Renal function after hip arthroplasty and isoxazolylpenicillin prophylaxis

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Two different isoxazolylpenicillins (cloxacillin and dicloxacillin) were compared regarding impairment of renal function after total hip arthroplasty. 85 patients received dicloxacillin and 93 patients received cloxacillin as antibiotic prophylaxis. A total dose of 6 grams was given during a 36-hour period in doses of 1 gram pre-, per- and postoperatively. Creatinine in serum and β_2-microglobulin in serum and urine were determined preoperatively and 2, 4, and 10 days after the operation. The dicloxacillin-treated patients had an increase in creatinine and β_2-microglobulin in serum that was not seen in the cloxacillin group. The increase indicates a transient injury in the process of glomerular filtration. Although the increase was temporary and subclinical, a dose reduction is nevertheless recommended for older patients.

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In a study of patients operated on with knee and hip arthroplasties, Isacson and Collert (1984) observed an increased level of plasma creatinine, indicating an impairment of renal function in 35 out of 278 patients who received dicloxacillin as antibiotic prophylaxis. In a retrospective study of 789 patients treated with cloxacillin or dicloxacillin after hip arthroplasty operation, Hedström and Hybinette (1988) found 16 cases of serious increases of plasma creatinine in patients treated with dicloxacillin, but only minor increases when cloxacillin was used. In a prospective study of 70 patients who underwent hip arthroplasty in our hospital and were given dicloxacillin pre-, per- and postoperatively as antibiotic prophylaxis, Wahlström et al. (1992) found a transient increase of creatinine postoperatively, and also an increase in β_2-microglobulin in serum and urine.

We have now compared renal functions after total hip arthroplasty when the two different isoxazolylpenicillins (cloxacillin and dicloxacillin) were given as prophylaxis.

Patients and methods

All hip arthroplasty patients treated on two wards of the Department of Orthopedics at the Linköping University Hospital were involved in a prospective study (Table 1). Patients younger than 65 years, patients with hypersensitivity to penicillin, or patients with renal disease were excluded.

Table 1. Patient series

	Dicloxacillin	Cloxacillin
Number	85	93
Women	50	47
Men	35	46
Age	74 (65–86)	74 (65–89)
Rheumatoid arthritis	7	6
Primary arthroplasty	70	85
Rearthroplasty	15	8
Type of endoprosthesis		
ITH[a]	53	45
Lubinus SP[b]	31	48
Rippenprotes[b]	1	0
NSAID	23	23
ASA (aspirin)	3	6

[a]Richards International U.S.A.
[b]Waldemar Link, Germany

The first part of the study (Group A) involved 85 patients who were operated on from May 1987 to October 1988 and were given prophylaxis with dicloxacillin. The second part of the study (Group B) was carried out from February 1990 to March 1991 and involved 93 patients who were given prophylaxis with cloxacillin.

The dorsolateral approach was utilized. Methyl methacrylate bone cement, CMV (CMV Laboratories, U.K.), was used on the primary arthroplasties and Palacos cum gentamicin (Essex, U.K.) on the rearthroplasties. The operations were routinely done

Table 2. $ß_2$-microglobulin in urine (mean *SE*). Reference value < 370 mg/L

Day	Dicloxacillin n 85	Cloxacillin n 93
0 (preop)	161 *13*	560 *221*
2	3722 *762*	3792 *603*
4	3669 *834*	3412 *729*
10	340 *79*	806 *375*

No significant differences between the groups

Table 3. $ß_2$-microglobulin in serum (mean *SE*). Reference value 1.0–2.5 mg/L

Day	Dicloxacillin n 85	Cloxacillin n 93	*P*-value
0 (preop)	2.35 *0.10*	2.20 *0.10*	0.3
2	2.52 *0.17*	2.05 *0.08*	0.008
4	2.87 *0.15*	2.31 *0.09*	0.001
10	3.14 *0.14*	2.82 *0.11*	0.07

Table 4. Creatinine in serum (mean *SE*). Reference value 50–115 mmol/L

Day	Dicloxacillin n 85	Cloxacillin n 93	*P*-value
0 (preop)	87 *2.8*	86 *1.8*	0.6
2	109 *5.7*	87 *3.0*	0.001
4	99 *4.3*	82 *2.6*	0.001
10	95 *3.7*	83 *1.8*	0.004

Table 5. $ß_2$-microglobulin in serum (mean *SE*) of patients treated with NSAID/ASA. Reference value 1.0–2.5 mg/L

Day	NSAID/ASA n 54	non-NSAID/ASA n 124	*P*-value
0 (preop)	2.41 *0.13*	2.22 *0.08*	0.2
2	2.62 *0.22*	2.10 *0.08*	0.006
4	2.75 *0.17*	2.47 *0.10*	0.1
10	3.23 *0.15*	2.86 *0.10*	0.05

under spinal anesthesia. Sagman (erythrocyte concentrate), Macrodex (Pharmacia, Sweden) and crystalloids were used for blood loss-substitution.

Macrodex (500 mL) was given 2 days following operation to prevent thromboembolism. Dicloxacillin (Diclocil, Bristol Myers AB, Sweden) or cloxacillin (Ekvacillin, Astra Läkemedel AB, Sweden), 1 gram, was given as an intravenous infusion 1–2 hours preoperatively, during operation, 1–2 hours postoperatively and 3 additional times with 8-hour intervals between doses. A total of 6 grams of dicloxacillin or cloxacillin was administered during a 30–36-hour period.

