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Short Course Netilmicin Prophylaxis in Renal Stone Surgery

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Summary. Following surgery for the removal of intrarenal calculi 30% of patients will develop severe wound complications. This study assesses the role of a short course of netilmicin given over the operative period, in 20 consecutive patients. Preoperative studies demonstrated that whilst 20% of patients had bacterial growth in the urine, culture of the removed calculus demonstrated that 50% of the stones exhibited a significant bacterial growth. Of the 20 patients, only one developed a wound complication. Following the preoperative dose, satisfactory netilmicin levels were obtained and no patient had levels > 1 $\mu g\ ml^{-1}$ by 7 h. Despite some degree of renal impairment, serum urea and creatinine values were unaffected.

Key words: Netilmicin, Antibiotic prophylaxis, Aminoglycosides, Renal stone surgery.

Introduction

The presence of an intrarenal calculus is often complicated by superadded infection commonly caused by *Proteus sp.* and *E. coli*, which further compounds renal damage. In the absence of preoperative antibiotic prophylaxis, 30% of patients undergoing surgery for removal of intrarenal calculi will develop severe postoperative wound and urinary tract complications [1, 5, 7].

Antibiotic prophylaxis in renal stone surgery has been aimed at eradicating preoperative urinary tract infection, and on a long term basis to prevent recurrence of infection [2]. The use of a short course of antibiotics to cover the immediate operative period and minimize postoperative wound complications has not previously been studied.

Netilmicin is an aminoglycoside antibiotic effective against the major Gram negative organisms commonly associated with renal calculi. The role of a short course of Netilmicin as a prophylactic agent in renal stone surgery has been assessed.

Patients and Methods

Twenty consecutive patients (9 males, 11 females), undergoing surgery for removal of intrarenal or obstructing calculi were studied. Ten patients had upper ureteric or renal pelvic obstruction, eight patients had staghorn calculi associated with recurrent urinary tract infection and diminished renal function, and two patients had recurrent intrarenal calculi. The age range of the patients was 24 to 70 years with a mean age (± SEM) of 42.6 (± 3) years.

Prior to surgery, renal function was assessed by measurement of the serum urea and creatinine, and a routine preoperative intravenous pyelogram (IVP) was performed in all patients In the eight patients with staghorn calculi, the IVP failed to demonstrate satisfactory excretion of dye from the affected kidney. Creatinine clearance and isotope renograms were performed to assess the degree of function in the involved kidney. In these eight patients creatinine clearance ranged from 29 to 84 ml min^{-1} with a mean (± SEM) of 60 (± 10) ml min^{-1}. Isotope renography demonstrated that the percentage function of the affected kidney ranged from 0 to 40%, with a mean of 19.7 (± 9)%.

In the four days prior to surgery a routine mid-stream sample of urine (MSSU) was obtained for bacterial culture, and was positive in four patients. All subjects received 100 mg netilmicin as an IM bolus, 12 h and 1 h preoperatively, and 100 mg 12 h postoperatively. Serum netilmicin levels were measured at 30 min intervals throughout the operation and hourly for 6 h in the postoperative period.

Netilmicin serum assays were performed by the "Emit" system (Syva, Paulo Alto, California, USA). At operation bacteriological swabs from the wound, intrarenal tissue and pelvic urine were taken for culture, and in sixteen of the twenty patients the stone was cultured by the method of Nemoy and Stamey [6]. In the postoperative period, samples were taken from the wound drain, t tube and MSSU (or catheter urine), on days 1 and 4.

All specimens were inoculated using a 1/300 ml standard loop onto C.L.E.D. agar and 5% Horse Blood Agar and incubated in an atmosphere of 5% CO_2 in air for 48 h. A positive result was recorded when the yield was greater than 10^8 organisms/litre. Organisms were identified using standard methods. Gram negative aerobic bacilli were identified using the AP120E system (Analytab Prod. Inc., Basingstoke, Hampshire, U.K.). Antibiotic sensitivity testing was performed by the disc diffusion method using *E. coli* N.C.T.C. 10418 as control organism for urinary isolates and Staph. Aureus N.C.T.C. 6571 for isolates from other sources.

Serum urea and creatinine were measured on the first and third postoperative days.

