THE PHARMACOKINETICS OF SIMPLEX-TOBRAMYCIN BONE CEMENT

Sterling G, Crawford R, Crawford S, Faithfull G, Potter J
+Queensland University of Technology and Prince Charles Hospital, Brisbane, Australia

Introduction

The use of antibiotic-laden bone cements has become popular as a prophylactic measure against deep infection in total hip replacement (THR). Tobramycin has a spec trim of activity similar to gentamicin with some studies suggesting it may have a more active in vitro effect against Pseudomonas (Reynolds 1989). Tobramycin impregnated Simplex cement (Simplex T) has been commercially available for a number of years in Europe and Australia. In spite of this, the safety profile of this product and its local efficacy has not been established. The aim of this prospective study was to establish the pharmacokinetics of Simplex T and to determine if its safety profile is consistent with its clinical use.

Materials and Methods

Ten consecutive patients with osteoarthritis of the hip underwent a cemented primary total hip replacement. Ethics committee approval was obtained and all patients were consented before being entered into the trial. One of the 10 patients had pre-existing renal failure.

A cemented Exeter prosthesis was inserted in all patients with an all polyethylene acetabular component. An indwelling catheter was inserted pre-operatively, this was emptied at the time of insertion of the femoral cement, and this time was recorded as time zero.

Each unit of Simplex-T contains 1.0g of tobramycin as a sulphate. One mix was used for the acetabulum and two for the femur. All cement not inserted was retained and weighed. All urine and drainage fluid was collected for 48 hours post-operatively. Serum tobramycin and creatinine levels were measured for 72 hours post operatively. Times of collection are listed below in table 1. Tobramycin concentrations were asayed on a dimensional RxL clinical chemistry system using a PETINA method (Particle enhanced turbimetric inhibition immunoassay). The lower limit of detection for this assay is approximately 0.18mg/l.

Pharmacokinetic Blood Wound Urine
Evaluation Exudate
Pre-op x
1 hour x x
3 hours x x x
12 hours x x
24 hours x x x
48 hours x x x
72 hours x x

Table 1. Specimen collection times

Results

Very high concentrations of tobramycin were seen in the drainage fluid with mean levels at 1 hour of 103 mg/ L declining to 15.1 mg/L (range 8.4-22.2 mg/L) at 48 hours. Serum tobramycin reached a peak at 3 hours (mean 0.94 mg/L) declining to a mean of 0.2 mg by 48 hours. Mean urinary tobramycin concentrations peaked at 57.8 mg/L (26.7-107.6 mg/L) at 12 hours with a decline to 12.6 mg/L by 24 hours. Measurement of total 48 hour tobramycin excretion against total cement implanted by weight showed a direct relationship (r = 0.97).

All patients except 1 showed normal renal function throughout the study. The one patient who showed a transient rise in creatinine had a pre-operative creatinine of 0.15 mmol/L. This rose to a maximum of 0.21mmol/L at 24 hours and returned to normal by day 5. The pattern of change in renal function was not thought to be due to Tobramycin toxicity.

Discussion

Our study demonstrates very effective local delivery of tobramycin from Simplex-T bone cement. Local levels were 220 times higher than systemic levels at 1 hour. The peak recorded serum tobramycin level was 2.1 mg/L in the patient with pre-existing renal failure. The threshold for renal toxicity from Tobramycin is said to be 6.0-1012.0 mg/L (Reynolds 1989).

Simplex-T delivers very high local bacteriacidal concentrations of Tobramycin. Systemic absorption is minimal, with rapid renal excretion. We believe this is the first study to show a direct relation ship between the amount of antibiotic cement implanted and the cumulative clearance. Based on this study, the pharmacokinetic profile of Simplex-T bone cement appears to be appropriate for its use in total hip replacement.

References


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