Comparative efficacy and safety of amoxycillin, cephalexin and pivmecillinam in typhoid fever.

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Fifty-one patients with bacteriologically proven typhoid fever were treated with amoxycillin, 1 g four times daily, cephalexin 500 mg four times daily and pivmecillinam 400 mg four times daily, all drugs were given orally. Amoxycillin is effective in all 17 patients, with a mean duration of therapy before defervescence of 6.4 days. Pivmecillinam proved to be effective in 13 out of 17 cases, with complete defervescence in 8.6 days. Only 12 out of 17 in the cephalexin group responded with a mean defervescence of 8.9 days. No adverse effect occurred in amoxycillin group. Mild to moderate epigastric discomfort, nausea and vomiting were experienced by three and five patients treated with cephalexin and pivmecillinam respectively.

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ปทุมพิศ สุวรรณฤทธิ์, สมใจ เรืองภูประโยชน์, สติล ขาวชิริพงษ์, การศึกษาการรักษาให้ยาฟอกปนเข้มข้นยาแอมฟอกซิลีน, เศพฟแล็กซินและฟิวมิคิลีนเมม. จุฬาลงกรณ์มหาวิทยาลัย 2529 ทุกวัน; 30 (11) : 1105-1108

คณภูริชานันธ์ ศึกษาการใช้ยาแอมฟอกซิลีน, เศพฟแล็กซิน และฟิวมิคิลีนเมม. ในผู้ป่วยไข้ระดับ 51 ราย โดยให้ยาในขนาด 1 กรัม, 500 มิลลิกรัม และ 400 มิลลิกรัม ตามลำดับ, รับประทานวันละ 4 ครั้ง ระยะเวลา 5-9 วัน (6.4 วัน) ติดตามการรักษา 100 เศพฟแล็กซิน ให้ผลการรักษาไม่ดีทั้งนั้น ติดตามการรักษา 70.6 ใช้ยา 6-11 วัน (8.9 วัน) ฟิวมิคิลีนเมม ผลดีในตัวผู้ป่วย ใช้ยา 6-11 วัน (8.6 วัน) ติดตามการรักษา 76.5 ผลผ่านเพียงจากจะมีผลดีของศพฟแล็กซิน ในผู้ป่วยและผู้ป่วยที่รักษาได้รับยาฟิวมิคิลีนเมม และฟิวมิคิลีนเมม ผลการใช้ยาทั้งหมด 3 ราชันและ 4 ราชัน ตามลำดับ

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New approaches to the treatment of enteric fever need to be explored in view of the occurrence of Chloramphenicol and ampicillin-resistant Salmonella typhi throughout the world\(^1\)\(^,\)\(^2\) Other agents which are known to be effective in typhoid fever include thiamphenicol\(^3\), amoxycillin\(^4\) and co-trimoxazole\(^5\). Unfortunately as many strains are also resistant to these antimicrobial agents, there is a clear need for clinical trials of new drugs.

Pivmecillinam, pivaloloxymethyl ester of mecillinam, is absorbed from the gastrointestinal tract and hydrolysed to mecillinam which is highly active against Escherichia coli and Salmonella typhi\(^6\). Preliminary in vitro studies have shown that cephalaxin, a first generation oral cephalosporin, is also active against Salmonella typhi. The purpose of this study was to evaluate the comparative efficacy and safety of pivmecillinam, cephalaxin and amoxycillin in typhoid fever.

**Material and Method**

All adult patients who had clinical signs and symptoms suggestive of typhoid fever were admitted to the medical wards of Chulalongkorn Hospital.

The patients in this study comprised of 51 adult who were in fair condition. Further patient details are shown in Table I. After a pre-treatment evaluation, a complete blood count, liver function test, serum creatinine, albumin and globulin were performed, before the antimicrobial therapy, on day 7 and 14 of therapy, and 14 days after the completion of the antimicrobial therapy. The cultures of blood, stool and urine were performed before therapy and on days 3,7 and 14 of antimicrobial therapy. Dosage schedules of antibiotics were amoxycillin 1 g. four times daily, cephalaxin 500 mg four times daily and pivmecillinam 400 mg four times daily; all drugs were given orally. These three drugs were randomly assigned to patients. All patients were evaluated in several ways. The clinical course was measured by the number of days during which the patient’s oral temperature exceeded 37.2°C. Bacteriological cure was assessed by the number of days before the blood culture became negative. All patients were kept in the hospital until the completion of antimicrobial treatment. A case was considered as a treatment failure if it showed no clinical response within 10 days.

