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Original Article

Azithromycin vs. chloramphenicol for uncomplicated typhoid fever in children

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Abstract

Background The emergence of multiple-drug-resistant *Salmonella typhi* strains has made it necessary to evaluate new agents for the treatment of typhoid fever. Azithromycin has in vitro activity against many enteric pathogens, including *Salmonella spp*. However, there is not enough evidence to compare azithromycin with first-line antibiotics currently used.

Objective To analyze the efficacy of azithromycin compared to that of chloramphenicol as a first-line drug in the therapy of uncomplicated typhoid fever in children.

Methods We conducted a randomized open trial from November 2011 to March 2012 on 60 children aged 2-13 years with uncomplicated typhoid fever. Subjects were randomly assigned to receive either azithromycin (10 mg/kgBW/day orally once daily) or chloramphenicol (100 mg/kgBW/day orally in four divided doses) for 7 days. Efficacy was measured by recording clinical cures and fever clearance times. Data was analyzed with Chi-square and T-tests.

Results All of 30 patients in the azithromycin group and 28 out of the 30 patients in the chloramphenicol group were cured (P=0.246). Fever clearance time was shorter in the azithromycin group (mean 37.9 (SD 32.75) hours, 95%CI 25.67 to 50.13) than in the chloramphenicol group (mean 49 (SD 45.83) hours, 95%CI 31.89 to 66.11).

Conclusions The efficacy of azithromycin is similar to that of choramphenicol in the treatment of uncomplicated typhoid fever in children. Azithromycin has shorter fever clearance time and higher cure rate compared to those of chloramphenicol, although these results are not statistically significant. **[Paediatr Indones. 2013;53:155-9.]**.

Keywords: *azithromycin, chloramphenicol, efficacy, treatment, typhoid fever*

Typhoid fever is a systemic infection caused by the bacterium *Salmonella typhi*. In Indonesia, typhoid fever is still an endemic disease with high incidence.[1] The emergence of multiple-drug-resistant (MDR) *Salmonella typhi* strains resistant to chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole, have made it necessary to evaluate new agents for the treatment of typhoid fever.[2] Relapse and chronic carriage was found after chloramphenicol therapy. Side effects of chloramphenicol such as bone marrow depression and aplastic anemia have also forced physicians to seek alternatives to therapy with chloramphenicol.[2,3]

Azithromycin is a derivative of the basic macrolide with better activity than erythromycin against Gram negative bacteria. It has in vitro activity against many enteric pathogens, including *Salmonella spp*.[4] However, there is not enough evidence to compare azithromycin with the first-line antibiotics currently used. The objective of this study was to analyze the efficacy of azithromycin, a new macrolide, compared to that of chloramphenicol, as a first-line drug for therapy of uncomplicated typhoid fever in children.

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Methods

We conducted a randomized open trial from November 2011 to March 2012, at the Department of Child Health, Sam Ratulangi University/Prof. Dr. R.D. Kandou Hospital, Manado. The study was approved by the Ethics Committee of Sam Ratulangi University Medical School, Prof. Dr.R.D Kandou Hospital.

Subjects were children aged 2-13 years with uncomplicated typhoid fever. Uncomplicated typhoid fever was defined as a history of documented fever for at least 7 days accompanied by at least one of the clinical features suggestive of typhoid fever (abdominal pain and tenderness, diarrhea or constipation, nausea or vomiting, coated tongue and hepatosplenomegaly) and had positive Tubex test (≥4). Written informed consent was provided by all subjects' parents prior to enrollment. We excluded children with severe malnutrition, history of hypersensitivity reactions to azithromycin or chloramphenicol, history of *S. enteritidis* infection, other diseases such as dengue fever, malaria, pneumonia, tuberculosis or urinary tract infection, as well as those who had received azithromycin or chloramphenicol within the 7 days prior to enrollment, but we did not exclude children who had taken other antibiotics.

Subjects were randomly assigned based on a random list generated by computer to receive either azithromycin (oral 10 mg/kgBW/day once daily) or chloramphenicol (oral 100 mg/kgBW/day in four divided doses) for 7 days. Full blood counts, Tubex tests and urinalyses were performed before therapy. Additional urine cultures were performed in patients with white blood cell counts greater than 5 cells per high power field in their urinalyses, to rule out urinary tract infection.

Patients were examined daily until hospital discharge, with particular reference to clinical symptoms, fever clearance time, any side effects of the drugs, and any complications of the disease. The response to treatment was assessed by clinical parameters (resolution of clinical symptoms and signs), fever clearance time (time in hours from the start of antibiotic administation until body temperature fell to less than 37.5°C and remained so for 48 hours) and development of complications. Patients were considered cured if their fever disappeared, all signs and symptoms of typhoid fever resolved, and there was no complication or severe side effect up to the last day of the treatment. A clinical treatment failure was defined as the persistence of fever and symptoms after completing the treatment or the development of severe complications (severe gastrointestinal bleeding, intestinal perforation, shock, or coma) during treatment, requiring a change in therapy. Patients who failed were retreated with ceftriaxone at 80 mg/kgBW/day for 7 days.

