Bone levels of cephradine and cefuroxime after intravenous administration in patients undergoing total hip replacement

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Summary. A randomised, comparative study is reported of single intravenous doses of cephradine 2 g or cefuroxime 1.5 g given as prophylactic cover for total hip replacements in 40 patients. The serum and bone levels of cephalosporin achieved were higher in the cephradine treated group in proportion to the higher dose employed. Both agents provided adequate bone levels on average, cephradine 25.34 mcg/g, cefuroxime 17.39 mcg/g, although bone penetration was more variable with cefuroxime.

Résumé. Dans cette étude comparative randomisée, 40 patients ont reçu une dose intraveineuse unique de 2 g de céphradine ou de 1.5 g de céfuroxime en tant que couverture prophylactique d'arthroplastie totale de hanche. Les concentrations sérées et osseuses de céphalosporine ont été plus élevées dans le groupe traité par la céphradine, en rapport avec l'utilisation d'une dose plus importante. Des concentrations osseuses adéquates ont été obtenues en moyenne avec les deux produits (25.34 mcg/g avec la céphradine et 17.39 mcg/g avec le céfuroxime) bien que la pénétration osseuse ait été plus variable avec le céfuroxime.

Key words: Hip replacement, intravenous administration, Cephradine, Cefuroxime

Introduction

Deep infection following elective joint replacement surgery, although rare, can be disastrous for the patient concerned and all possible measures are taken to reduce it to a minimum. Prophylactic systemic antibiotics are widely used and have been shown to be effective, probably having an additive beneficial effect with clean air systems [6]. Cephalosporins, particularly earlier 'generation' compounds, with good anti-staphylococcal activity are suitable for prophylactic cover of orthopaedic procedures. They also cover Gram-negative organisms which do contribute to deep sepsis following joint replacements [7]. Cephradine prophylaxis has been associated with a deep infection rate of 0.3% in a long-term study of hip replacements [2] and similar low infection rates have been reported with other cephalosporins [3].

Cephradine and cefuroxime are two cephalosporins widely used by orthopaedic surgeons. They are both effective anti-staphylococcal agents with similar high stabilities to beta-lactamases [9].

The bone penetration of these cephalosporins has been investigated separately and both have been shown to achieve levels which exceed those needed to inhibit Staphylococci and other common pathogens [5, 1]. An intravenous injection at the time of induction of anaesthesia has been shown to provide optimal bone levels of cephalosporin [8]. Techniques of extraction of antibiotics from bone tissue are critical in determining the levels obtained, and separate studies from different centres cannot be relied upon to provide proper comparative data. Since the relative bone penetration of cephalosporins is a major factor in choosing an agent for routine use, a direct comparison of the bone penetrations of cephradine and cefuroxime after normal prophylactic doses was undertaken.

Methods

Forty patients undergoing elective hip arthroplasty were randomly allocated to receive cephradine or cefuroxime given as
a slow intravenous bolus at the time of induction of anaesthesia. The doses used were cephradine 2 g and cefuroxime 1.5 g. Patients who had received antibiotics in the 7 days preceding surgery were excluded, as were those allergic to cephalosporins, those with impairment of renal or hepatic function and those undergoing revision surgery. A sample of blood was taken immediately before giving the cephalosporin to check that no antimicrobial activity was present at this stage. Further blood samples were taken at 10 min and 2 h after administration of the antibiotic, and also at the time of removal of the head of the femur. Serum was separated from all blood samples and stored at $-20^\circ$C until assayed. The head of the femur was wiped dry and also stored at $-20^\circ$C until assayed for cephalosporin content.

**Assay**

Assays were undertaken by a plate diffusion method employing Sarcina lutea ATCC 9341. Standard curves were constructed for both antibiotics. Recovery of spiked serum samples was approximately 100%. Serum samples were diluted in phosphate buffer. Bone samples were reduced to a fine powder and shaken for 1 h in phosphate buffer to elute the antibiotic. All assays were undertaken in triplicate. Limits of detection for cephradine in serum and bone were 0.05 mg/l and 0.05 mcg/g respectively and for cefuroxime in serum and bone 0.1 mg/l and 0.1 mcg/g respectively.

**Results**

Sixteen male and 24 female patients were studied. One patient in the cephradine group was excluded from analysis because only 1 g was given. The average age of the group was 63.3 years (range 19 to 84). All patients tolerated the antibiotics well.

The average time from administration of antibiotic to removal of the head of the femur and the taking of the simultaneous serum sample was 20.3 min (SD 4.74) in the cephradine group and 24.2 min (SD 9.10) in the cefuroxime group. The average time elapsed between the injection and the 'ten minute' serum sample was, for cephradine and cefuroxime respectively, 12.75 and 14.72 min and for the '2 h' samples, 2 h 6 min and 2 h 12 min respectively.

All predose samples showed no antibiotic activity. Serum levels are shown in Fig. 1 together with the usual MICs for cephradine and cefuroxime against Staphylococcus aureus [4].

Bone levels are shown in Table I together with the bone:serum ratio. The bone levels found in cephradine treated patients were higher than in those who received cefuroxime ($P<0.1$ unpaired 't' test). Two patients had both hips replaced on different occasions and each was randomised to receive cephradine for one hip and cefuroxime for the other. These patients are indicated in the table.

**Discussion**

This study confirms earlier investigations with cephradine and cefuroxime which indicate that both agents penetrate bone well in most patients. Levels in bone were, on average, higher for both agents than the concentrations required to inhibit pathogens which may cause deep infection after joint replacement. The bone:serum ratios were approximately 0.2 for both cephalosporins, and this is similar to ratios recorded at another centre for cefuroxime [5]. Serum levels were higher for cephradine in the ten minute sample and in the sample taken at the time of removal of the head of the femur, but this is probably a reflection of the 2 g cephradine and 1.5 g cefuroxime doses given. Bone levels were also higher for cephradine than cefuroxime ($P<0.1$) and are in proportion to the higher cephradine dose. The relative doses employed were, however, in the ratio of those which are employed in clinical practice, i.e., cephradine 1: cefuroxime 0.75.

Two patients in the cephradine group had avascular necrosis of the femoral head which might tend to reduce bone levels. These patients had bone levels (20.9 and 21.8 mcg/g) below the average for the cephradine group but not significantly so.

It is noteworthy that the bone concentrations in the cefuroxime group were more variable than in the cephradine group. In one cefuroxime patient it was not possible to detect any cephalosporin in the bone sample, despite an adequate