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Nephrotoxicity in isoxazolylpenicillin prophylaxis in hip surgery

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In 789 courses of antibiotic prophylaxis in hip arthroplasty surgery, either dicloxacillin (Diclocil®) or cloxacillin (Ekvacillin®) was used during two different time periods. The surgical methods, anesthesia, preoperative and postoperative care of the patients, and laboratory procedures were the same all the time. Changes in creatinine values were used as a method for evaluating the impact on renal function. When using dicloxacillin, a pathologic increase of creatinine was noted in 12 and 13 percent by two different calculation methods. Sixteen patients (4.2 percent) had a severe creatinine increase during the first postoperative week after dicloxacillin prophylaxis, requiring dialysis in 2 patients. Cloxacillin had only a marginal impact on renal function. Patients above aged 70 years were more vulnerable as regards renal function than younger persons, and the impairment was slightly dose related in all ages. In the dicloxacillin group, preoperative use of antiphlogistic drugs was correlated with reduced postoperative renal function.

Increases of serum creatinine after antibiotic prophylaxis in arthroplasties have been reported by Gudmundsson et al. (1983) and Isacson and Collert (1984). After a patient at Kalmar Hospital had developed renal insufficiency following a hip-joint replacement and dicloxacillin prophylaxis, attention was directed to this complication. Sixteen cases with moderate to severe renal insufficiency have been noted, and we have retrospectively analyzed a patient material from Kalmar focusing principally on factors that might have significance for reduced kidney function subsequent to hip arthroplasties and antibiotic prophylaxis.

Patients and methods

At Kalmar Hospital, arthroplasties have been performed under antibiotic prophylaxis since 1970. Through 1975, only a few operations were performed and cloxacillin was chosen for prophylaxis. In 1976, dicloxacillin was selected.

During the period 1974–1985 inclusive, 723 patients had primary arthroplasties and 107 were reoperated on because of mechanical problems; infected arthroplasties were not included in the reoperated on group. Antibiotic prophylaxis was given to all these patients. It was started parenterally 1–2 hours before operation and from the second day peroral dosage forms were used. The daily dose of cloxacillin was fairly constant, 4 g in 99 percent of the patients, and the duration of prophylaxis was 5 days and included oral flucloxacillin 1 g t.i.d. The daily prophylactic dosage of dicloxacillin averaged 3.7 g during the first 3 years (1977–1979). This was then reduced in 1980–1982 inclusive to 3.0 g, mostly given for 7 days; only 2.7 percent of the patients received more than 4 g.

During the period studied, surgical methods, anesthesia, preoperative and postoperative care of the patients, and laboratory procedures were unchanged.

Surgical methods. All the operations were perfor-

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med in a conventional operating theater. The Charnley total hip was inserted through a posterior incision, and CMV-polymethylmethacrylate bone cement was used.

Anesthesia and postoperative care. The anesthesia was usually epidural, and rarely full anesthesia was used. Prophylaxis against thrombosis was usually Macrodex-Dextran®, 500 ml given in the morning before the operation and again on the first and third postoperative days. Blood losses peroperatively and postoperatively were replaced with whole blood and crystalloids, such as Rehydrex® and Normodex®.

Chemical laboratory analysis. The assays were performed according to the routine methods at the chemical laboratory department. Serum creatinine (Method: Jaffés reactions – normal ranges: males 53–106 μmol/L, females 35–88 μmol/L) and blood hemoglobin were recorded. Serum creatinine was determined preoperatively, on the first postoperative day, and 1 week postoperatively. Hemoglobin was recorded preoperatively and repeatedly during the first 2 postoperative weeks.

