Acta Orthop Scand 55, 405–406, 1984

Is dicloxacillin nephrotoxic?

Guest Editorial

Folke Nordbring

Department of Infectious Diseases, University Hospital in Lund, Sweden

In this issue, Isacson & Collert report a previously unrecognized impairment of the renal function in patients subjected to joint replacement. This side-effect appeared in 35/278 patients who received prophylaxis with intravenous dicloxacillin, either alone or in combination with gentamicin bone cement. The amazingly high figure of 13 per cent contrasted with a rate of 0/72 (0 per cent) among patients in whom only gentamicin cement was used. Naturally, the suspicion arose that the administration of isoxazolylpenicillin caused the renal complication. Similar experiences were reported from another orthopaedic department in Sweden. The renal impairment was so severe in two of Isacson and Collert's cases that dialysis was required. One patient died in cardiac failure, to which renal failure may have contributed.

If there is a true connection between dicloxacillin prophylaxis and the raised serum creatinine and increased urinary excretion of beta-2-microglobulin, as reported, it is indeed a remarkable finding. There seems to be only one similar report in the literature, although dicloxacillin has been in clinical use for approximately 20 years. In Germany, Köhler et al. (1975) treated 10 patients with high intravenous doses of dicloxacillin (8-16 g/24 h) and noted a transient increase in serum creatinine. They considered the toxic effect to be dose related. The latest editions of *Meyler's Side Effects of Drugs* (Dukes 1975, 1980), covering the years 1972–1980, do not mention nephrotoxic reactions after dicloxacillin therapy. In a recent survey of antistaphylococcal penicillins, including a review of side-effects, Neu (1982) only mentions the well-known interstitial nephritis, most often appearing after therapy with methicillin. This reaction is characterized by fever, rash, eosinophilia, haematuria, proteinuria and occasionally renal insufficiency; thus it is a syndrome quite different from that reported by Isacson & Collert.

How is it that observations of renal disturbances after dicloxacillin prophylaxis have not been reported until now? Although it is known that a certain period of clinical experience may be required until a potential nephrotoxicity is detected – for example, it took about 5 years for cephaloridine (Kabins & Cohen 1966) – consideration must be given to the possibility that some new disturbing factor has appeared. Is there interaction – as the authors suggest – with some other drug or fluid given during the operative procedure, either during anaesthesia or later on? Is it possible that the pharmaceutical composition of the substance for injection has been changed?

The dosage used could be contributory to the reaction. The patients with renal complications were old: all over 60 years with a mean age of 76. At this age there is a physiological reduction of the renal function, although routine tests like serum creatinine do not disclose the functional impairment. The renal impairment might be enhanced by the surgical trauma. As a result of ageing, the serum half-life of betalactam antibiotics is markedly prolonged (Linglöf et al. 1980, Ljungberg & Nilsson-Ehle 1983). Administration of 1 g dicloxacillin intravenously every 6 h for 2 days certainly causes an accumulation of the antibiotic in serum. No data are available, however, as no serum monitoring was carried out. The different pharmacokinetics in elderly persons must be taken into account more in future clinical practice.

Isacson & Collert compared data from one period with dicloxacillin prophylaxis with those from a subsequent period with gentamicin cement. Such a comparison is hazardous and hardly acceptable, however, because a number of biases may lead to wrong conclusions. The only way to find out whether dicloxacillin is nephrotoxic or not is to perform a prospective, strictly randomized comparative study of the effect of dicloxacillin with that of gentamicin cement. The doses of dicloxacillin should be adjusted to the high age of most of the patients and to the purpose of the prophylaxis. The following doses are suggested: 1 g dicloxacillin at the start of the anaesthesia, and 1 g 12 h later; thus only two doses are given in the first 24 h, and no more. Monitoring of serum and urinary concentrations should be done. The renal function should be carefully studied before and after the operation and the prophylaxis, using reliable methods such as ^{51}CrEDTA clearance.

The observations reported by Isacson & Collert should stimulate more investigations of potentially harmful drug effects in the elderly: more drugs are used in the old and sick than in the young and healthy who are usually recruited for the drug trials on which dosage recommendations are based.

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