Assuming a failure rate of 5% in the azithromycin arm, a minimum sample size of 24 patients per group would give an 80% power to detect a 20% difference in failure rate at a 5% significance level. Clinical cure proportions were compared with the Chi-square test. The fever clearance times were compared using independent T-test. A P value of < 0.05 indicated a significant difference between the two groups.

Results

From November 2011 to March 2012, 65 children with uncomplicated typhoid fever aged 2 – 13 years were recruited into our study. Three children from the azithromycin group and two children from the chloramphenicol group were subsequently dropped from the study. Sixty children completed the study, with 30 children in each group (**Figure 1**).

Table 1 shows the epidemiological, clinical, and laboratory features between study groups. There were

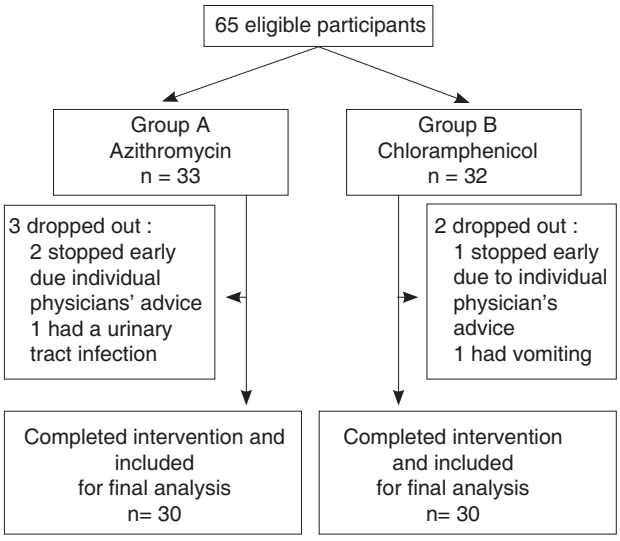

Figure 1. Study profile flow chart

17 and 16 males in azithromycin and chloramphenicol groups, respectively. Mean age was 6.04 (SD 3.09) years in the azithromycin group and 6.18 (SD 2.55) years in the chloramphenicol group. Anorexia was the most common presenting feature after fever, followed by nausea and vomiting. Complete blood count laboratory values on admission were within normal limits for both study groups.

Table 2 shows the treatment outcome for both groups. Fever clearance time was shorter in the azithromycin group (mean 37.9 hours) compared to the chloramphenicol group (mean 49 hours), but the results were not statistically significant (P=0.285). All patients treated with azithromycin and all but two of the patients treated with chloramphenicol were cured. The two patients with clinical failures in the chloramphenicol group were considered to be not cured as a result of their slow fever resolution without other symptoms. These two subjects received ceftriaxone for an additional 7 days after the 7 days

Table 1. Epidemiological, clinical, and laboratory features of subjects

Characteristics	Azithromycin group (n=30)	Chloramphenicol group (n=30)
Sex, n		
Male	17	16
Female	13	14
Mean age (SD), years	6.04 (3.09)	6.18 (2.55)
Mean body weight (SD), kg	21.43 (13.54)	19.90 (6.97)
Mean body mass index (SD), kg/m^2	15.94 (3.29)	19.43 (2.40)
Nutritional status, n		
Mild malnutrition	8	4
Normal nutrition	18	25
Overweight	2	1
Obese	2	0
Mean length of fever before admission (SD), days	7.30 (0.75)	8.36 (3.24)
Mean body temperature on admission (SD), ^{0}C	37.95 (0.51)	37.95 (0.47)
Previously took other antibiotics, n	11	12
Clinical manifestations on admission, n		
Anorexia	26	25
Coated tongue	10	12
Constipation	9	11
Flatulence	2	5
Diarrhea	5	9
Nausea	16	20
Vomiting	13	17
Abdominal discomfort	13	15
Cough	11	10
Hepatomegaly	4	17
Laboratory values on admission		
Mean hemoglobin (SD), g/dL	11.75 (1.39)	11.98 (1.57)
Mean leukocytes (SD), per mm^3	7,294.0 (3450.3)	9,207.3 (3762.2)
Mean platelets (SD), per mm^3	247,767 (112,811)	274,710 (121,185)
Mean hematocrit (SD), %	35.08 (4.39)	35.73 (4.69)

Table 2. Treatment outcomes in both groups

Parameter	Azithromycin group		Chloramphenicol group		P value
	n=30	95% CI	n=30	95% CI	
Mean fever clearance time (SD), hours	37.90 (32.75)	25.67 to 50.13	49.00 (45.83)	31.89 to 66.11	0.285
Clinically cured, n	30		28		0.246

of chloramphenicol. Both of them subsequently had complete cures without significant consequences.

Adverse events occurred in two patients treated with azithromycin, with the development of abdominal discomfort and cough, but in none of the patients treated with chloramphenicol. The adverse events were not severe and did not result in medication changes.