Evaluation of renal function impairment. Estimation of changes of creatinine compared with preoperative values is a crude method for studying the impact on renal function. However, in this retrospective analysis, it was the only available method. The means and ranges, increase of creatinine by at least 45 μmol/L (Smith's definition), and proportions of patients having more than 115 μmol/L in creatinine were calculated; the patients were grouped in 10 percent intervals. In this way the sensitivity could be increased when searching for correlations between patient factors and impact on renal function. Serum creatinine investigations were repeated on the first postoperative day and 1 week postoperatively during 683 courses of antibiotic prophylaxis. Thus, some data are missing from the last occasion, but these patients had either a decrease in or a similar serum creatinine on the first postoperative day compared with the preoperative values. The mean preoperative creatinine value in the dicloxacillin group was 84.9 (40–230) μmol/L, and in the cloxacillin group 89.7 (50–183) μmol/L. There was a slightly lower mean in the women than in the men; the difference was not as great as in a healthy population.

Patient characteristics. Totally, the 723 patients were given 835 prophylaxis courses of the various antibiotics. Dicloxacillin was the main prophylaxis during the years 1976 through 1981 and cloxacillin after that. Dicloxacillin was used in 378 evaluative courses (45 percent) and cloxacillin in 411 (49 percent) in a total of 677 patients in whom hip-joint prostheses were inserted mainly owing to coxarthrosis (Table 1). Two patients given isoxazolylpenicillins could not be evaluated (0.2 per cent). Other antibiotics than isoxazolylpenicillins were used in 44 courses (5.3 percent) mainly because of known penicillin hypersensitivity. These courses are not evaluated in the following. No abnormal findings were recorded in these patients.

At the operation the mean ages of the patients were 68 (50–84) and 69 (35–85) years in the dicloxacillin and cloxacillin groups, respectively. During the last years of the period studied, a greater number of older patients than earlier were operated on, which is in turn reflected by a higher proportion of patients in the age-group 80–85 years who were given cloxacillin. There was a slight female dominance (57 percent). Concomitant preoperative diseases in the 2 prophylaxis groups were similar (Table 2).

Because of the joint diseases, antiphlogistic drugs had been given continuously before the operation to 40 percent in both prophylaxis

Table 1. Indications for hip arthroplasty related to prophylactic drug

	Dicloxacillin	Cloxacillin	Total
Arthrosis	318	335	653
Rheumatoid arthritis	38	35	73
Sequelae of femoral neck fracture	14	21	35
Late complications of arthroplasties	5	19	24
Other indications	3	1	4
	378	411	789

Table 2. Frequency (percent) of concomitant diseases in the two prophylaxis groups. More than one disease occurred in some patients

	Dicloxacillin	Cloxacillin
Angina pectoris	12	15
Arterial hypertension	20	16
Congestive heart failure	12	7
Preoperative kidney disease	1	2

Table 3. Per- and postoperative variables related to prophylactic drug. Values are mean (SD)

	Dicloxacillin	Cloxacillin
Preoperative blood pressure (mmHg)	145 (23)	149 (21)
Min. perop. blood pressure (mmHg)	101 (20)	99 (17)
Operation time (min)	122 (32)	134 (35)
Blood volume loss (L)	1.57 (0.70)	1.6 (0.72)
Blood substitution (units)	3.75 (2.9)	3.10 (1.8)
Fluid substitution (L)	4.09 (0.83)	3.97 (0.64)

groups, notably indomethacin (23 percent of all the patients), ibuprofen (6 percent), naproxen (5.7 percent), or piroxicam (4.6 percent).

Perioperative events. The operation time, blood-pressure falls, blood loss, and blood and fluid substitution were similar in both prophylaxis groups (Table 3).

Results

Postoperative renal function The proportions of patients with creatinine values above 115 μmol/L increased particularly in the dicloxacillin group (Table 4). Totally, 13 percent of the patients had preoperative creatinine levels within reference values, and more than 115 μmol/L on the first postoperative day. According to Smith's definition, 12 percent in the dicloxacillin group and 0.8 percent in the cloxacillin group had a renal impairment.

