Antibiotics are often administered prophylactically in spinal procedures to reduce the risk of infection of the disc space. It is still not known which antibiotics are able to penetrate the intervertebral disc effectively. In a prospective, randomised, double-blind clinical study, we examined the penetration of the intervertebral discs of two commonly used antibiotics, cefuroxime and gentamicin. The patients, randomised into two groups, received either 1.5 g of cefuroxime or 5 mg/kg of gentamicin prophylactically two hours before their intervertebral discs were removed. A specimen of blood, from which serum antibiotic levels were determined, was obtained at the time of discectomy. Therapeutic levels of antibiotic were detectable in the intervertebral discs of the ten patients who received gentamicin. Only two of the ten patients (20%) who received cefuroxime had a quantifiable level of antibiotic in their discs although therapeutic serum levels of cefuroxime were found in all ten patients. Our results show that cefuroxime does not diffuse into human intervertebral discs as readily as gentamicin. It is possible that the charge due to ionisable groups on the antibiotics can influence the penetration of the antibiotics. We therefore recommend the use of gentamicin in a single prophylactic dose for all spinal procedures in order to reduce the risk of discitis.

Received 2 October 2001; Accepted 13 March 2002

C. C. Tai, MRCS, Specialist Registrar
N. A. Quraishi, MRCS, Specialist Registrar
J. Batten, PhD, Research Assistant
M. Kalra, MB BS, Clinical Assistant
S. P. F. Hughes, FRCS, Professor
Department of Musculoskeletal Surgery, Faculty of Medicine, Imperial College of Science, Technology and Medicine, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK.

S. Want, PhD, Clinical Scientist
Department of Microbiology, Hammersmith Hospital, Hammersmith Hospital Campus, Du Cane Road, London W12 0HS, UK.

Correspondence should be sent to Mr C. C. Tai at the Department of Trauma and Orthopaedic Surgery, Barnet Hospital, Thames House, Wellhouse Lane, Barnet, Hertfordshire EN5 3DJ, UK.

©2002 British Editorial Society of Bone and Joint Surgery 0301-620X/02/712862 $2.00

Infection of the disc space, or discitis, can occur after haematogenous seeding from a distant source or by iatrogenic introduction of bacteria during procedures which violate the disc. It can also spread from a contiguous source of infection. The reported incidence of infection of the disc space after spinal surgery varies from 0.75% to 4%.6,7 Since the introduction of sensitive MRI which can detect disruption of the disc, there has been an increase in the number of operative procedures for the diagnosis and treatment of such disorders. Studies have suggested that the true incidence of postoperative discitis is higher than has been previously appreciated.6,7 Discitis is a debilitating disorder with a high morbidity. Prophylaxis against infection during spinal surgery has thus been advocated3,5,7-12 There is still controversy, however, as to which antibiotics are capable of penetrating the disc in effective therapeutic concentrations.7,10,12-16

The efficacy of antibiotics depends upon both the anatomy and the permeability of the intervertebral disc. In the adult, this is the largest avascular structure in the body.17 Intradiscal nutrition and levels of permeation of antibiotics depend on passive diffusion through the adjacent bony and cartilagenous endplates and the surrounding annulus fibrosus.17,18 In turn, the permeability of the disc depends on the pore size of the matrix, as well as the molecular weight and charge of the solutes.19

Studies of the penetration of different antibiotics into the lumbar disc of man and animals have shown mixed results.7,9,10,12-16,20-22 There is considerable evidence to suggest that the charge on antibiotics, because of their ionisable groups, is important in determining their ability to diffuse into the disc.12,20,22 A recent in vitro study using a mouse model has suggested that gentamicin may be more effective than cefuroxime since it is positively charged. It may therefore diffuse more rapidly into the negatively-charged disc than negatively-charged cefuroxime.13 Despite their widespread use in all branches of surgery, there has been no study of the penetration of cefuroxime and gentamicin into the human intervertebral disc.

We have therefore compared in a randomised, double-blind prospective study the penetration of the human intervertebral disc by gentamicin and cefuroxime used prophylactically in spinal surgery. We also determined whether the uptake was within the therapeutic range after intravenous administration of a bolus dose of antibiotic.
Patients and Methods

Between November 1999 and December 2000 we assessed preoperatively 20 patients who were to undergo spinal disc surgery for their suitability to take part in the study. There were eight men and 12 women with a mean age of 52 years (28 to 64). The selection criteria included patients with normal renal function, no previous history of otological damage, no previous adverse reaction to any antibiotic, and no administration of either gentamicin or cefuroxime during the previous six months. Patients then consented and were randomly assigned to receive either cefuroxime or gentamicin. Samples of human disc were obtained during the discectomy.

Each patient received either 1.5 g of cefuroxime or 5 mg/kg of gentamicin intravenously two hours before surgery.

