THE IMPORTANCE OF CEPHRADINE IN HIP SURGERY

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Effective concentrations of antibiotic in the fluid bathing implanted hip prostheses are essential to prevent infection by micro-organisms. Twenty patients undergoing total hip replacement were given one gram of Cephradine intramuscularly one hour before operation and one other received a single bolus of Cephradine intravenously before operation. The concentrations of antibiotic were greater and persisted longer in the tissue fluid than in the blood. The antibiotic was sufficient to inhibit most micro-organisms causing contamination. We recommend that Cephradine is given intramuscularly one hour before operation and at six-hourly intervals after operation until the drainage tubes and intravenous lines have been removed.

The high incidence of infection complicating total hip replacement has haunted many surgeons so much that prophylactic antibiotics are now commonly used in these operations (Garrod, Lambert and O'Grady 1973; Parsons et al. 1978). The prosthesis is implanted into tissues which are damaged by the operative procedure. These tissues and the surface of the prosthesis are bathed in fluid which forms a good medium for bacterial growth. Micro-organisms may reach the site of operation from the wound edge, from the air or in the blood. The presence of intravenous tubes, cannulas, central venous pressure tubes and urinary catheters after the operation increase the risk of bacterial infection. The drainage tubing also provides a potential source of entry for micro-organisms. In selecting an antibiotic to use in this situation several factors should be considered including: activity against Staphylococcus aureus and transient micro-organisms frequently present in the region; the ability to achieve effective concentrations in the region of the prosthesis; and the ease of administration.

The success of a prophylactic antibiotic is probably more dependent on the concentration in the tissue fluid at the site of operation than that in the serum of the circulating blood (British Medical Journal editorial 1973). If the concentrations of the antibiotic in the tissue fluid are bactericidal then any contaminating micro-organisms from the patient and environment will not cause infection. If these concentrations are maintained in the fluid bathing the prosthesis during the vulnerable periods then infection is less likely. Guyton (1963) devised a method of implanting perforated capsules into the tissues of dogs. Calnan et al. (1972) and Chisholm et al. (1973) applied this technique to perforated Silastic tubes with closed ends which were buried subcutaneously. After four weeks, when the cylinders were filled with granulation-like tissue lacking the acute inflammatory features, samples of fluid were removed using a fine syringe two or three times a day for assay of the antibiotic. These results showed that the maximal concentration of antibiotic in the tissue fluid was reached more slowly than that in the blood and the subsequent fall was also slower. Concentrations exerting an antibacterial effect were therefore maintained much longer in the tissue fluid. These experiments involved fluids from tissues with chronic inflammation and it can be argued that the results are not applicable to either normal or acutely inflamed tissues.

Closed vacuum drainage systems are often used to prevent haematoma or accumulation of tissue fluid at the site of operation. The drainage material can therefore be easily collected for assay of the antibiotic without causing additional discomfort to the patient during total hip replacement.

MATERIALS AND METHODS

Over a period of 18 months we reviewed 21 patients who underwent total hip replacement. Twenty patients received one gram of Cephradine intramuscularly one hour before operation, two received a further one gram intravenous bolus during the operation when the methylmethacrylate cement was being inserted and one patient received only a single intravenous bolus at induction of anaesthesia.
Table 1. Mean concentrations of Cephradine in the blood and tissue fluids (mg/l) in 20 patients who received one gram of Cephradine one hour before operation

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time taken</th>
<th>Single dose$^1$ of Cephradine</th>
<th>Additional dose$^2$ of Cephradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>At induction</td>
<td>12.3 (3-30)$^*$</td>
<td>150</td>
</tr>
<tr>
<td>Tissue fluid</td>
<td>At operation</td>
<td>21.1 (16-86)</td>
<td>130</td>
</tr>
<tr>
<td>Tissue fluid</td>
<td>After operation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 hour</td>
<td>21.0 (8-53)</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>2 hours</td>
<td>21.3 (7-54)</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>3 hours</td>
<td>14.8 (5-35)</td>
<td>60</td>
</tr>
</tbody>
</table>

$^*$Range given in parentheses
$^1$18 patients
$^2$2 patients received an additional one gram of Cephradine