The renal function tests were performed preoperatively and on Days 2, 4, and 10 after operation. Creatinine in serum was determined by the alkaline picrate method adapted to the Hitachi 717 instrument (Bartels et al. 1972). $ß_2$-microglobulin in urine and serum were analyzed with a radioimmunoassay (Phadebas, Pharmacia, Sweden; Evrin et al. 1971, Evrin and Wibell 1972). An 8-hour urine sample was required for the analysis. Alka-Seltzer was given the day before the test to alkalize the urine, since $ß_2$-microglobulin is destroyed in acidic urine (Kjellström and Piscator 1977).

For statistical analysis, the Student's *t*-tests, two-tailed for paired and unpaired observations, were used and checked in both StatView and StatWork computer programs with significance level 0.05.

Results

There was a large increase of $ß_2$-microglobulin in urine postoperatively (Table 2). The values reached a maximum on Days 2–4 and were almost normalized on the tenth day after operation. There were no differences between the two groups.

$ß_2$-microglobulin in serum increased significantly in both groups from the preoperative test to Day 10 after operation (Table 3). There were significant differences between the groups on the 2nd and 4th postoperative days, i.e., with higher values in the dicloxacillin group.

The mean values of creatinine in serum were within normal ranges, but there were statistically highly significant differences between the two groups (Table 4). The dicloxacillin group displayed higher values 2, 4 and 10 days after the operation. The use of Non Steroid Anti Inflammatory Drugs (NSAID) or AceticSalicylAcid-drugs (ASA) did not affect the concentration of creatinine in serum or $ß_2$-microglobulin in urine (Table 5). $ß_2$-microglobulin in serum on Day 2 was significantly higher in the NSAID-treated patients in both group A and group B.

Complications

Group A. 2 patients died postoperatively. One of these patients developed septicemia, followed by

anuria. The probable cause of the septicemia was a contaminated blood transfusion (*Staphylococcus epidermidis*) given one day after the operation. The other patient died 3 weeks after operation with heart failure and pneumonia. 2 patients had myocardial infarctions (nonfatal). One patient had a postoperative hip dislocation that was treated with closed reduction. One patient developed skin exanthema, most probably due to dicloxacillin, which had to be discontinued.

One late deep, possible hip infection occurred in a re-arthroplasty, probably secondary to an infection in the urinary tract. However, no bacteria were cultured from the hip. One superficial infection with *Staphylococcus aureus* was successfully treated with debridement and oral antibiotics.

Group B. 3 hematomas were evacuated, one of which was infected with *Staphylococcus aureus* and was successfully treated with debridement and oral antibiotics. One patient had a dislocation and was treated with closed reduction. One patient had a urinary tract infection and one was treated with a suprapubic catheter because of hypertrophic prostate. One deep venous thrombosis and one pulmonary embolus (nonfatal) developed.

Discussion

The differences between the groups concerning creatinine in serum postoperatively indicate a difference in postoperative glomerular filtration. The increase in group A is in accordance with the report from Hedström and Hybbinette (1988). The increase in $ß_2$-microglobulin in serum on Day 2 and on Day 4 in this group also is indicative of damage to glomerular filtration, which was not found in Group B.

The transient increase in excretion of $ß_2$-microglobulin in urine in both groups is in accordance with previous reports, in which Wide and Thorén (1972) and Walenkamp et al. (1983) reported that urine $ß_2$-microglobulin increased after major operations and trauma. The most probable explanation for the increase in $ß_2$-microglobulin in urine is that it was caused by diminished tubular reabsorption, probably due to the peroperative injury.

The increase in $ß_2$-microglobulin in serum that occurred in both groups together with an almost normalized excretion of $ß_2$-microglobulin in urine on Day 10 and a normalization of creatinine, could indicate a discrete decrease in glomerular filtration, but since $ß_2$-microglobulin belongs to the group of C-reactive proteins, it is more likely that the rise was part of an inflammatory-healing process. Thus, the increase in $ß_2$-microglobulin in serum on Day 10 is probably not a sign of a decreased glomerular filtration rate, but rather a sign of an inflammatory healing process (Wahlström et al. 1992).

Glomerular filtration measured as creatinine in serum and $ß_2$-microglobulin in serum was decreased in the early postoperative period in the group of patients who had been given dicloxacillin. Even if the increases in creatinine and $ß_2$-microglobulin in serum were small, and the effect on renal function was subclinical in the present study, this may be a factor which adds to age related decreased renal function in the elderly (Ljungberg and Nilsson-Ehle 1987).

With increased age and decreased renal function in the average hip arthroplasty patient, there is a subsequent risk of accumulation of the drugs and the dose should be reduced, especially for dicloxacillin.

The increased level on Day 2 of $ß_2$-microglobulin in serum of the patients treated with NSAID or ASA preparations seems to support the suggestion by Hedström and Hybinette (1988) that NSAID may enhance the nephrotoxic effect of antibiotics on renal function. However, since creatinine in serum was not increased in the NSAID-treated patients, it is not likely that the use of NSAID is an important factor affecting renal impairment. On the other hand, the increase in $ß_2$-microglobulin in serum could be an indication of a greater vulnerability to trauma among patients needing NSAID/ASA.

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