นิพนธ์ต้นฉบับ

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 cephlexin and pivmecillinam respectively.

พรรณพิศ สุวรรณกูล, สมใจ เหรียญประยูร, สดใส เวชชาชีวะ. การศึกษาการรักษาไข้ทัยฟอยด์ด้วยยาอะม็อกสิซิลลิน, เศพฟาเล็กซินและพัยเมซิลลิแนม. จุฬาลงกรณ์เวชสาร 2529 พฤศจิกายน; 30 (11) : 1105-1108

คณะผู้รายงานได้ศึกษาการใช้ยาอะม็อกสิซิลลิน, เศพฟาเล็กซิน และพัยเมซิลลิแนม ในผู้ป่วยไข้ทัยฟอยด์ 51 ราย โดยให้ยาในขนาด 1 กรัม, 500 มิลลิกรัม และ 400 มิลลิกรัม ตามลำดับ, รับประทานวันละ 4 ครั้ง อะม็อกสิซิลลิน ยังคงให้ผลดีเหมือนการศึกษาก่อน ๆ ไข้ลงภายใน 5-9 วัน (6.4 วัน) อัตราการหายร้อยละ 100 เศพฟาเล็กซิน ให้ผลการรักษาไม่สู้ดีนัก อัตราการหายร้อยละ 70.6 ไข้ลง 6-11 วัน (8.9 วัน) พัยเมซิลลินแนม ผลก็ไม่ดีเช่นกัน ไข้ลง 6-11 วัน (8.6 วัน) อัตราการหายร้อยละ 76.5 ผลข้างเคียงจากอะม็อกสิซิลลินไม่มีเลยในขณะที่ผู้ป่วยได้รับยาเศพฟาเล็กซินและพัยเมซิลลิแนม มีอาการปวดแน่นท้องบริเวณลิ้นปี่ และอาเจียนมาก จนต้องหยุดยา 3 และ 4 ราย 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 cephalexin, a first generation oral cephalosporin, is also active against Salmonella typhi. The purpose of this study was to evaluate the comparative efficacy and safty of pivmecillinam, cephalexin 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, cephalexin 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 druing 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 cephalexin 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 cephalexin and 13 out of 17 with pivmecillinam. Patients receiving amoxycillin tended to become afebrile sooner than those on cephalexin and pivmecillinam. The mean duration of treatment before complete defervescence in patients receiving amoxycillin (6.4 days) was less than in the cephalexin 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.

Treatment Group	Age (yr.)	Male/Female	Time from onset to treatment (days)	First afebrile day (temp. < 37.2° C)	Failure
Amoxycillin	20.7	10/7	11	5-9 (6.4)	0
Cephalexin	19.8	9/8	10.1	6-11 (8.9)	5
Pivmecillinam	21.4	11/6	9.8	6-11 (8.6)	4

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.

Treatment Group	Number of patients with positive blood cultures after antimicrobial treatment		
	Day 0	Day 3	Day 7
Amoxycillin	17	0	0
Cephalexin	17	2	0
Pivmecillinam	17	2	0

After the discontinuation of treatment, all patients were followed for a period of eight weeks; no relapse occured 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 moderale 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.[7,8] 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 cephalexin and pivmecillinam in typhoid fever, but the adverse effects of cephalexin and pivmecillinam suggest that these two drugs are not valuable alternatives to the other antimicrobial agents. There were 3 cases in the cephalexin 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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