Table 1. Positive bacteriological findings in eight patients following renal stone surgery

Patient No.		4	5	6	9	12	14	15	18
Postoperative samples									
MSSU	Day 1	–		*E. coli*	–	*Proteus mirabilis*	–	–	–
	Day 4	*Strep. faecalis*	*E. coli* + *Strep. faecalis*	*E. coli*	–	*Proteus mirabilis*	*Proteus mirabilis*	*E. coli*	*E. coli*
Wound Drain	Day 1	–	–	*E. coli*	–	–	*Proteus mirabilis*	–	–
	Day 4	–	*Strep. faecalis*	*E. coli*	*Strep. faecalis*	–	–	*E. coli*	–
T tube	Day 1	–	–	–	–	–	*Proteus mirabilis*	–	–
	Day 4	–	–	–	–	–	–	–	*E. coli*
Stone culture		–	–	–	–	*Proteus mirabilis*	*Proteus mirabilis*	*E. coli*	*E. coli*
Postop. wound complication		–	–	–	–	–	–	Ureteric fistula	–

Statistical Methods

(1) Analysis of the difference between the mean values of preoperative and postoperative serum creatinine and urea values was carried out by using the paired t test.

(2) Analysis of the change in serum netilmicin levels with time was performed by the method of least squares. Calculation of the derived slope gave a value for the rate of change in serum netilmicin per unit time, and allowed calculation of the half life of serum netilmicin (t_{50}).

Results

Thirteen patients underwent pyelorureterolithotomy; nine for the removal of a single stone, three for the removal of multiple stones and one for the removal of a staghorn calculus. Four patients with staghorn calculi had pyelonephrolithotomy and the remaining three patients (with staghorn calculi) had pyelonephrolithotomy with renal artery occlusion. In the latter three cases ischaemic renal damage was prevented by the intravenous administration of inosine ten minutes before cross clamping [8]. At operation fourteen patients had a t tube inserted into the ureter to allow drainage of urine, and all patients had a wound drain inserted into the peri-renal space.

Bacteriology at Operation. Two of the twenty patients had a positive bacterial culture from the wound swab (*E. coli*). Six patients demonstrated identical bacterial growth from both the kidney swab and the pelvic urine (three *E. coli* alone; three a mixed growth of *Proteus mirabilis* and *E. coli*). Five of these patients cultured identical organisms from the stone (two *E. coli* alone; three a mixed *Proteus mirabilis* and *E. coli*), one stone was not cultured. A further 11 stones were cultured and only three demonstrated bacterial growth, two staghorn calculi grew *Proteus mirabilis* alone, and one solitary calculus grew *E. coli* from both the stone and pelvic urine.

Postoperative Bacteriology. One patient died in the early postoperative period (day 4) from an intracerebral haemorrhage. Of the nineteen surviving patients, seven had a positive culture from the postoperative MSSU, three having an identical culture from the wound drain. One patient had an identical growth from the MSSU, wound drain and t tube and a further patient had an identical culture in both the MSSU and t tube. One patient had a positive culture in the wound drain alone (Table 1). In four of the eight patients with a positive bacterial culture from either the wound drain, t tube or MSSU, the organisms isolated were identical to those cultured from the calculus. In the remaining four patients, the stone was not cultured in two patients, and no organisms were isolated from the stone in the final two patients. In the nineteen patients assessed in the postoperative period, only one patient (No. 15) developed a clinically significant wound complication. A urinary fistula developed due to a second stone obstructing the distal ureter necessitating further exploration. The obstructing stone was removed without incident and the fistula rapidly resolved.

The mean (± SEM) serum netilmicin level at 1 h was 6 (± 0.5) $\mu g\ ml^{-1}$ and at $1^1/_2$ h was 4.5 (± 0.4) $\mu g\ ml^{-1}$

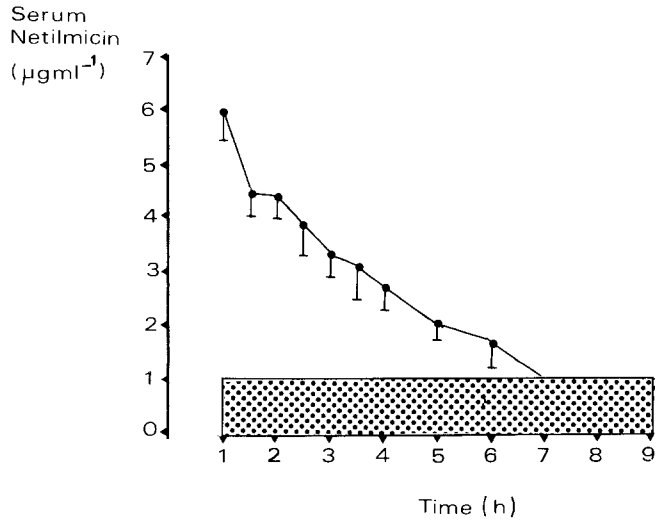

Fig. 1. To show the change in mean (± SEM) values in serum netilmicin ($\mu g\ ml^{-1}$), in 20 patients, following a 100 mg bolus dose

