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Renal impairment after high doses of dicloxacillin-prophylaxis in joint replacement surgery

The frequency of postoperative renal impairment after total hip and knee replacement was studied prospectively in 350 patients without signs of pre-existing renal disease. The first 278 patients were given dicloxacillin as prophylaxis against infection. In the remaining 72 patients dicloxacillin was excluded and gentamicin-impregnated cement was used as the only infection prophylaxis. In 35 patients in the first group (13 per cent), postoperative serum-creatinine was increased to pathological values. Thirteen of these patients were clinically affected, two had to be dialysed, and one died. In the second group there was no case of renal impairment. It is concluded that the systemic administration of antibiotics may be a cause of postoperative illness due to renal impairment.

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At Sabbatsberg Hospital, Stockholm, 139 total hip and knee replacements were performed during 1980. Among these cases we observed six patients who unexpectedly suffered an episode of postoperative renal failure. The number of renal failures was much higher than anticipated. Previous authors have reported an incidence of 0.5 per cent of renal failure after general surgery (Littmann et al. 1979). We have only found one earlier study of renal function after total joint replacement (Gelman et al. 1979).

Many antibiotics are known to be nephrotoxic. Our prime suspect was the gentamicin used in the bone cement in some of our cases, but retrospectively we could not find any correlation between its use and the occurrence of renal impairment.

In spite of earlier reports of its innocuousness (Wilson et al. 1975, Visuri et al. 1976), we began to suspect that the antibiotic given as infection prophylaxis, dicloxacillin, might be one of the factors involved in the etiology of renal impairment. In order to study the frequency and causes of renal impairment after joint replacement surgery, we started a prospective study in January 1981.

Patients and methods

From January 1981 to November 1982, 367 total hip or knee replacements, using polymethylmethacrylate, were performed at Sabbatsberg Hospital. After exclusion of 17 patients, who had clinical or laboratory signs of pre-existing renal or urological disease, 350 patients (299 total hip and 51 knee replacements) remained for the prospective study. Their mean age was 70 (34–89) years, 99 were male and 251 female. The preoperative diagnosis was arthrosis in 217 cases, rheumatoid arthritis in 25, and complications after fracture of the femoral neck in 108 cases. The operations were performed in a standard operating theatre. Epidural anesthesia was used with a stationary catheter through which bupivacaine hydrochloride was given.

Antibiotics and patient groups

From January 1981 to April 1982, 278 patients were operated on with dicloxacillin as infection prophylaxis (the dicloxacillin group). In preparing the intravenous solution, 1 g of dicloxacillin was dissolved in 100 ml of sterile water or isotonic saline. The solution was given over 15–30 min. The first intravenous infusion of 1 g was given 2 h before operation. Thereafter 1 g was administered as an intravenous infusion 4 times daily during the next 2 days. On the third day 1 g was given orally 4 times. Thus 13 g was given in the course of slightly more than 3 days.

In 102 patients in the dicloxacillin group, gentamicin cement was used; 0.5 g of powdered gentamicin was added to 40 g cement. This was done in those cases where we judged the risk of postoperative infection to be increased, e.g. patients with previous hip surgery, diabetics or patients with certain skin disorders. In all other patients in this group, CMW bone cement without any antibiotics was used.

From April to November 1982, 72 patients were operated on without dicloxacillin prophylaxis. Gentamicin-impregnated cement was used as the only infection prophylaxis in all these cases (the gentamicin group). Except for the exclusion of dicloxacillin and the consistent use of gentamicin-impregnated cement, no other change was made in the pre-, intra- or postoperative procedure.

Postoperative routines and laboratory tests

500 ml of dextran was given on the day of operation and 500 ml on the first postoperative day in order to prevent postoperative thrombosis. The intra- and postoperative blood loss was compensated for with cooled stored blood, which was heated to body temperature before infusion. During and after the operation, the patients were given intravenous electrolyte solutions (Ringerdex, Rehydrex, Normodex and Inverdex) until they were able to manage their own fluid intake, which generally occurred on the second day after the operation. We kept records of the fluid intake and urine production during the first postoperative week. Before the operation, a standard autochemist blood test which included serum creatinine (normal value below 120 μmol/l) was taken. This test was repeated on the fourth and tenth postoperative days. In order to find out whether hemoglobinemia or myoglobinemia had any influence on the development of renal impairment, the serum haptoglobin level was recorded. If serum creatinine increased or urine production decreased, a 24-h creatinine test was taken in order to get a more exact measure of renal function. We also made continuous notes of the clinical status of the patients with special reference to allergic or uremic manifestations. In 110 patients, the last 44 from the dicloxacillin group and the first 66 from the gentamicin group, the above tests were supplemented with a postoperative creatinine clearance test and pre- and postoperative determinations of beta-2-microglobulin in all patients; this protein has a low molecular weight of 11 800 and is freely filtered through the renal glomeruli and almost totally reabsorbed in the proximal tubuli (Evrin & Wibell 1972). In patients with tubular dysfunction, an increased amount, i.e. more than 400 μg/l, is found in the urine. The test is very sensitive and can be used to detect even subtle impairment of renal function (Peterson et al. 1969, Wibell & Karlsson 1976).

Results

In the dicloxacillin group, we found postoperative serum creatinine raised to pathological values in 35 of the 278 patients or 13 per cent. Ten of these were men and 25 women and their mean age was 76 (60–89) years. Eleven patients had a preoperative history of cardiovascular disease as hypertension (nine patients), intermittent claudication (one patient), and auricular fibrillation (one patient). In nine of these patients, gentamicin-impregnated cement was also used. The mean postoperative serum creatinine was 302 (135–1278) μmol/l, and the postoperative clearance was 33 (5–69) ml/min/1.73 m^2 body surface. The mean amount of blood transfusion was 2120 (800–4400) ml. There was no significant difference in fluid intake between the affected 35 patients and the non-affected patients in the dicloxacillin group, but we observed oliguria of short duration in seven of the affected patients; urine production was less than 500 ml/24 h. This generally occurred on the third day after the operation and lasted for 2 days. In another three cases the urinary sediment contained an increased number of red blood cells.