In 16 patients (4.2 percent) the serum creatinine values rose from 70–100 μmol/L to 200–830 μmol/L during the first postoperative week. All of these patients had been given dicloxacillin (mean 3.5 g/day) as prophylaxis. The patients were 71 (52–79) years of age, and all but 1 had coxarthrosis. From a nomogram calculation based on creatinine values, age, sex, and body weight, the preoperative creatinine clearance in these patients was 71 (37–125) ml/min. Dialysis was considered in 6 patients and was performed in 2 of them. Most of the increased creatinine values normalized spontaneously within 6 weeks. No patient died of impaired renal function.

About one tenth of all the patients had a 30 percent increase or more in the postoperative creatinine values compared with the preoperative value. This figure was considered as a moderate to severe creatinine increase and was chosen in the search for factors with correlation to impact on renal function. However, in several patients such an increase occurred within the reference values.

No correlation with concomitant diseases or preoperative kidney function was noted. Reduced kidney function was independent of perioperative events (Table 3). Reoperation did not increase the risk of renal dysfunction. The highest daily dose of dicloxacillin influenced slightly the degree of renal impairment. There was no correlation with duration of prophylaxis.

Patients 70 years of age or older were more vulnerable with regard to renal function. This was seen mainly in the dicloxacillin group, in which 19 percent had abnormal creatinine values 1 week postoperatively. In patients below 70 years of age, the corresponding figure was 8 percent.

In the dicloxacillin group, there was a higher increase of creatinine 1 week postoperatively in patients on antiphlogistic drugs ($P = 0.015$) than in patients without this treatment. Eleven of the 16 patients with severe renal impairment had antiphlogistic drugs. No correlation between antiphlogistic drugs and antibiotic prophylaxis was found in the cloxacillin group ($P = 0.017$).

Discussion

Generally, in retrospective studies the results must be interpreted cautiously. However, in our

Table 4. Serum creatinine values (mean (range) μmol/L) repeatedly assayed in 683 courses of prophylaxis

	Dicloxacillin n 305		Cloxacillin n 378	
		> 115 μmol/L percent		> 115 μmol/L percent
Preoperative	86 (40–230)	9	90 (50–180)	10
1st postop. day	99 (40–320)	20	90 (42–200)	14
1 week postop.	108 (40–830)	18	87 (31–182)	7

analysis, we cannot repudiate the fact that 16 patients (4.2 percent) receiving dicloxacillin prophylaxis in a mean daily dose of 3.5 grams had a considerable increase in their postoperative creatinine values. Dialysis was necessary in 2 patients. The demand on an antibiotic prophylaxis must be that the severe adverse events should not exceed the protective efficacy.

Only a few studies on the impact of drugs on renal function during antibiotic prophylaxis have been performed. Isacson and Collert (1984) found that the postoperative serum creatinine increased to pathologic values in 13 percent of their patients, i.e., the same as our finding. When compared with Gudmundsson et al. (1983) – who reported a pathologic increase of serum creatinine after dicloxacillin prophylaxis in 10 percent of their patients using Smith's definition as a criterion for renal impairment – we had a corresponding finding in 12 percent of our patients.

The cause of renal impairment is hitherto unclear. Köhler et al. (1975) have considered a dose-related effect of dicloxacillin. Such a mechanism has also been proposed by Nordbring (1984) in elderly patients undergoing a surgical trauma. In our analysis, we found a slight correlation with dose and age, but it was not conclusive. Another mechanism might be an interaction between other drugs – such as antiphlogistic drugs – and dicloxacillin. Our patients on antiphlogistics had greater impairment of renal function than others in the dicloxacillin group. Such a correlation was not found in patients given cloxacillin. The pathophysiology of this is not known. Dicloxacillin and cloxacillin differ slightly in chemical composition and protein binding. Antiphlogistic drugs may sometimes cause nephrotoxicity, and like isoxazolylpenicillins they are highly protein-bound. Further studies on interaction between isoxazolylpenicillins and antiphlogistic drugs are warranted and so are prospective, comparative investigations on antibiotic prophylaxis and nephrotoxicity as proposed by Nordbring (1984).

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