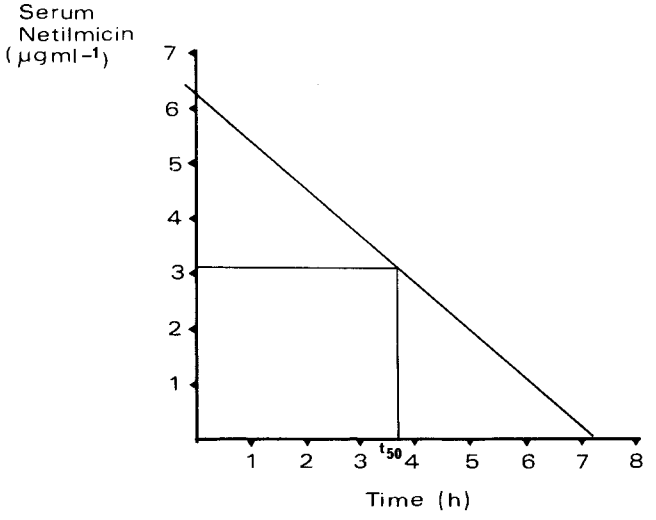

Fig. 2. To illustrate the derived slope of the plot of the rate of change in serum netilmicin per unit time. The t_{50} represents the calculated mean half life of serum netilmicin (t_{50} = 3.7 h)

(Fig. 1). In all patients the serum netilmicin level at 7 h following an IM bolus injection of 100 mg was less than 1 μg/ml. The calculated mean half life (t_{50}) of a 100 mg bolus IM injection of Netilmicin was 3.7 h (Fig. 2).

The mean (± SEM) preoperative urea was 6.1 (± 1.1) mmol l^{-1}, and on days 1 and 3 were 5.5 (± 0.8) and 4.8 (± 0.6) mmol l^{-1} respectively (Fig. 3). The mean preoperative serum creatinine was 97 (± 12.6) μmol l^{-1} and on days 1 and 3 were 97.8 (± 9.3) and 90.3 (9.7) μmol l^{-1} respectively (Fig. 4). No significant differences between the mean preoperative and postoperative values for serum urea and creatinine were noted.

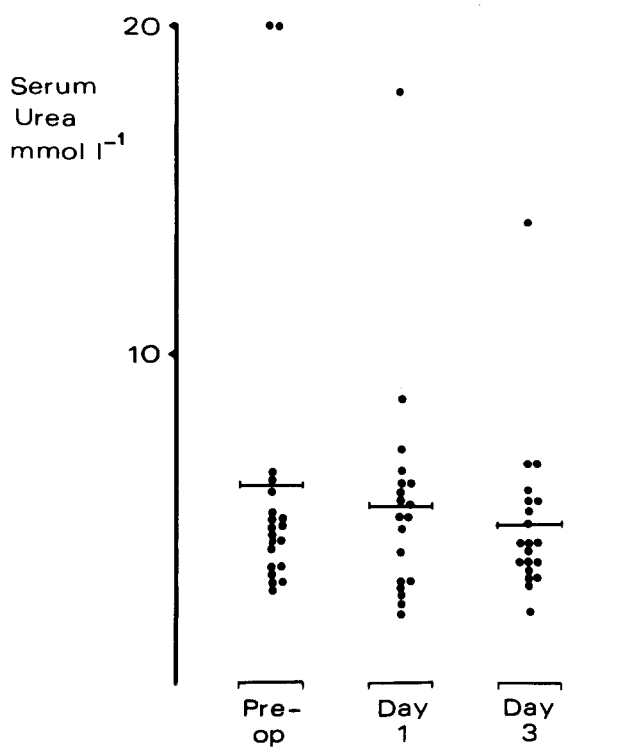

Fig. 3. To show the preoperative and subsequent postoperative values of serum urea (mmol l^{-1})

