

Safeness of Simplex-tobramycin bone cement in patients with renal dysfunction undergoing total hip replacement

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ABSTRACT

Purpose. To compare the pharmacokinetic profile of tobramycin in blood, urine, and at the operative site following the use of Simplex-tobramycin bone cement in primary total hip replacement between patients with and without renal dysfunction.

Methods. Six patients with renal dysfunction underwent cemented primary total hip replacement for osteoarthritis. The elution characteristics of Simplex-tobramycin bone cement in the 6 patients with renal dysfunction were compared with 9 patients who had normal renal function. Blood, urine, and drainage fluid specimens were collected for 72 hours postoperatively.

Results. Very high concentrations of tobramycin were seen in the drainage fluid of the 2 groups. Mean serum tobramycin levels peaked at postoperative 3 hours, and declined rapidly to negligible levels at 72 hours in both groups. Mean urinary tobramycin concentrations peaked at postoperative 12 hours and declined rapidly until 48 hours in both groups. Urinary

tobramycin was excreted significantly more slowly in renal dysfunction group in the first 12 hours, but not thereafter. Although serum creatinine levels of the renal dysfunction group were higher throughout the study period, the difference was not significant. Both groups achieved excellent local delivery of the antibiotic with minimal systemic concentrations.

Conclusion. Simplex-tobramycin bone cement appears to be an effective and safe means to deliver antibiotic for patients with renal dysfunction who undergo total hip replacement.

Key words: arthroplasty, replacement, hip; bone cements; kidney failure; pharmacokinetics; tobramycin

INTRODUCTION

Antibiotic-laden acrylic bone cement is a popular prophylactic measure against deep infection following total hip replacement and is most effective when combined with systemic antibiotics.^{1,2} Gentamicin-impregnated cement and Simplex antibiotic

Table 1
Specimen collection schedule*

Pharmacokinetic evaluation	Preoperative	Postoperative					
		1 hour	3 hours	12 hours	24 hours	48 hours	72 hours
Blood	√	√	√	√	√	√	√
Wound exudates		√	√		√	√	
Urine			√	√	√	√	

* 0 hour is the time of bone cement application

cement with erythromycin (500 mg) and colistin (240 mg) [Howmedica, Limerick, Ireland] are widely available and have good safety and pharmacokinetic profiles.^{3,4} However, antibiotic-resistant organisms continue to pose challenges to the management of infections following total joint replacement.⁵

Tobramycin seems to be a better antibiotic to mix with bone cement than other antibiotics because most gram-negative and -positive organisms are susceptible to tobramycin (including organisms not susceptible to systemic administration).⁵ Tobramycin is less ototoxic and nephrotoxic than gentamicin, and has been shown to elute at higher concentrations than gentamicin in bone cements from Palacos (Richards, Mississauga, Canada), Simplex (Stryker, Rutherford [NJ], US), or Zimmer (Zimmer, Warsaw [IN], US).^{6,7} Mixing tobramycin to Simplex P cement swiftly established safe and effective bactericidal levels at the operative site, while serum concentrations were negligible after only 24 hours.⁸⁻¹⁰

Mixing antibiotics to bone cement may result in weakening of the cement, development of antibiotic-resistant bacteria, and systemic toxicity. Tobramycin had no effect on the mechanical characteristics of Simplex bone cement.¹¹⁻¹³ Bone cement mixed with antibiotics prevents infective loosening for up to 14 years and decreases the risk of aseptic loosening. This suggests that mechanical changes caused by adding antibiotics to cement are discernible.¹⁴ It is highly unlikely that the use of antibiotic cement causes systemic toxicity and renal impairment. Higher renal impairment rate was reported in patients treated with systemic dicloxacillin alone (13%) than with gentamicin-impregnated cement alone (0%).¹⁵ However, a case of acute renal failure was reported following the use of a gentamicin-impregnated spacer for a 2-stage revision total knee arthroplasty.¹⁶

The pharmacokinetic profile of commercially prepared Simplex-tobramycin bone cement (Howmedica, Limerick, Ireland; 1 g tobramycin sulphate; 40 g powder, 20 ml liquid) has been published.¹⁷ However, the safety of Simplex-tobramycin bone cement in patients with renal

dysfunction has not been reported. This study compares the pharmacokinetic profile of tobramycin in blood, urine, and drainage fluid at the operative site following the use of Simplex-tobramycin bone cement in primary total hip replacement between patients with and without renal dysfunction.

MATERIALS AND METHODS

From July to December 2004, 6 consecutive patients with pre-existing renal dysfunction (abnormal serum creatinine level: male, >120 µmol/l; female, >100 µmol/l) underwent primary cemented total hip replacement for osteoarthritis in The Prince Charles Hospital in Chermside, Queensland, Australia. Blood, urine, and drainage fluid specimens were collected for 72 hours. Tobramycin levels of drainage fluid and serum, serum creatinine levels, and urinary excretion of tobramycin of the 6 patients were compared with 9 patients with normal renal function, whose results were previously reported.¹⁵ Patients with active infection, malignancy at the operative site, or known sensitivity to aminoglycosides or acrylic bone cement were excluded. All patients received cephalothin 1 g every 6 hours for 24 hours. Additional intravenous tobramycin was not used.