RESULTS

In the 20 patients who received one gram of Cephradine intramuscularly one hour before operation the mean concentration of Cephradine in the blood at induction was 12.3 milligrams per litre (range 3 to 30) and had risen further to 14.6 milligrams per litre by the time the prosthesis was inserted (Table I). The mean concentration of Cephradine in the tissue fluids (21.1 milligrams per litre, range 6 to 86) was markedly higher than that in the blood during the operation and in the early period after the operation (Fig. 1 and Table II). In the two patients who were given an additional intravenous dose of Cephradine at operation, even higher levels were obtained. The one patient who was given only a single dose of Cephradine intravenously also showed a high concentration in the tissue fluid (27 milligrams per litre) which was maintained at 7.0 milligrams per litre three hours after the operation.
When a second dose of Cephradine was given to five patients three hours after the operation the mean concentration in both the blood and tissue fluid rose considerably to 66 milligrams per litre and 51 milligrams per litre (Fig. 2 and Table III). Therefore doses of Cephradine given regularly after operation should control any micro-organisms entering the circulation through the various types of tubing necessary for the operation.

**DISCUSSION**

Cephradine was chosen as a prophylactic antibiotic in this study for the following reasons. It has a broad spectrum effect against most Gram-positive micro-organisms, including *Staphylococcus aureus*, and many of the Gram-negative micro-organisms which may contaminate the area of operation (Lacey and Stokes 1977; Parsons et al. 1978). The mean inhibitory concentration for Cephradine against *Staphylococcus aureus* as reported by Neiss (1973) is 0.3 milligrams per litre and the mean bactericidal concentration is 1.5 milligrams per litre. Cephradine acts against the bacteria by interfering with synthesis of the cell wall and is more resistant than Cephaloridine, Cephazolin, Cephalothin and Methicillin to the β-lactamases produced by the bacteria. All of these cephalosporins are destroyed by the cephalosporinase produced by *Enterobacteriaceae* (Selwyn 1977).

Cephradine has very low protein binding (six per cent) and most of it is available in the unbound form. It can therefore reach the tissue fluid more easily (Selwyn 1976). Under normal conditions Cephradine is almost exclusively excreted by the kidneys with 90 per cent appearing in the urine within 24 hours. Renal toxicity is a hazard with Cephaloridine (Mandell 1973) and also with Cephalothin (Carling et al. 1975) and Cephazolin (Silverblatt, Harrison and Turck 1973). In contrast, Cephalexin and Cephradine have minimal toxicity in animals and man (Selwyn 1976). Cephradine has an advantage over most cephalosporins in that it can be administered by the oral, intramuscular and intravenous routes (McAllister 1976).

Garrod, Lambert and O’Grady (1973) defined effective antibiotic therapy as “that when the concentration in blood exceeds the mean inhibitory concentration by several fold for most of the time between one dose and the next” which is an extremely vague definition. The mean inhibitory concentration of Cephradine for *Staphylococcus aureus* producing penicillinase is 1.45 milligrams per litre (Lacey and Stokes 1977). This concentration was exceeded in the blood and tissue fluid of all our patients. The operation area may also be contaminated by small numbers of faecal micro-organisms such as *Escherichia coli*, which are eliminated by concentrations of 6.0 milligrams per litre Cephradine. The concentrations in the blood were slightly lower than this amount in some patients but those in the tissue fluids were always adequate.

From the results of this study we believe that one gram of Cephradine given intramuscularly will have an antibiotic effect sufficient to prevent infection during the operation. Micro-organisms which lodge in the damaged tissue around the prosthesis after the operation may be disseminated from drip sites or suction drainage sites into the blood stream. Therefore effective antibiotic activity must be maintained until all sources of infection are removed from the body. This study shows that effective amounts of Cephradine are obtained in the tissue fluid and blood during the operation. The relatively long half-life in tissue fluid enables effective amounts of Cephradine to be maintained for between six and eight hours. We believe that this is the period when the patient is most vulnerable to infection and we consider that Cephradine is a suitable prophylactic antibiotic for use in hip replacement. We recommend that one gram of Cephradine is given intramuscularly one hour before operation, and that additional doses of one gram are given intravenously at six-hour intervals after the operation until removal of the vacuum drainage system. The last dose should be given immediately before the intravenous line and the drain are removed.
REFERENCES