Statistical comparisons were performed by the Student’s T test.

**Result**

Fifty-one patients with positive blood culture for salmonella typhi were evaluated in this study. There were no significant differences among the three treatment groups regarding their age, sex, distribution, and interval between the onset of symptoms and the initiation of therapy. All salmonella typhi recovered from the fifty-one patients proved to be susceptible to amoxycillin cephalaxin and pivmecillinam.

The response to therapy is presented in table I. The acute infection was satisfactorily controlled in all 17 patients treated with amoxycillin, but only 12 out of 17 with cephalaxin and 13 out of 17 with pivmecillinam. Patients receiving amoxycillin tended to become afebrile sooner than those on cephalaxin and pivmecillinam. The mean duration of treatment before complete defervescence in patients receiving amoxycillin (6.4 days) was less than in the cephalaxin and pivmecillinam treated groups (8.9 and 8.6 days respectively, p < 0.05).
Table I  Clinical responses in 51 patients treated with amoxycillin, cephalexin and pivmecillinam.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age (yr.)</th>
<th>Male/Female</th>
<th>Time from onset to treatment (days)</th>
<th>First afebrile day (temp. &lt; 37.2° C)</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxycillin</td>
<td>20.7</td>
<td>10/7</td>
<td>11</td>
<td>5.9 (6.4)</td>
<td>0</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>19.8</td>
<td>9/8</td>
<td>10.1</td>
<td>6.11 (8.9)</td>
<td>5</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>21.4</td>
<td>11/6</td>
<td>9.8</td>
<td>6.11 (8.6)</td>
<td>4</td>
</tr>
</tbody>
</table>

Blood cultures became negative within three days in all those treated with amoxycillin, while positive cultures persisted longer in the cephalexin and pivmecillinam groups (table II).

Table II  Bacteriological responses in the three treatment groups.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of patients with positive blood cultures after antimicrobial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td>17</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>17</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>17</td>
</tr>
</tbody>
</table>

After the discontinuation of treatment, all patients were followed for a period of eight weeks; no relapse occurred during this follow-up period. A one year follow-up was possible in only three patients.

There were no serious side-effects in all treatment groups. Mild to moderate epigastric discomfort, nausea and vomiting were experienced by three and five patients taking cephalexin and pivmecillinam respectively. There were no evidences of any adverse effects on haemopoitic, hepatic or renal functions in all patients.

Discussion

Ampicillin, amoxycillin and co-trimaxazole have been shown to be effective in typhoid fever but patients usually responded somewhat more slowly than on chloramphenicol or thiamphenicol. The efficacy and safety of pivmecillinam in typhoid fever from previous studies tended to be good. However in this study, although all salmonella typhi isolates were sensitive to pivmecillinam, the clinical response and defervescence were slower than on amoxycillin (statistically significant). There was also a significant difference in the cure rates between amoxycillin and pivmecillinam.

Of the few oral cephalosporin antibiotics available for clinical use, the results of this preliminary study indicate that cephalexin is inferior to amoxycillin, since only 12 out of 17 patients responded to
this antibiotic with a mean time of 8.9 days before complete defervescence. More clinical studies are required drawn before any conclusion can be draw regarding the efficacy of cephalaxin and pivmecillinam in typhoid fever, but the adverse effects of cephalaxin and pivmecillinam suggest that these two drugs are not valuable alternatives to the other antimicrobial agents. There were 3 cases in the cephalaxin treatment group and 4 in pivmecillinam group that had to be discontinued from the trial because of severe epigastric discomfort and vomiting.

On the basis of the present evaluation we feel that amoxycillin continues to be one of the effective antibiotic treatment of typhoid fever with freedom from side-effects as an added advantage.

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References


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