ANTIBIOTIC PROPHYLAXIS WITH CEFUROXIME
IN ARTHROPLASTY OF THE KNEE

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A randomised prospective trial was undertaken of antibiotic prophylaxis given at various intervals before inflation of the tourniquet for arthroplasty of the knee. Cefuroxime assays of bone and subcutaneous fat from samples collected throughout the operation demonstrated that an interval of 10 minutes was necessary to obtain adequate prophylaxis. Improvement in the timing of antibiotic prophylaxis may result in a reduction in the incidence of infection.

Several recent reports demonstrate that the incidence of infection after arthroplasty of the knee is uncomfortably high in some series, ranging from 0.8% to 10.3% in unconstrained prostheses (Walker and Schurman 1984; Goodfellow and O'Conner 1986) and from 4.8% to 12.5% in hinged prostheses (Rand, Morrey and Bryan 1984; Walker and Schurman 1984). Deep infection of a cemented knee replacement remains a very difficult therapeutic problem (Rand et al. 1984). Salvage of the prosthesis is occasionally possible by early debridement and irradiation or by delayed exchange arthroplasty (Insall, Thompson and Brause 1983). Arthrodesis is often necessary though in this situation it may fail to achieve bony union (Johnson and Bannister 1986).

Prevention of infection is therefore particularly important. A major factor in reducing infection is the proper use of prophylactic antibiotics which must be present in adequate bactericidal concentrations in the wound during the operation (Burke 1961). Cephalosporins can be used alone to provide antibiotic cover against the range of potential pathogens, and have been shown to penetrate bone well in arthroplasty of the hip. A threedose regime of cefuroxime is commonly chosen because of its efficacy, wide spectrum and low toxicity (Hughes et al. 1982). However, some studies have noted inexplicably low local concentrations of the antibiotic about the knee during the arthroplasty (Dash et al. 1982). Analysis of the antibiotic regime used in Bristol demonstrated that the anaesthetist often failed to administer the antibiotic before application of the tourniquet (Johnson and Bannister 1986). This present study was undertaken to determine the pharmacokinetics of cefuroxime in conjunction with a tourniquet, and to see whether inadequate prophylaxis could result from incorrect timing of antibiotic administration.

METHOD

A prospective trial was undertaken of 22 patients undergoing arthroplasty of the knee at the Nuffield Orthopaedic Centre, Oxford. The patients were assessed for their age, weight, haemoglobin and blood urea concentration, and divided in a random manner into four groups to receive 1.5 g of cefuroxime by intravenous injection 5, 10, 15 or 20 minutes respectively before inflation of the tourniquet.

At the time of inflation of the tourniquet a sample of peripheral venous blood was taken and the serum separated. Throughout each operation small samples of subcutaneous fat were excised from the wound at regular intervals. Samples of bone were collected when available, the time and site of excision of each sample being noted. The serum and tissue samples were stored at −40°C, until a blind assay was carried out (by Glaxo Research Laboratories).

The antibiotic was extracted from the bone and fat samples by the method described by Dash (Dash et al. 1982). The serum was prepared for assay by the addition of an equal volume of 5% perchloric acid to precipitate the serum proteins. The solutions obtained were assayed by high-performance liquid chromatography using a column (10 × 4.6 cm) filled with Spherisorb packing. The mobile phase (12% acetonitrile in 0.05M-ammonium phosphate adjusted to pH 3.0 with phosphoric acid) was allowed to flow through the column at 2 ml/min at room temperature. The cefuroxime was detected by ultraviolet absorbance at a wavelength of 260 nm. The results of the cefuroxime concentration in the samples were corrected by colorimetric estimation for the presence of any blood contamination. The results were
subjected to statistical evaluation using the chi-square test, Fisher’s exact test and the Mann-Whitney U-test.

An estimation of the cefuroxime half-life in the bone and fat in the limb isolated from the general circulation was calculated from these results.

*Staphylococcus aureus* is the principal cause of postoperative infection after knee arthroplasty (Johnson and Bannister 1986) and the minimum inhibitory concentration (MIC) of cefuroxime is 0.5 to 1.0 μg/ml (Barry et al. 1977). The minimum bactericidal concentration (MBC) is the level usually presumed to be adequate for antibiotic prophylaxis and this is conventionally assumed to be four times the MIC (Quintiliani and Nightingale 1984). For the purpose of this study an average tissue concentration of 4.0 μg/g was considered to constitute adequate prophylaxis.