Discussion

The results of this comparative, randomized trial of azithromycin and chloramphenicol for typhoid fever indicated that both treatments were similarly effective, resulting in clinical cure rates of 93–100% within 7 days.

In our study, clinical cure rates of 100% for subjects who received azithromycin compared favorably with findings from past azithromycin trials for treatment of typhoid fever.[5] The mean fever clearance time of 1.5–2.0 days after the start of treatment in the two treatment groups indicated that most patients responded promptly to therapy. These results compared favorably with other antimicrobial agents tested for typhoid fever, including ceftriaxone, cefixime, and fluoroquinolones,[4,6-10] as well as confirmed the findings of trials in Egypt, India and Vietnam in which azithromycin was deemed effective against infections caused by *S. typhi*.[5,9-13]

It is interesting that in our study the fever clearance times were shorter than those of past trials.[5,9,10,12,13] Butler *et al*.[5] reported that in adult patients randomized to receive either azithromycin 500 mg orally once daily for 7 days or chloramphenicol 2–3 g orally in four divided doses for 14 days, fever clearance times were shorter in the azithromycin group (mean 98.4 hours) than in the chloramphenicol group (mean 103.2 hours), but the results were not statistically significant. There was marked heterogeneity for fever clearance times in children and adults using azithromycin for typhoid in past studies by Parry *et al*.[9] (139.2 hours), Dolecek *et al*.[10] (106 hours), Aggarwal *et al*.[12] (82.8 hours), and Girgis *et al*.[13] (91.2 hours). Furthermore, Frenck *et al*.[7] found that fever clearance time in children and adolescents with clinical typhoid fever who were treated with oral azithromycin 10 mg/kg/day for seven days was 4.1 days.

The discrepancy in fever clearance times between trials may be caused by various factors, including methodological differences, different geographical locations, age of the study group, the dose of drugs used, severity of disease or clinical condition of patients, previous antibiotic treatment and immune status. Past trials were conducted in Asian countries where MDR *S. typhi* have been reported, including Pakistan, India, and Vietnam.[5,9,10,12,13] A prospective study performed in Delhi at intervals of three years (1999, 2002 and 2005) found that the incidence of MDR *S. typhi* sequentially increased from 34% in 1999 to 66% in 2005.[14] Another past trial was conducted in Southern Vietnam, an area characterized by a very high proportion of MDR, 88%.[10] Unlike other regions of Southeast Asia where MDR was common, reported levels of antibiotic resistance in *S. typhi* from Indonesia, was only 6.8% in 2007.[15] It has been observed in some studies that, as compared with the children infected by sensitive *S. typhi* strains, children with MDR *S. typhi* are sicker and more toxic in presentation.[16] This could explain the relatively short fever clearance times in our study for both antibiotic groups. In our study, 23 of 60 subjects received other antibiotics (other than chloramphenicol and azithromycin) prior to enrollment. This could also have influenced the fever clearance times, though the proportion of subjects' receiving previous antibiotics between the study groups was similar.

The two drugs studied here were different in regard to their administration, pharmacokinetics, therapeutic principles and side effects. Azithromycin was given once daily in a dose of 10 mg/kgBW per day for 7 days, whereas chloramphenicol was given four times a day in doses of 100 mg/kgBW body weight per day for 7 days. Both antibiotics penetrate into cells effectively, and this intracellular penetration explains the effective therapeutic activity against the predominantly intracellular pathogen *S. typhi*. On the other hand, serum concentrations of azithromycin which have been reported to be in the range of 0.04–0.4 mg/L during treatment are less than the minimum inhibitory concentration (MIC) of azithromycin against *S. typhi*. It was also less than the serum concentrations of 5.5–57 mg/L reported for chloramphenicol during treatment of typhoid fever. The ability of azithromycin to achieve intracellular concentrations in monocytes

231 times greater than the serum concentrations and in polymorphonuclear leukocytes 83 times greater than the serum concentrations, as well as a long intracellular concentration half-life of 2–3 days of the, appears to be essential for azithromycin's therapeutic activity in typhoid fever.[5,17]

Adverse events, including gastrointestinal symptoms and cough, were reported by two patients treated with azithromycin in our trial, but these events were not serious and did not require discontinuation of therapy. These events principally occurred within the first 1-2 days of treatment and did not require therapy or alteration of the treatment regimen. Although it cannot be proven, many of the gastrointestinal events were likely associated with the underlying disease and not with the treatment.[18]

This study was not a blinded trial, which is one of its limitations. Another limitation was that we did not perform blood cultures as the gold standard to diagnose typhoid fever, nor did we perform antimicrobial sensitivity tests on the bacteria.

In conclusion, the efficacy of azithromycin is similar to that of choramphenicol in the treatment of uncomplicated typhoid fever in children. Azithromycin shows shorter fever clearance time and higher cure rates compared to chloramphenicol, in the therapy of uncomplicated typhoid fever in children, although these results are not statistically significant.

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