TIMING OF ANTIBIOTIC ADMINISTRATION IN KNEE REPLACEMENT UNDER TOURNIQUET

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Cephamandole levels in serum and drain fluid were measured in 32 knee replacement operations to determine the benefit of an intravenous dose of antibiotic at the time of tourniquet deflation. Concentrations of cephamandole in drain fluid were directly proportional to the serum concentration at the time of tourniquet release. A 'tourniquet-release' dose of antibiotic increased drain fluid concentration threefold.

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It is standard practice to give parenteral antibiotics during operations involving orthopaedic implants, but the effects of isolating the operative site with a tourniquet have not been extensively studied. One recent report suggested that a fourfold rise in infection was associated with the use of a tourniquet (Salam et al 1991).

In an experimental model, a therapeutic concentration of antibiotic in the tissues at the time of bacterial inoculation prevented infection (Burke 1961), but an antibiotic administered after tourniquet inflation may not reach the exsanguinated limb. Bannister et al (1988) studied tissue concentrations of antibiotic in bone and fat and concluded that at least five minutes should elapse between the administration of the antibiotic and tourniquet inflation. We have studied the effect of a bolus of antibiotic administered at the time of tourniquet release, to determine whether increasing the serum antibiotic level at that stage would raise the concentration at the operative site.

PATIENTS AND METHODS

We studied prospectively 29 patients undergoing 32 total knee replacements (three patients had bilateral procedures at separate operations). Approval for the investigation was given by the hospital ethical committee, and informed consent was obtained from the patients. No patient had a known allergy to beta-lactam antibiotics. Cephamandole was chosen since it achieves a higher concentration in bone than cephalothin (Schruman, Hirshman and Burton 1980) or cefuroxime (Leigh et al 1982) and is active against coagulase-negative staphylococci (Davies et al 1986).

Antibiotic regimes
Control group A were given 1 g of cephamandole five minutes before tourniquet inflation.
Control group B had 2 g of cephamandole five minutes before tourniquet inflation.
Study group C had 1 g of cephamandole five minutes before tourniquet inflation and a 'tourniquet-release dose' of 1 g five minutes before tourniquet release.

All patients had a 1 g dose of cephamandole six hours later.

Statistical design. Patients were allocated to the three groups by stratified randomisation with a block size of four. This allocated twice the number of patients to group C to allow comparison with groups A and B combined. Those with planned bilateral operations were randomised separately so that a control regime was used on one side and a tourniquet-release dose given for the other side. Groups were compared by analysis of variance and correlations were examined by Pearson's correlation.

Operation. A primary cemented total knee arthroplasty was performed on all patients through a parapatellar incision, using closed suction drainage after the procedure.

Specimen collection. The first intravenous dose of cephamandole was given slowly over five minutes; on comple-
tion of this injection a venous specimen was taken from the other arm. The tourniquet was inflated exactly five minutes later. After the operation, blood samples were taken at the time of tourniquet release. Samples of drain fluid were aspirated from the drain line ten minutes after tourniquet release and again immediately before the next dose of antibiotic, after six hours. A simultaneous venous sample was also taken at that time. All specimens were refrigerated, centrifuged and stored until batch analysis was carried out.

**Antibiotic assay.** Samples were assayed by reverse-phase, high-performance liquid chromatography (Aziz et al 1978). Cephamandole was analysed on a C18 column, detected by ultraviolet absorbance at 268 nm and...
quantified by peak height. The minimum level of detection of cefamandole was 1 mg/l. The accuracy and precision of the assay were < 5.8% and < 1% respectively.

RESULTS

Of the 32 operations 16 were in the tourniquet-release group C, and eight in each of the control groups A and B. There were no significant differences in the patients' weights, tourniquet time or time of sampling serum or drain fluid. The results from the three groups are given in Figure 1. The mean drain fluid concentration at tourniquet release was significantly higher in group C at 44.5 mg/l than in group B, 23.2 mg/l or group A, 14.6 mg/l (p = 0.003).

A more detailed analysis of more frequent blood and drain specimens was undertaken in three patients, one from each regime (Fig. 2). The half-life of cefamandole in these three patients averaged 66 minutes. The concentration in the drain fluid in each case fell as the serum concentration decreased and rose again within an hour of the subsequent antibiotic dose. Analysis of simultaneous measurements of drain and serum concentration showed a very significant correlation (Fig. 3; Pearson's correlation 0.54, p < 0.001).

There was evidence of later wound infection in four patients, all from control group A. Culture showed Staphylococcus aureus in two, and a coagulase-negative staphylococcus in the other two. The organisms were not resistant to cefamandole, and all four infections resolved within two weeks with restriction of mobilisation and antibiotic treatment.

DISCUSSION

Effective prophylaxis against wound infection requires adequate concentrations of appropriate antibiotics at the site of the operation (Kaiser 1986), and the dose and the timing of administration are particularly important when a tourniquet is used (Bannister et al 1988; Friedman et al 1990). The duration of antimicrobial activity depends on the half-life of the agent: for cefamandole this has been reported to be 54 minutes in healthy adults (Kucers and Bennett 1987); in our series it was 66 minutes. When a tourniquet has been applied, the limb is excluded from the systemic circulation, and penetration of the drug to the operative site is limited. When a tourniquet is released, bleeding is profuse, and the initial haematoma would be expected to have a concentration which reflects the current systemic level. This systemic concentration from the initial dose will have fallen by this time, and the antibiotic levels in our first drain samples were directly proportional to the serum concentrations at the time of tourniquet release (Fig. 3).

The concentration of antibiotic at the operative site needed for prophylaxis is unknown, but it is generally accepted that the level in the serum should be from two to four times the minimal inhibitory concentration (MIC90; Reeves et al 1978). The most common organisms cultured from infected hip and knee arthroplasties are Staphylococcus aureus, Staphylococcus albus and Escherichia coli (Hope et al 1989; Lettin et al 1990; Windsor et al 1990). An appropriate concentration of cefamandole to counter these organisms is 2 mg/l (Kucers and Bennett 1987), but the presence of foreign material can increase the likelihood of a wound infection (Howe 1966). The published data on the MIC90 of antibiotics to bacteria do not take account of the presence of an implant and it seems probable that the concentration necessary to prevent infection in these circumstances could be as high as 16 mg/l. The trend towards the use of short duration antibiotic prophylaxis is to be commended, but greater care may be required to achieve adequate levels.

Kaiser (1986) suggested that a large dose of antibiotic be given before tourniquet inflation. In our study the control regime of 2 g at induction produced a drain fluid concentration which was not significantly better than that achieved by a 1 g dose, probably because of the short half-life of the beta-lactam antibiotics.

Antibiotic levels in the tissues at the knee can be greatly increased by administering antibiotics directly into a foot vein (Hoddinott 1990), and this method may prevent bacterial inoculation of the tissues from becoming established. An unknown factor is the relative importance of bacterial inoculation on the surfaces of implants. Gristina, Naylor and Webb (1990) have suggested that Gram-positive staphylococci compete with tissue cells to be the first to colonise the surface of implants in a race for the surface.

The administration of 1 g of antibiotic before tourniquet inflation and a second 1 g at tourniquet release resulted in a significant increase in antibiotic concentration both in the serum and the drain fluid. The high local concentration in the initial wound haematoma, adjacent to the implant, should increase the protection against
infection. When a surgeon operates distal to a tourniquet consideration must be given not only to the selection of antibiotic prophylaxis but also to its dose and the timing of its administration. We believe that antibiotic prophylaxis should include a tourniquet-release dose.

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