During the operation, any disc tissue removed was collected and the concentration of antibiotic determined. At the time of removal of the disc, 5 ml of blood were taken for comparative serum analysis of concentrations of antibiotic.

Processing of disc material. Each sample of disc tissue was received in a sterile container. Specimens were washed clean of any excess blood, weighed accurately to 0.1 mg and homogenised manually in 1.0 ml of sterile water using a glass homogeniser. The samples were agitated on a flask shaker for four hours and then centrifuged at 6500 rpm for five minutes. A bacterial growth-inhibition assay, which has been described previously, was used to measure the concentration of cefuroxime in the supernatants of disc homogenate and serum samples. Zones of inhibition from the samples were used to calculate the concentration of antibiotic by reference to a standard curve. Samples containing gentamicin were measured using a fluorescence polarisation immunoassay. This technique is based on competition for binding sites on a specific antibody, between the antibiotic in the sample and a labelled antibiotic of known concentration. After the reaction, any excess labelled antibiotic produces an endpoint value inversely proportional to the amount of antibiotic in the sample.

Results

In all ten discs from the patients who received gentamicin, levels of antibiotic were detectable and quantifiable. By contrast, in the disc of patients given cefuroxime, only two of ten had concentrations which were measurable (Table I).

In all patients, the serum antibiotic concentrations were also determined. The mean concentration of serum gentamicin was 12.1 µg/ml (8 to 15) and the mean concentration of gentamicin in the disc 5.9 µg/g (1.1 to 12). The penetration of gentamicin from blood to the disc thus averaged 50%.

The serum concentration of cefuroxime was at least 40 µg/ml (the lowest value was 12.5 µg/ml), but its penetration of the disc was only measurable in two of the ten samples. No zone of inhibition occurred around any of the remaining eight samples. The concentration of cefuroxime in these samples must therefore have been less than 0.6 µg/ml, the lower limit of the assay.

No patient developed side-effects from the antibiotics or a postoperative discitis during a follow-up period of six months.

Discussion

Discitis is usually iatrogenic and results either from invasive radiological procedures or spinal surgery. A substantial proportion (67% to 87%) of patients is unable to resume their former work despite adequate therapy for postoperative discitis. Fortunately, intravenous administration of perioperative antibiotics reduces the incidence of postoperative infection. For this to be effective, it is necessary to know whether the antibiotics penetrate the intervertebral disc and whether the degree of penetration achieves a therapeutic level. Since the human adult disc is an avascular structure, antibiotics enter the disc by passive diffusion. Variation in the rate of diffusion for different antibiotics would thus be expected since this may be affected by many factors, including molecular size and charge, serum protein binding, and antibiotic solubility in different tissues.

In this study, gentamicin and cefuroxime were selected because of their broad-spectrum antibacterial effect and established prophylactic efficacy in orthopaedic surgery. The most common causative agent in spinal infection is Staphylococcus aureus, but the incidence of Pseudomonas aeruginosa, as well as other Gram-negative bacteria, is
A dose of 2 g of ceftriaxone was necessary to achieve an effective therapeutic level. By contrast, Gibson et al.\(^{14}\) were unable to retrieve any cefradine or flucloxacillin from the intervertebral discs of 25 patients undergoing anterior surgery for scoliosis. Using rabbit models, Eismont et al.\(^{15}\) also reported no detectable levels of antibiotics in the intervertebral discs after intravenous administration of either cephalothin or oxacillin.

Gentamicin has been shown to penetrate rabbit discs more readily than penicillin by Riley et al.\(^{20}\) who concluded that the charge effect influenced the penetration and distribution of antibiotics. This view was supported by Currier et al.\(^{22}\) who showed that the concentration of gentamicin in the rabbit disc peaked at two hours after an intravenous bolus of the antibiotic. Similarly, other studies\(^{12}\) have demonstrated that positively-charged glycopeptide antibiotics, such as vancomycin and teicoplanin, can penetrate the disc and reach adequate antimicrobial levels.

In our previous experimental study using mouse models,\(^{13}\) we showed that antibiotics which were able to diffuse into the disc were positively charged and those which were unable to penetrate the disc were negatively charged. This observation agrees with that of Urban et al.\(^{17}\) who found that the electrical charge of molecules was an important factor in the ability of solutes to diffuse into the nucleus pulposus. Although the size of the molecule, protein binding, and other molecular characteristics also play an important role in the transport and exchange of antibiotics, our study indicates that molecular polarity is dominant in this interaction.

In our patients, the mean concentration of gentamicin of 5.9 \(\mu g/g\) was achieved in the discs two hours after intravenous administration. This is clinically therapeutic, since the minimum inhibition concentration (MIC) against *Staphylococcus aureus* for gentamicin is 0.12 to 1.0 \(\mu g/ml\). This provides a large therapeutic margin for error since the level in the disc is 5 to 50 times greater than the MIC. The ease of diffusion into the disc is also shown by this experiment, since the level of gentamicin in the disc was 50% of the serum level two hours after injection.

