

TREATMENT OF JAPANESE PATIENTS WITH ENTERIC FEVER USING AZITHROMYCIN AND MIC LEVELS FOR CAUSATIVE ORGANISMS

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Abstract. In Japan azithromycin (AZM) has been used to treat enteric fever caused by bacteria with resistance to fluoroquinolones; however, the dose, length of treatment and effectiveness of AZM among Japanese patients with enteric fever is unclear. We studied 5 Japanese adults and 1 Japanese child with enteric fever (4 had typhoid fever and 2 had paratyphoid fever) who were treated with oral AZM. The treatment regimens were: 1,000 mg as a single or in 2 divided doses on the 1st day, followed by 500 mg as a single dose daily for 5-6 additional days, or 500 mg as a single dose daily for 10 days. The minimum inhibitory concentrations (MICs) for AZM against 5 causative organisms were investigated with an E-test. Good clinical results were observed in the 5 adult patients but treatment failure was seen in the 1 child patient with typhoid fever; no adverse reactions were found. MICs of AZM were 4 g/ml against *S. Typhi* in 2 patients, 8 g/ml against *S. Typhi* in 2 patients, and 32 g/ml against *S. Paratyphi A* in 1 patient. Our findings indicate AZM may be a reasonable choice for treatment of Japanese adult patients with enteric fever.

Keywords: azithromycin, typhoid fever, paratyphoid fever

INTRODUCTION

Enteric fever, caused by an infection with *Salmonella enterica* subspecies *enterica* serovar Typhi (*S. Typhi*) and *Salmonella enterica* subspecies *enterica* serovar Paratyphi A (*S. Paratyphi A*) are important infectious diseases in tropical and subtropical areas of the world. Chloramphenicol (CP) has traditionally been the drug of choice

for enteric fever; however, *S. Typhi* and *S. Paratyphi A* strains with resistance to CP have spread in endemic areas. Third generation cephalosporins, fluoroquinolones and azithromycin (AZM) have been used to treat enteric fever. Recently, *S. Typhi* and *S. Paratyphi A* strains with resistance to fluoroquinolones have been reported among Japanese patients (Fuke *et al*, 2004; Suzuki and Sugimoto, 2008). The use of some third generation cephalosporins is limited because of the need for parenteral administration. AZM has begun to be used more frequently for patients with enteric fever in Japan; however, there are few publications investigating the use of

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Table 1
Patient profiles.

Case no.	Disease	Age (years)	Sex	Place contracted
1	TF	12	F	Indonesia
2	TF	22	F	India or Nepal
3	TF	30	M	India
4	TF	32	F	India or Nepal
5	PTF	30	M	Bangladesh
6	PTF	40	M	Sri Lanka

TF, typhoid fever; PTF, paratyphoid fever

AZM in the treatment of Japanese patients with enteric fever (Mizuno *et al*, 2008). We treated Japanese patients with enteric fever using oral of AZM, and determined the minimum inhibitory concentrations (MICs) of AZM against *S. Typhi* and *S. Paratyphi A*.

MATERIALS AND METHODS

Patients

We treated 6 Japanese patients with enteric fever (4 with typhoid fever and 2 with paratyphoid fever) using AZM. The profiles of the 6 patients are shown in Table 1. *S. Typhi* or *S. Paratyphi A* were confirmed in the blood of all of our patients on the same day as AZM treatment was begun. Three patients (cases 1, 2 and 3) had been previously treated with other antimicrobial agents; case 3 had received other antimicrobials 15 days prior to AZM administration. Three patients (cases 4, 5 and 6) received no antimicrobial agents prior to AZM administration.

Treatment

The treatment regimen is shown in Table 2.

Therapeutic evaluation

A good clinical result was defined as the maximum body temperature being

under 38.0°C 4 days after starting AZM and the body temperature being under 37°C after the end of AZM treatment. Treatment failure was defined as a maximum body temperature >38.0°C 4 days after starting AZM treatment.

A favorable bacterial result was defined as a case in which the causative organism was not found in the stool of patients with 3 continuous bowel movements at an interval of 24 hours or longer, 48 hours after the end of AZM treatment and one month after the onset of disease.

Measurement of MICs

MICs of AZM against *S. Typhi* isolated from the 4 patients and against *S. Paratyphi A* from one patient were investigated with the E-test. The MIC of AZM against the other patient with *S. Paratyphi A* was not determined.