Table I. Antibiotic concentrations in bone and fat in relation to the time of injection

<table>
<thead>
<tr>
<th>Interval between injection and tourniquet</th>
<th>Number of patients</th>
<th>Antacid concentration (μg/g)</th>
<th>In bone</th>
<th>In fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>s.d.</td>
</tr>
<tr>
<td>5 minutes</td>
<td>7</td>
<td></td>
<td>27.3</td>
<td>5.0</td>
</tr>
<tr>
<td>10 minutes</td>
<td>6</td>
<td></td>
<td>25.4</td>
<td>13.7</td>
</tr>
<tr>
<td>15 minutes</td>
<td>5</td>
<td></td>
<td>19.5</td>
<td>4.3</td>
</tr>
<tr>
<td>20 minutes</td>
<td>4</td>
<td></td>
<td>20.8</td>
<td>9.3</td>
</tr>
</tbody>
</table>

RESULTS

The groups of patients receiving antibiotics at 5, 10, 15 and 20 minutes were found not to differ significantly in their ages, weights or renal function. Therefore the distribution of the drug and its renal clearance can be assumed to be the same in each of the patient groups.

The results of the antibiotic assays of the sample of subcutaneous fat taken from the wound during surgery demonstrated that after an interval of five minutes six of seven patients (86%) obtained inadequate antibiotic penetration into the subcutaneous fat. When an interval of 10 minutes or more was allowed, all the 15 patients obtained adequate tissue concentrations (p < 0.001) (Fig. 1 and Table I). In two patients who had an interval of 10 minutes or more some of the fat samples showed concentrations lower than 4 μg/g, even though the average concentration for the two patients exceeded 4 μg/g: both these patients weighed over 80 kg.

Bone samples demonstrated significantly higher antibiotic concentrations than did the fat samples (mean 22.9 μg/g compared to 8.9 μg/g; p < 0.0001). All the patients obtained adequate antibiotic prophylaxis in bone even after the shortest interval of five minutes (Fig. 1 and Table I). The mean antibiotic concentrations in the femur (22.3 μg/g) were not significantly different from those found in the tibia (23.6 μg/g) or patella (23.9 μg/g). This suggests that the antibiotic rapidly penetrates all bones equally.

The half-life of cefuroxime in the subcutaneous fat was prolonged by the tourniquet and demonstrated no significant reduction over the period of operation. The half-life in the bone isolated from the general circulation was 121 minutes.

One patient underwent sequential bilateral knee arthroplasty and was not given an additional dose of antibiotics before inflation of the second tourniquet 135 minutes after the injection of antibiotic. The concentration of antibiotic was adequate during the first procedure, but was inadequate in both the wound, and to a lesser extent in the bone, during the second procedure (Fig. 2).

The early clinical results were good with no inpatient sepsis being recorded. No conclusion is drawn from the lack of infection as the numbers involved are inadequate for such an analysis.
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DISCUSSION

This prospective randomised trial has shown that the timing of the antibiotic injection is important for adequate prophylaxis. This is particularly so for fat which appears to absorb cefuroxime slower than does bone. Cefuroxime appears to be able to penetrate bone in adequate amounts within five minutes and its concentration in the limb isolated from the general circulation decreases very slowly over the course of the operation, with a half-life of 121 minutes. As cefuroxime is not metabolised in the body to any significant extent, the reduction in the concentration must be a result of redistribution between the tissues in the leg, or be due to elution of antibiotic via the intramedullary circulation of the femur. The pharmacokinetics of cefuroxime in the subcutaneous fat of the limb isolated by a tourniquet is different: its uptake is slower and in order to obtain adequate concentrations an interval of at least 10 minutes must be allowed before application of the tourniquet. The cefuroxime levels in the subcutaneous fat do not significantly decrease over the course of the operation, which may be due to the absence of any effective circulation through the fat whilst the tourniquet is inflated.

The high incidence of superficial infection which was found in Bristol and its serious consequences (Johnson and Bannister 1986) may result from inadequate antibiotic prophylaxis, not in the bone but in the subcutaneous fat of the wound. Attention to the timing of antibiotic injection can ensure adequate prophylaxis. Differences in the protocol of antibiotic administration in different centres may account for the wide differences in the incidence of infection following arthroplasty of the knee. A similar protocol is recommended for antibiotic prophylaxis in elbow, ankle or other joint replacements performed under a tourniquet.

The antibiotic concentrations in the second of sequential bilateral knee replacements were inadequate after a single injection of antibiotic. A second prophylactic dose appears to be necessary before inflation of the second tourniquet, but this requires further investigation. Lower concentrations were achieved in patients weighing 80 kg or more and these patients may benefit from a larger dose of antibiotic.

Conclusion. In order to ensure adequate antibiotic prophylaxis in arthroplasty of the knee, the injection of antibiotic should be given before or immediately after the induction of the anaesthetic, to allow an interval of at least 10 minutes for tissue absorption before inflation of the tourniquet.

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REFERENCES