By contrast, the penetration of the discs by cefuroxime was disappointing. One of the explanations could be that the assay method used was insufficiently sensitive to allow detection of only small amounts of cefuroxime, but the lower limit for detection of cefuroxime in our study was 0.6 \(\mu g/ml\) which is close to its MIC against *Staphylococcus aureus* species. Thus, although the antibiotic may be present in the discs, it is likely to be below the therapeutic level. In the two specimens in which cefuroxime was detectable, the serum levels were both greater than 50 \(\mu g/ml\). This probably relates to a high dose of cefuroxime relative to the weight of the patient and suggests that in order to penetrate the disc effectively, a higher dose of cefuroxime (<1.5 g) may be necessary. This agrees with the findings of Rhoten et al.\(^{10}\) and Lang et al.\(^{15}\) who suggested that higher doses of cephalosporins are required to achieve therapeutic levels in the disc. Recently, Hoelscher et al.\(^{24}\) have shown that high

### Table II. Summary of published data on penetration of disc tissue by antibiotics and the electrical charge of the antibiotic

<table>
<thead>
<tr>
<th>Authors</th>
<th>Antibiotic</th>
<th>Electrical charge</th>
<th>Penetration of disc</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eismont et al.</td>
<td>Cefuroxime Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Mouse</td>
</tr>
<tr>
<td>Gibson et al.</td>
<td>Cefradine Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Human</td>
</tr>
<tr>
<td>Fraser et al.</td>
<td>Cefazolin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Sheep</td>
</tr>
<tr>
<td>Boscardin et al.</td>
<td>Cefazolin Neutral</td>
<td>Negative</td>
<td>Yes</td>
<td>Human</td>
</tr>
<tr>
<td>Rhoten et al.</td>
<td>Cefazolin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Human</td>
</tr>
<tr>
<td>Lang et al.</td>
<td>Ceftriaxone Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Mouse</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Gentamicin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Gentamicin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Mouse</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Gentamicin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Gentamicin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Mouse</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Oxacillin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Rhoten et al.</td>
<td>Oxacillin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Human</td>
</tr>
<tr>
<td>Gibson et al.</td>
<td>Flucloxacillin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Human</td>
</tr>
<tr>
<td>Riley et al.</td>
<td>Penicillin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Benzylpenicillin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Mouse</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Amoxycillin Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Mouse</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>Co-Amoxiclav Neutral</td>
<td>Negative</td>
<td>No</td>
<td>Mouse</td>
</tr>
<tr>
<td>Scuderi et al.</td>
<td>Vancomycin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Scuderi et al.</td>
<td>Teicoplanin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Rabbit</td>
</tr>
<tr>
<td>Eismont et al.</td>
<td>Ciprofloxacin Neutral</td>
<td>Positive</td>
<td>Yes</td>
<td>Mouse</td>
</tr>
</tbody>
</table>

---

Gentamicin has been used widely in clinical practice against both Gram-positive and Gram-negative organisms. Its important side-effects are ototoxicity, nephrotoxicity, and antibiotic-associated colitis. Most are dose-related. No patient in our study developed any side-effect.
doses of antibiotics, including both cephalosporins and aminoglycosides, could have deleterious effects on the survival of cultured disc cells, cell proliferation and metabolic rates.

In this study, the presentation of the data as a percentage of serum antibiotic levels two hours after administration must be qualified since the serum and disc will each have a curve of antibiotic level against time. The angle of the slope and the magnitude of the peaks for these two curves will be different. Since the half-life in serum is 1.4 to 1.8 hours for cefuroxime and up to four hours (2 to 4) for gentamicin, and the serum concentrations of the antibiotics were high during removal of the disc, the interval of two hours chosen for this study seems to be appropriate.

We have investigated only the penetration of pathological discs by antibiotics and not normal discs such as may be the case in the correction of spinal deformities. Gibson et al. have shown that neither cefradine nor flucloxacillin, both negatively-charged antibiotics, were detected in either the nucleus pulposus or the annulus fibrosus of a normal human intervertebral disc, despite high blood levels of antibiotics. It is therefore likely that the penetration of the antibiotics is similar in normal and pathological discs. Further conclusions can only be drawn from future studies.

Since invasive techniques and procedures are increasingly used in the diagnosis and treatment of human disc diseases, the possibility of infection of the disc may also increase. It is therefore imperative that a broad-spectrum antibiotic which is known to penetrate the intervertebral disc readily should be administered prophylactically. Based on our results, we recommend the use of gentamicin in a single dose, given at an appropriate time, whenever the intervertebral disc is entered. Rigid adherence to strict aseptic technique is also essential.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References