A Preliminary Report on Cephradine

W. P. LEARY, A. C. ASMAL, C. J. LOCKETT, B. BIMA

SUMMARY

Plasma cephradine levels were measured after parenteral and oral administration to healthy adults. Plasma cephradine concentrations of 7 - 15 μg/ml were measured after 0.5 g had been administered by mouth, and concentrations of 12 - 57 μg/ml were measured after parenteral administration; they fell to 3 μg/ml within 240 minutes except after intramuscular administration. The results of an open clinical trial conducted among 10 patients suffering from urinary tract infections were satisfactory.

Cephradine is a relatively new semisynthetic cephalosporin, recently registered for clinical use in South Africa. Investigations elsewhere indicate that the activity and pharmacology of cephradine are similar to those of cephalaxin to which it bears a structural resemblance. It is acid-stable, well absorbed by mouth, and minimally protein-bound. Cephradine is bactericidal in vitro for a wide variety of Gram-positive and Gram-negative bacteria, and is particularly effective against pneumococci, streptococci, and Staphylococcus aureus, and moderately so against some strains of Escherichia coli, Proteus mirabilis, and Klebsiella.1-3

This article reports a series of preliminary experiments in which plasma cephradine levels were measured after the antibiotic had been administered to healthy adults by various routes, and an open clinical trial was conducted among 10 patients with urinary tract infections.

METHODS

Single doses of cephradine were administered orally, intramuscularly, and intravenously, in random order, to 10 healthy volunteers. Cephradine capsules and suspension were given in doses of 0.5 g and parenteral preparations in doses of 0.5 g and 1 g. There was an interval of at least 72 hours between each dose of cephradine, and the volunteers were asked to report any unusual symptoms experienced during the course of the experiment.

Venous blood was drawn immediately before drug administration, and 30, 60, 90, 150, 240 and 360 minutes thereafter. Samples were also taken 5 minutes after intravenous and intramuscular injections. Plasma cephradine concentrations were measured by means of a modified version of the method of Thornhill et al.4 Significant differences between the various cephradine preparations and routes of administration were determined by applying Student's t-test to paired comparisons of plasma cephradine levels at each time interval.

Midstream urine specimens were collected from 30 patients admitted to the wards of King Edward VIII Hospital, Durban, with suspected urinary tract infections. Urine cultures confirmed the provisional diagnosis in 10 patients, all of whom were infected by organisms sensitive to cephradine. Each patient was then treated with cephradine capsules 0.5 g every 6 hours and a careful record of the clinical response to this regimen was kept. Midstream urine specimens were collected at 48-hour intervals for microscopy and culture.

RESULTS

An over-all impression of the plasma cephradine levels which were recorded may be obtained from the graphs in Figs 1 and 2.

There were higher plasma antibiotic levels after intravenous injection than after oral and intramuscular dosage, although the effect lasted only 60 - 90 minutes. Intramuscular injection of 1 g cephradine produced relatively high plasma concentrations, which were maintained for

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TABLE I. RESULTS OF TRIAL OF CEPHRADINE IN PATIENTS WITH URINARY INFECTION

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Primary diagnosis</th>
<th>Organism</th>
<th>Response to cephradine 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>F</td>
<td>Diabetes mellitus</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>F</td>
<td>Diabetes mellitus</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>F</td>
<td>Diabetes mellitus</td>
<td>Proteus sp.</td>
<td>Clinical and bacteriological cure 48 h and candidiasis at 96 h</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>M</td>
<td>Diabetes mellitus</td>
<td>E. coli</td>
<td>Resistant infection with Pseudomonas sp. emerged at 96 h</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>F</td>
<td>Diabetes mellitus</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h and candidiasis at 96 h</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>F</td>
<td>Diabetes mellitus</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>F</td>
<td>Carcinoma (cervix)</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>F</td>
<td>Disseminated sclerosis</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>F</td>
<td>Congestive cardiac failure</td>
<td>E. coli</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>F</td>
<td>Acute cystitis</td>
<td>Proteus sp.</td>
<td>Clinical and bacteriological cure 48 h</td>
</tr>
</tbody>
</table>

 approximatley 96 hours of treatment with cephradine. Both patients were diabetic. No other adverse response occurred.