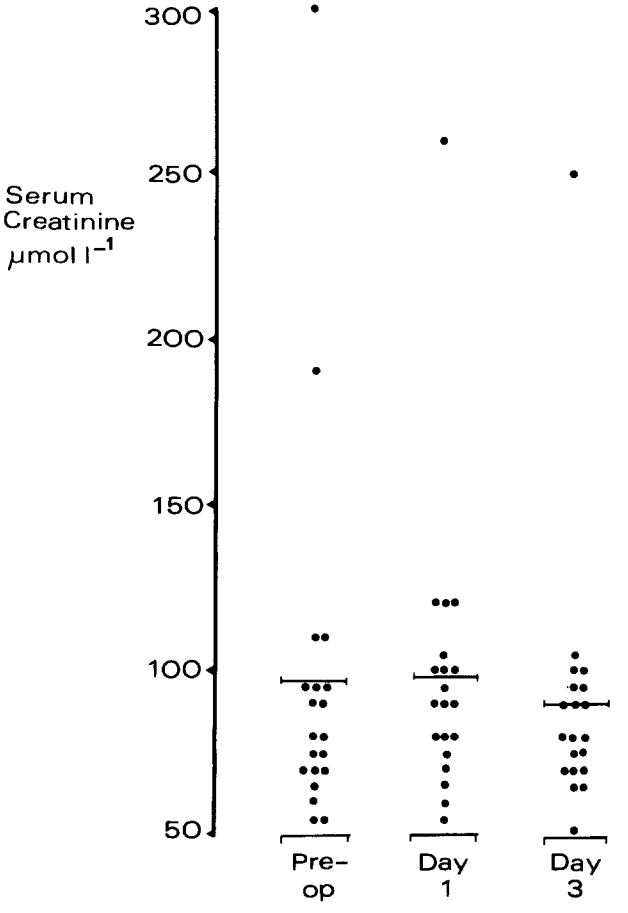

Fig. 4. To show the preoperative and subsequent postoperative values of serum creatinine (μmol l^{-1})

Discussion

Removal of intrarenal calculi may be associated with a wound and urinary tract complication rate ranging from 5 to 30% [1, 5, 7]. Between 1978 and 1981, 98 consecutive operations were performed for the removal of intrarenal calculi in the Department of Urology in the Glasgow Royal Infirmary. The incidence of severe wound complication and urinary fistula formation in this series was 25%. In each case the wound discharge persisted for longer than 10 days and bacteria cultured demonstrated a significant growth of organisms.

It has long been recognised that there is a strong association between renal stone disease and recurrent urinary tract infections [2, 3]. It has been shown that it is possible to demonstrate bacterial growth within a renal calculus in both the presence and absence of a proven urinary tract infection [3]. In the present study four of the twenty patients had a positive bacterial growth in the preoperative MSSU, whilst eight of the sixteen calculi cultured (50%) demonstrated bacterial growth from the stone. Urinary colonization by bacteria was transient in all but one case (the patient who developed an infected fistula), and the urines had become sterile by the sixth postoperative day. Careful follow-up demonstrated that urinary tract infection developed in only two of nineteen patients (10.4%), one with contralateral calculi and the second with residual calculi present. In both cases the patients were treated with the appropriate antibiotic. It is now felt that long-term single agent antibiotic therapy is unwarranted, as this may allow the development of antibiotic resistant bacteria that become increasingly more difficult to eradicate. It is also noted that postoperative bacterial contamination of the urine is transient, and will disappear by the sixth postoperative day. Prolonged therapy would therefore be of little value.

The role of antibiotic prophylaxis in renal stone surgery has hitherto been limited to the use of a course of antibiotic therapy to treat a preoperative proven urinary tract infection with the aim of preventing endotoxaemia resulting from the manipulation of an infected calculus [2]. The use of a short course of antibiotics to cover the immediate operative period has not previously been studied.

Netilmicin is an effective antibiotic against the commonly encountered organisms associated with renal calculi, namely *Proteus mirabilis, E. coli* and occasionally *Klebsiella*. The use of three 100 mg doses of netilmicin to cover the perioperative period resulted in satisfactory perioperative and postoperative serum levels of the antibiotic. Despite some degree of renal impairment related to the underlying stone disease, all patients had serum netilmicin levels of less than 1 $\mu g\ ml^{-1}$ 7 h following the IM injection. The mean half life of netilmicin following an IM bolus dose of 100 mg in these patients was found to be 3.7 h, which is similar to values noted in patients with normal renal function [4]. In the present study postoperative serum urea and creatinine were unaffected by the administration of the antibiotic.

In the nineteen patients assessed, only one patient developed a clinically significant wound complication. This was related to the mechanical obstruction of the distal ureter by a second calculus.

A 3-dose regimen of perioperative antibiotic prophylaxis is of value in renal stone surgery. Netilmicin appears to be a safe and effective antibiotic, and may be used in the diseased kidney complicated by renal calculi and the common Gram negative organisms.

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