The anesthesia records showed that intraoperative systolic blood pressure was in no case lower than 70 mmHg. Thirteen patients had slightly increased transminase values after the operation. The maximum ASAT value was 2.25 μkat/l (normal value below 0.70 μkat/l). The maximum ALAT value was 1.82 μkat/l (normal value below 0.70 μkat/l).

The serum haptoglobin level was somewhat higher after than before the operation. Thirteen of the 35 patients were clinically affected. They were tired and had difficulties in carrying out postoperative physiotherapy. One patient died from cardiac failure; renal impairment with serum creatinine values of 567 μmol/l was the main contributing cause. Two patients had to be dialysed. A transient rash developed in five patients. Except for the one who died, all patients eventually recovered.

The 243 patients from the dicloxacillin group

who did not show any signs of renal impairment were slightly younger with mean age 69 (34–84) years and the volume of blood transfusion was somewhat smaller, mean 1760 (0–7200) ml. Gentamicin-impregnated cement had been used in 93 of these patients. The mean postoperative creatinine clearance in this group was 76 ml/min/1.73 m^2 body surface.

In the gentamicin group, there were no patients with pathological postoperative serum creatinine values. The difference in number of patients with renal impairment in this group and the dicloxacillin group was significant (p less than 0.005). There was no difference between the groups with regard to age, preoperative diagnosis, type of operation or any other significant aspect. The postoperative creatinine clearance in the gentamicin group was 74 ml/min/1.73 m^2 body surface, which was almost the same as in the non-affected patients in the dicloxacillin group. Preoperatively, nine patients in the dicloxacillin group and three in the gentamicin group had an increased urinary level of beta-2-microglobulin. If these patients are excluded, the results show that excretion in the dicloxacillin group was increased in 15 of 35 patients, with a mean postoperative value of 8.9 (0.4–16) mg/l. Except for one case in the dicloxacillin group, all the examined patients with raised postoperative serum creatinine also had increased excretion of beta-2-microglobulin; in the gentamicin group, eight of 63 patients had an increased excretion with mean value 1611 (431–3862) µg/l. The difference was significant (p less than 0.01).

Discussion

Our study showed that 35 out of 278 patients who were given dicloxacillin prophylactically suffered from postoperative renal impairment. In the other group of 72 patients, who were not given antibiotics systemically, serum creatinine remained normal postoperatively. We have deliberately used the term "impairment" to stress the fact that we regard the findings in most of our cases as a milder form of renal malfunction rather than as acute renal failure. However, three of our patients did have classical renal failure and another ten cases had a more diffuse clinical picture with non-characteristic fatigue as the cardinal symptom. Renal failure seems to be a rare event after elective orthopedic surgery. Previous studies on this complication (Marshall 1971, Baek et al. 1975, Littman et al. 1979, Schuster 1980) do not include this type of surgery. The only exception is Gelman et al. (1979) who found renal failure in eight of 41 patients who underwent total hip replacement. They were able to correlate postoperative renal failure with the administration of previously frozen blood and nephrotoxic compounds used for wound irrigation. As we used neither of these substances, they could be excluded as an explanation of our findings.

At the beginning of our study we were uncertain if raised postoperative serum creatinine was a normal or a pathological reaction after a comparatively large surgical intervention in elderly patients such as a total hip or knee arthroplasty. Previous studies did not answer this question. In view of the fact that all signs of renal impairment disappeared when we ceased using dicloxacillin, we are inclined to regard even a small increase in postoperative serum creatinine as a pathological reaction.

There are no earlier reports of nephrotoxic reactions implicating dicloxacillin as an etiologic agent. However, our results show that prophylactically given dicloxacillin may have an adverse effect on renal function after total joint replacement. One possible reason for the nephrotoxic effect might be that the dose of dicloxacillin used was too high for these elderly patients. We did not, however, exceed the, at that time (1982), recommended maximum dose of 6 g daily. It seems more likely that the explanation may be some unknown interaction with another substance given in connection with the operation. The marked increase in beta-2-microglobulin excretion suggests some impairment of proximal tubulus function in the kidney. This increased excretion in 15/35 examined patients in the dicloxacillin group, as compared with 12 per cent in the gentamicin group, also indicates that renal impairment was even more common than could be shown with less sensitive methods. As the serum hap-

toglobulin level was higher after than before the operation, a transfusion reaction or myoglobinemia are less likely causes.

The efficiency of antibiotics in preventing infection after total joint replacement is well documented (Ericson et al. 1973, Chodak & Plaut 1977, Hill et al. 1981) and there is now general agreement on the necessity of antibiotic prophylaxis and/or a clean air environment in this kind of surgery (Lidwell et al. 1982). Good results have also been reported using gentamicin-impregnated cement as infection prophylaxis (Buchholz & Gartmann 1972). Josefsson et al. (1981) found, in a prospective study, that the number of deep infections was lower in a group of patients in whom gentamicin cement was used as infection prophylaxis as compared with patients given antibiotics systemically. So far, no deep infection has been diagnosed in any of our groups.

Hitherto, no side effects have been reported in connection with the use of gentamicin-impregnated cement. Thus, in the present state of knowledge, it seems to be a good alternative to systemically given antibiotics in the prevention of infection in total joint replacement. Further research might reveal the complication reported here as occurring more commonly than was previously believed.

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