RESULTS

Clinical and bacterial effectiveness

The results of the clinical and bacterial effectiveness are shown in Table 3. High fever (39.9°C) was seen 4 days after starting AZM in one patient (case 1) with *S. Typhi*; a blood culture was positive for *S. Typhi* on this patient 4 days after starting AZM treatment. This was considered

Table 2
AZM treatment regimen.

Case no.	AZM treatment regimen
1	1,000 mg as a single dose on the first day followed by 500 mg as a single dose daily for 5 additional days ^a
2	500 mg as a single dose daily for 10 days
3	1,000 mg as a single dose on the first day followed by 500 mg as a single dose daily for 6 additional days
4	1,000 mg as a single dose on the first day followed by 500 mg as a single dose daily for 5 additional days
5	1,000 mg divided into 2 doses on the first day followed by 500 mg as a single dose daily for 6 additional days
6	1,000 mg as a single dose on the first day followed by 500 mg as a single dose daily for 6 additional days

^a AZM was changed to norfloxacin 5 days after starting AZM treatment.

Table 3
Clinical and bacterial effectiveness of
AZM.

Case no.	Clinical effect	Bacteriological effect
1	Failure	Not done
2	Good	Good
3	Good	Good
4	Good	Good
5	Good	Good
6	Good	Good

to be a case of treatment failure. No adverse effects from AZM treatment were seen in any of the patients.

MIC levels

The MICs of AZM against *S. Typhi* isolated from cases 1, 2, 3 and 4 were 4 g/ml, 4 g/ml, 8 g/ml and 8 g/ml, respectively, and against *S. Paratyphi A* from case 5 was 32 g/ml.

DISCUSSION

It is difficult to estimate the effectiveness of AZM among Japanese patients

with enteric fever because the number of Japanese patients with enteric fever is small. Other antimicrobial agents, such as cephalosporins, fluoroquinolones, penicillins and macrolides, are the agents usually given to patients in Japan with fever. To evaluate the effectiveness of a particular antimicrobial agent, it is important to exclude the effect of other antimicrobial agents given previously. AZM was given to 3 patients at least 15 days after they had received their last dose of other antimicrobial agents and 3 patients received no antimicrobial agents prior to the administration of AZM in our study. All the patients complained of fever at the beginning of AZM treatment, and the causative organism was isolated from all patients on the day of or 1 day before AZM treatment. Therefore, we may exclude the effect of previously administered antimicrobial agents and fairly accurately estimate the effectiveness of AZM against enteric fever in our patients.

The treatment regimen with AZM in patients with enteric fever is unclear. Some studies have reported good thera-

peutic results against typhoid fever with the oral administration of 1,000 mg of AZM as a single dose on the first day of therapy followed by 500 mg as a single dose given daily for 6 additional days among adolescent and adult patients (Tribble *et al*, 1995; Girgis *et al*, 1999), 1,000 mg of AZM once daily for 5 days among adult and adolescent patients (Chinh *et al*, 2000), 20 mg/kg/day of AZM once daily for 5 days among children and adolescent patients (Frenck *et al*, 2004) and 10 mg/kg/day orally once daily for 7 days among children and adult patients (Parry *et al*, 2007). However, the AZM treatment regimen among Japanese patients with enteric fever has not been well studied. Further studies among Japanese patients with enteric fever are needed. Our treatment regimens are shown in Table 2. These may be viable treatment regimens for adult Japanese patients with enteric fever.

Capoor *et al* (2009), using the E-test, found MIC levels of AZM against *S. Typhi* and *S. Paratyphi* to range from ≤ 0.032 to ≤ 32 and 0.125 to ≤ 32 , respectively; with 44% of *S. Typhi* isolates and 41% of *S. Paratyphi A* isolates having MIC levels of 4-8 g/ml and only 2.3% of *S. Paratyphi* isolates had a MIC level of 32 g/ml. Therefore, the MIC levels in our study for *S. Typhi* were neither very high nor very low, but the MIC level for *S. Paratyphi A* in our study was high; this suggests AZM was effective against paratyphoid fever in spite of a high MIC level.

It has been reported the intracellular concentration of AZM in alveolar macrophages may be as high as 300 times the concentration of that in the serum (Panteix *et al*, 1993), and the intracellular concentration of AZM in monocytes may be 83 ± 55 times greater than the concentration in the plasma (Wildfeuer *et al*, 1996). *S. Typhi* and *S. Paratyphi A* are invasive

intracellular organisms; the effectiveness of AZM against *S. Typhi* and *S. Paratyphi A* may be attributable to its high intracellular concentration. Our findings indicate AZM is effective among adult Japanese patients with enteric fever, but further studies are needed to determine the treatment regimen.

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