Each patient received one mix of Simplex-tobramycin bone cement for the acetabular implant component and 2 mixes for the femoral component. Drainage fluids and urine were collected for 48 hours after prosthesis insertion. Venous blood samples were collected up to postoperative 72 hours. The specimen collection schedule is shown in Table 1. Serum tobramycin concentrations were assayed on a Dimension RxL clinical chemistry system (Dade Beuring, Newark [NJ], US) using a PETINIA method (particle-enhanced turbidometric inhibition immunoassay). The lower limit of detection for this assay is approximately 0.18 mg/l. Serum creatinine concentrations were assayed on the Dimension RxL analyser using a Jaffe reaction. Both specimens were collected at the same intervals.

Table 2
Patient characteristics

Patient No.	Sex	Age (years)	Height (cm)	Weight (kg)	Serum creatinine ($\mu\text{mol/l}$)
Normal renal function group (n=9)					
1	F	51	173	89	70
2	M	67	169	92	90
3	F	89	156	77	80
4	F	66	167	74	90
5	M	74	161	75	100
6	M	73	173	91	90
7	F	81	155	69	80
8	F	51	167	59	70
9	M	79	179	94	70
Mean (SD)		70.1 (12.9)	166.7 (8.1)	80.0 (12.1)	80* (10)
Renal dysfunction group (n=6)					
10	F	83	158	59	160
11	M	77	182	97	210
12	F	49	164	63	110
13	M	76	166	75	180
14	F	67	152	70	150
15	M	62	172	75	170
Mean (SD)		69.0 (12.3)	165.7 (10.5)	73.2 (13.3)	160* (30)

* $p < 0.05$

Table 3
Postoperative tobramycin levels in drainage fluid

Time point	Normal renal function group (mean, SD) [mg/l]	Renal dysfunction group (mean, SD) [mg/l]	p value*
1 hour	103.0 (42.9)	90.3 (26.3)	0.727
3 hours	70.9 (40.3)	71.5 (21.3)	0.689
24 hours	37.3 (13.9)	39.0 (11.4)	0.864
48 hours	15.8 (4.9)	20.8 (18.9)	0.683

* Mann-Whitney U test

Statistical analysis was performed using the Statistical Package for the Social Sciences (version 12.0, SPSS Inc, Chicago [IL], US). Parametric or non-parametric test was used depending on the type of data collated. Bonferroni's correction for multiple testing was used, and the p value for significance was adjusted accordingly. A p value of < 0.05 was considered significant. All data were tested for normality and found to be non-parametric with the exception of preoperative variables. Hence, the mean values of the preoperative variables were compared using the t -test, whereas the mean values of postoperative variables were compared using the Mann-Whitney U test.

RESULTS

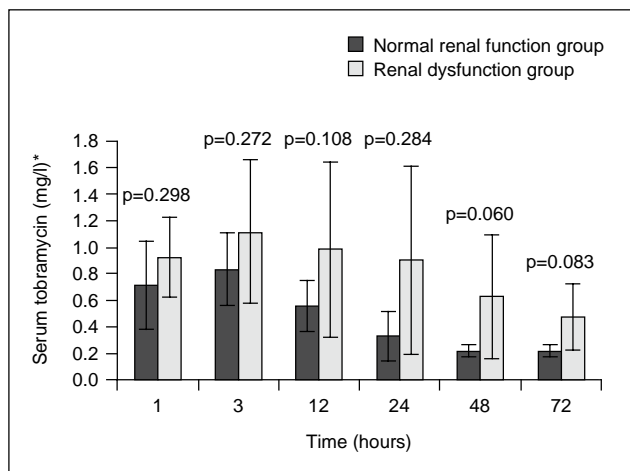
Patient characteristics of the normal renal function and renal dysfunction groups are presented in Table 2. All variables except serum creatinine levels were similar between the 2 groups. Tobramycin levels in drainage

fluid between the 2 groups were not significantly different at the 5% level using the Mann-Whitney U test (Table 3). Serum tobramycin levels of renal dysfunction patients were higher at each interval, but the difference was not significant (Fig. 1). Serum creatinine levels of the renal dysfunction group were significantly higher at every interval ($p < 0.05$, Fig. 2); Bonferroni's correction was applied at each interval. In both groups, urinary excretion of tobramycin was highest between 3 hours and 12 hours after prosthesis insertion. Urinary excretion levels were significantly different between the 2 groups at 3 hours ($p = 0.012$) and 12 hours ($p = 0.009$), but not at the other intervals (Fig. 3).

The peak serum tobramycin and peak serum creatinine levels for each patient were not correlated (Pearson correlation coefficient [r] = -0.416 ; $p = 0.411$).