**DISCUSSION**

Five cephalosporins with slightly different pharmacological and antimicrobial properties are available in South Africa. Cephaloridine, cephalaprin, and cephalothin are administered parenterally, whereas cephalaxin has been registered for oral use only. Cephradine, which resembles cephalaxin in structure, pharmacology and activity, is administered orally and parenterally. Similarities between the cephalosporins may sometimes cause difficulty in the choice of the preparation best suited to a particular patient. Cephaloridine, cephalothin, and cephalaprin are active against many organisms, although cephaloridine is less resistant to staphylococcal penicillinase and more nephrotoxic in high doses than cephalaxin or cephalothin. Cephradine and cephalaxin are slightly less active than the three other compounds available, but their advantage is that they may be given orally. In vitro studies suggest that the preliminary use of cephaloridine in patients who were subsequently given cephalaxin may be complicated by the rapid development of bacterial resistance. This might be prevented in vivo by the prescription of a different cephalosporin combination, or by the use of cephradine when a patient is likely to receive parenteral therapy followed by oral therapy.

The results of this study confirm other investigations. Plasma concentrations in excess of 3 µg/ml were measured after the administration of 0.5 - 1 g cephradine orally or by injection. Plasma levels fall below 3 µg/ml at 240 minutes, except when the drug is injected intramuscularly, but levels of 7 - 15 µg/ml at 60 - 90 minutes after drug administration suggest that dosage with cephradine every 6 hours might enhance the efficacy of this bactericide. These laboratory results, considered with those of our preliminary investigations of patients with urinary tract infection, indicate that cephradine is a useful member of the cephalosporin group of antibiotics. Like cephalaxin, it is well-absorbed orally, and
may be expected to control a variety of infections caused by Gram-positive and Gram-negative organisms, without major toxic effects. Clinicians who require continuity of therapy may consider it an advantage that this cephalosporin is also available in parenteral form.

We wish to thank Squibb SA (Pty) Ltd, who supplied Cefril, which was used in this study.

REFERENCES


Propanidid for Anaesthetic Induction at Caesarean Section

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SUMMARY

In 50 healthy mothers scheduled for elective Caesarean section, anaesthesia was induced with propanidid (7 mg/kg body weight). Thereafter, ventilation was controlled with nitrous oxide, oxygen and muscle relaxants. A further dose of propanidid (1 mg/kg body weight) was administered 3 minutes after the initial injection of this drug, as a means of preventing maternal awareness during equilibration with the anaesthetic gas mixture.

The acid-base status of the mothers before the induction of anaesthesia, and at delivery, revealed a mild degree of respiratory alkalosis with a compensatory metabolic acidosis.

Umbilical cord blood gas results indicated the presence of significant fetal acidosis, both respiratory (mean pCO₂ Uv 46.3 torr (SD 11.3) and Ua 54.3 torr (SD 12.0)), and metabolic (mean base excess Uv—9 mEq/l (SD 4.2) and Ua—11.8 mEq/l (SD 5.0)) in origin.

The average umbilical cord blood oxygen tensions were Uv 25.9 torr (SD 10), and Ua 15.4 torr (SD 8.5); mean maternal to fetal base-excess gradients were Ma-Uv 4.1 mEq/l (SD 2.8) and Ma-Ua 6.5 mEq/l (SD 3.5).

Five mothers (10%) offered convincing evidence of factual recall during surgery, and 3 of these were aware of pain. Nausea and vomiting occurred in 5 patients and in 4 there were clinical signs of postoperative chest infection.

The degree of fetal biochemical asphyxia, and the incidence of maternal awareness during surgery, were significantly greater than previously reported when thiopentone was used for the induction of anaesthesia for Caesarean section.

The results obtained are discussed, and the conclusion is drawn that propanidid for anaesthesia appears to offer no advantage over thiopentone in obstetric practice.


Propanidid, unlike the shortest-acting barbiturates, is not cumulative. After intravenous injection into the maternal circulation, the drug readily crosses the placental barrier, and equilibration of mother and infant occurs rapidly. However, depression of the newborn is infrequently associated with propanidid administration.²

In a previous communication, the use of propanidid as the sole anaesthetic agent for Caesarean section was