.
- Rybak MJ, Bailey EM, Lamp KC, *et al.* Pharmacokinetics and bactericidal rates of daptomycin and vancomycin in intravenous drug abusers being treated for gram-positive endocarditis and bacteraemia. *Antimicrob Agents Chemother* 1992;**36**:1109–14.
- Dickey JB, Thompson KD, Jay WM. Anterior chamber aspirate cultures after uncomplicated cataract surgery. *Am J Ophthalmol* 1991;**112**:278–82.
- Beigi B, Westlake W, Chang B, *et al.* The effect of intracameral perioperative antibiotics on microbial contamination of anterior chamber aspirates during phacoemulsification. *Eye* 1998;**12**:390–4.
- Gordon YJ. Vancomycin prophylaxis and emerging resistance: are ophthalmologists the villains? The heroes? *Am J Ophthalmol* 2001;**131**:371–6.
- Axer-Siegel R, Stiebel-Kalish H, Rosenblatt I, *et al.* Cystoid macular edema after cataract surgery with intraocular vancomycin. *Ophthalmology* 1999;**106**:1660–4.