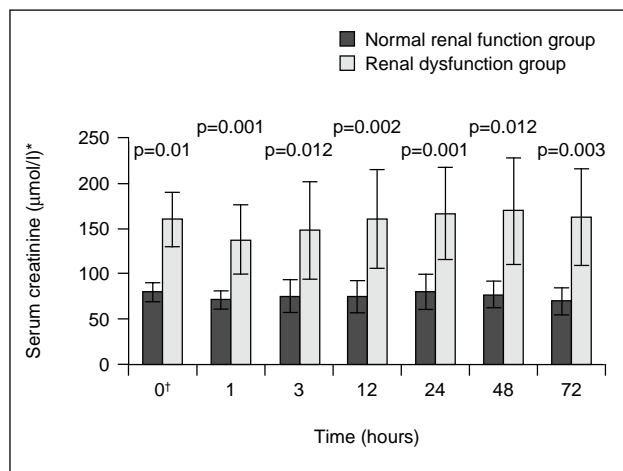
DISCUSSION

Tobramycin is an aminoglycoside closely related to



* Error bars denote SDs

Figure 1 Serum tobramycin levels of the 2 groups



* Error bars denote SDs

† 0 hour denotes preoperative level

Figure 2 Serum creatinine levels of the 2 groups

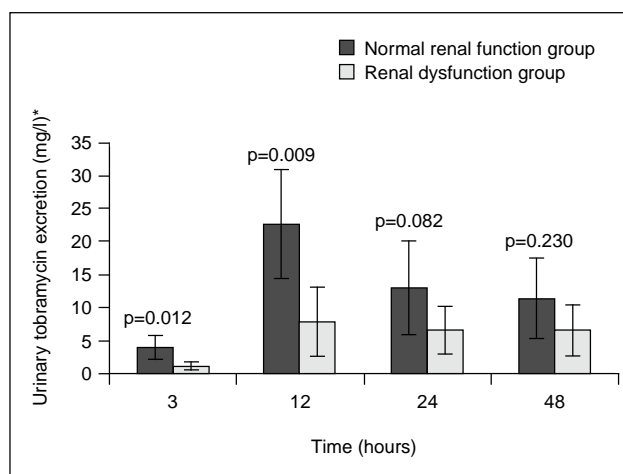
gentamicin. They have a similar spectrum of activity, but tobramycin is slightly more active against *Pseudomonas* and less ototoxic and nephrotoxic than gentamicin at the operative site.^{5,7} Because its elution characteristics are superior to gentamicin,⁶ tobramycin is the preferred additive to acrylic bone cement for the prevention of periprosthetic infection.

Tobramycin is locally concentrated in the drainage fluid with minimal systemic absorption and has no systemic side-effects when mixing tobramycin powder with cement.⁸⁻¹⁰ Tobramycin levels at the operative site were similar in both groups and far exceeded the minimum inhibitory concentration for common pathogenic bacteria, even after 48 hours.^{7,12,13}

Systemic absorption was minimal in both groups: mean serum tobramycin levels peaked at postoperative 3 hours, then gradually declined to negligible levels at 72 hours. Although the renal dysfunction group had higher systemic concentrations at all intervals, the difference was not significant. The mean peak serum tobramycin level of each group was below 2 mg/l (only one patient peaked at 2.1 mg/l at one interval). Although prolonged elevation of serum tobramycin levels above 2 mg/l is not recommended, the threshold for nephrotoxicity has been reported to be 6.0–12.0 mg/l.^{7,13}

Serum creatinine levels were significantly higher in the renal dysfunction group throughout the study period. Mean values in both groups dropped at postoperative one hour and then gradually rose back to preoperative levels at 72 hours. The dip probably represents a fluid load from the perioperative period resulting in dilution and a drop in serum creatinine.

In both groups, urinary tobramycin was rapidly



* Error bars denote SDs

Figure 3 Urinary tobramycin excretion levels of the 2 groups

excreted in the first 12 hours after prosthesis insertion with a gradual decline thereafter. The renal dysfunction group excreted less rapidly, and its urinary tobramycin levels remained higher for a longer time than the normal renal group.

This study are clinically relevant because the patients are moderately renal dysfunctional and are representative of elective surgical candidates. It is hard to extrapolate these data to patients with severe renal dysfunction (i.e. dialysis) who may not be suitable for elective surgery. However, no correlation was found between peak serum tobramycin and peak serum creatinine levels, so it is probably safe to use

Simplex-tobramycin bone cement in patients with severe renal dysfunction as well.

Simplex-tobramycin bone cement delivers very high local bactericidal concentrations of tobramycin. It has minimal systemic absorption with rapid urinary

excretion, even in patients with moderate renal dysfunction. The pharmacokinetic profile of Simplex-tobramycin bone cement appears to be effective and safe for patients with renal dysfunction undergoing elective total hip replacement.

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