We prospectively investigated a consecutive series of ten patients undergoing a cemented primary total hip replacement (THR) for osteoarthritis in order to establish the elution characteristics of Simplex-tobramycin bone cement (Howmedica, Limerick, Ireland). Specimens of blood, urine and drainage fluid were collected for 72 hours postoperatively. Very high concentrations of tobramycin were found in the drainage fluid, with mean levels at one hour of 103 mg/l, which steadily declined to 15.1 mg/l after 48 hours. The mean serum tobramycin levels reached a peak of 0.94 mg/l at three hours and declined rapidly to 0.2 mg/l by 48 hours. The mean urinary tobramycin levels peaked at 57.8 mg/l at 12 hours with a rapid decline to 12.6 mg/l by 24 hours.

There was a direct correlation between the amount of tobramycin bone cement which was implanted and the amount of tobramycin systemically absorbed. Excellent local delivery was achieved with minimal systemic concentrations. Simplex-tobramycin bone cement is an efficient and safe method for the delivery of antibiotics after THR.

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Antibiotic-laden acrylic bone cement has become popular as a prophylactic measure against the devastating complication of deep infection after total hip replacement (THR). It has been shown to be most effective when used in combination with systemic antibiotics.1,2

Commercially available gentamicin-impregnated cement and Simplex antibiotic cement with erythromycin (500 mg) and colistin (240 mg) (Howmedica, Limerick, Ireland) are widely available. Their safety and pharmacokinetic characteristics are well documented.3,4 Despite this, resistant strains of organism are providing renewed challenges in the management of the infected total joint replacement.5

Tobramycin may be an effective antibiotic when mixed with bone cement. At levels achievable at the operative site with tobramycin-impregnated cement, all common Gram-negative and most Gram-positive organisms are susceptible, including organisms which are not susceptible to systemic antibiotics.5 Tobramycin is less ototoxic and nephrotoxic than gentamicin and has been shown to elute at higher concentrations than gentamicin from Palacos (Richards, Mississauga, Canada), Simplex (Howmedica) and Zimmer (Warsaw, Indiana) cements.6,7

Tobramycin has already been used successfully in several studies in which it was added to Simplex P at the time of surgery.8-10 Safe and effective bactericidal levels are swiftly established at the site of the implant, while serum concentrations are negligible after only 24 hours. In addition, it has been shown that tobramycin does not affect the mechanical characteristics of Simplex bone cement.11,12

The pharmacokinetics of tobramycin using commercially prepared Simplex-tobramycin bone cement (Howmedica; 1 g tobramycin sulphate; 40 g powder, 20 ml liquid) have not been well documented. We have therefore identified the pharmacokinetic characteristics of tobramycin in blood, urine and at the operative site after the use of Simplex-tobramycin bone cement in primary THR.

Patients and Methods

We selected prospectively ten consecutive patients who required a primary THR for osteoarthritis. All patients with active infection, malignancy at the operative site or sensitivity to aminoglycosides or acrylic bone cement were excluded from the study group. The details of the patients are shown in Table I. Additional intravenous tobramycin was not used in these patients. One had evidence of pre-existing renal dysfunction, as determined by the preoperative level of serum creatinine, but this was not considered to be a contraindication to the use of tobramycin bone cement.
In all patients one mix of Simplex-tobramycin bone cement was used for the acetabular component and two mixes for the femoral component. The cement which was not implanted was retained and the total cement volume was measured by weight. All drainage fluid and urine was collected for 48 hours after the operation, divided into the time periods shown in Table II. Venous blood samples were collected in parallel. The concentrations of tobramycin were assayed on a Dimension RxL clinical chemistry system using a PETINIA method (Particle Enhanced Turbinometric Inhibition Immunoassay) (Dade Beuring, Newark, New Jersey). The lower limit of detection for this assay is approximately 0.18 mg/l. Serum creatinine concentrations were also measured, which allowed the calculation of creatinine clearance.

### Results

The serum tobramycin levels are shown in Figure 1. In all but one patient there was a rapid decline to negligible levels within 24 hours. This patient (case 6; Table I) had an initial level of 1.1 mg/l at one hour, which rose to a maximum of 2.1 mg/l at 12 hours, and steadily declined after this. She also had pre-existing renal dysfunction of unknown aetiology and the serum creatinine rose from 0.15 mmol/l preoperatively to a peak of 0.21 mmol/l after 24 hours (Fig. 2). The renal function had improved to its preoperative level by day five. All other patients had normal renal function throughout the study period.

The levels of tobramycin in the drainage fluid are shown in Figure 3. Very high initial concentrations were observed.
with these levels showing a gradual decline to a mean of 15.1 mg/l (8.4 to 22.2) after 48 hours. Urinary excretion of tobramycin was maximal in the period 3 to 12 hours after insertion of the prosthesis (mean concentration 58.6 mg/l; range 26.7 to 107.6). This gradually declined to a mean of 9.2 mg/l (2.9 to 27.6) at 48 hours. The net effect was a 48-hour cumulative excretion as shown in Figure 4. There was a direct relationship between the weight of cement implanted (Table I) and the cumulative excretion of tobramycin at 48 hours (Fig. 5).

Discussion

Tobramycin is an aminoglycoside which is closely related to gentamicin. At levels seen at the operative site, it has a similar spectrum of activity, but is slightly more active against *Pseudomonas* and is less ototoxic and nephrotoxic than gentamicin. Its elution characteristics are superior to those of gentamicin. It is therefore an attractive alternative as an additive to acrylic bone cement in the prevention of periprosthetic infection.

Studies have shown very high, local concentrations of tobramycin with minimal systemic absorption and no systemic side-effects when using tobramycin powder mixed with cement at the time of surgery. Our study has shown that there is effective local delivery of tobramycin by the commercially available Simplex-tobramycin bone cement. Levels achieved at the operative site were far in excess of the minimum inhibitory concentration for common pathogenic bacteria, even after 48 hours.

Systemic absorption was minimal and in most patients tobramycin was excreted rapidly. In one patient only, the serum concentration was higher and peaked later. The most likely cause of this renal failure was inadequate, perioperative fluid replacement with subsequent dehydration and renal hypoperfusion, as reflected in the relative increase in the serum creatinine concentration. A tobramycin-induced renal impairment would be associated with a more delayed and prolonged response. The peak recorded serum tobramycin level was 2.1 mg/l (Fig. 2). Although sustained elevations above 2 mg/l are not recommended, the threshold for nephrotoxicity is said to be 6.0 to 12.0 mg/l.

Simplex-tobramycin bone cement delivers very high, local, bactericidal concentrations of tobramycin. Systemic absorption is minimal with rapid renal excretion. Based on our study, the pharmacokinetic characteristics of Simplex-tobramycin bone cement appear to be appropriate for use in THR.

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