Department of Pharmacy, Gifu University Hospital[1]; Phain Pharmacy[2]; Tanpopo Pharmacy Co., Ltd., Gifu University branch[3]; Laboratory of Community Pharmaceutics, Gifu Pharmaceutical University[4]; Kirara Pharmacy Co., Ltd., Gifu University branch[5]; Ain Pharmacy Co., Ltd., Gifu University branch[6], Gifu, Japan

A survey on diarrhea and convenience of intake associated with a single-dose extended release formulation of azithromycin

S. Okayasu[1], K. Matsuura[1], Y. Kondoh[2], E. Tsuruta[3], E. Takashima[4], M. Suzuki[5], T. Nagai[6], K. Yasuda[1], Y. Itoh[1]

Received August 14, 2010, accepted September 24, 2010

Prof. Yoshinori Itoh, Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, 501-1194 Gifu, Japan
yositou@gifu-u.ac.jp

Pharmazie 66: 226–229 (2011) *doi: 10.1691/ph.2011.0712*

The development of a single-dose extended release formulation of azithromycin (AZ-SR) improves the adherence. However, gastrointestinal side effects such as diarrhea are frequent adverse drug reactions. The aim of the present study was to investigate the incidence of patient-reported in a diarrhea and the convenience of intake of AZ-SR in an Asian population. To assess the incidence of diarrhea and convenience of intake, patient-reported in a questionnaire about the incidence, onset, duration and severity of diarrhea, shape of stool, and patients' impression on taste. The drug was prepared and used in common with the hospital pharmacy and the community pharmacy. AZ-SR was prescribed in 96 outpatients, among whom 81 patients received the medicine and the questionnaire at the hospital pharmacy or one of five neighboring community pharmacies. The recovery of the questionnaire was 40.7%. Diarrhea occurred in 18 of 33 patients (54.5%), which was more freqŭent than in earlier reports, although the symptom was mild (grade 1–2) and occurred in most cases within 2 days. Approximately one third of patients reported inconvenience in taking the formulation in respect of the ease (36.4%), amount (42.4%), and unpleasant bitter taste (36.4%). We report here the importance of collaboration between hospital pharmacists and community pharmacists in providing accurate drug information, including the incidence of diarrhea, to patients receiving AZ-SR.

1. Introduction

Azithromycin is a macrolide antibiotic with a broad spectrum of activity against gram-positive and gram-negative bacteria, including *Hemophilus influenzae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Staphylococcus aureus,* and *Mycobacterium avium* (Whitman and Tunkel 1992). Since azithromycin has a long elimination half-life, prescription of a single 500-mg tablet formulation for 3 days is clinically effective (Cooper et al. 1990). Recently, a single-dose 2-g azithromycin extended release formulation (Zithromac® SR dry syrup, AZ-SR) has been developed. This formulation needs to be administered only once to attain plasma concentrations with total area under the plasma concentration-time curves (AUC) similar to those obtained by a 3-day dose regimen with tablet formulation (Lo et al. 2009). However, gastrointestinal dysfunction such as diarrhea, nausea, vomiting and abdominal pain are common adverse drug reactions (ADRs) associated with macrolide antibiotics (Zervos et al. 2007). Saiman et al. (2003) showed that the incidence of diarrhea as measured by the record during patient visits or by the telephone interviews is 23% (20 of 87 patients) in patients receiving 250 mg-500 mg oral azithromycin tablets. Meanwhile, the incidence of diarrhea/loose stools associated with a single-dose extended release formulation of azithromycin is reported to be 11%–14% (Drehobl et al. 2005; Marple et al. 2007; Hansfield et al. 1994). On the other hand, Liu et al. (2007) compared the efficacy, safety and pharmacokinetics of azithromycin between a single-dose extended-release formulation and a 3-day immediate-release tablet in healthy adult subjects. They showed that diarrhea occured in 3 out of 12 subjects (25%) receiving a single-dose extended-release formulation, while no diarrhea developed in 12 subjects who took 3-day immediate-release tablet. In contrast, Jorgensen (2009) reported that the incidence of diarrhea is similar (11%) between a single-dose extended release formulation and 3-day azithromycin tablets. However, the incidence of diarrhea associated with AZ-SR in the Asian population is still unknown.

Antibiotics often cause alterations in the intestinal microflora, which lead to diarrhea (Hooker and DiPire 1988). On the other hand, it has been shown that the gastrointestinal ADRs to macrolide compounds result at least in part to the motilin-like action of this class of antibiotics (von Rosensteil and Adam). Motilin, an intestinal polypeptide that is involved in the bowel movement, contributes to the pathophysiology of diarrhea in the irritable bowel syndrome (Oberg et al. 1987). In the present study, we surveyed by a questionnaire the incidence of diarrhea in outpatients receiving AZ-SR in collaboration with hospital pharmacy and community pharmacies. The patients' impression on the convenience in taking the formulation was also investigated.

2. Investigations and results

AZ-SR was prescribed most frequently from the oral surgery department (50.5%), followed by the respiratory internal medicine (17.1%), hematological medicine (8.1%), and cardiovascular internal medicine (6.3%). Eighty-one patients received

Table 1: Pharmacies where AZ-SR was dispensed, and numbers of questionnaire distributed and recovered during

Pharmacies	Number of questionnaire distributed	% of total prescription	Number of questionnaires recovered	Recovery (%)
Phain Pharmacy	20	24.7	6	30.0
Community Pharmaceutics of Gifu Pharmaceutical University	15	18.5	8	53.3
Gifu University Hospital Pharmacy	15	18.5	4	26.7
Tanpopo Pharmacy	13	16.0	9	69.2
Kirara Pharmacy	10	12.3	3	30.0
Ain Pharmacy	8	9.9	3	37.5
Total	81		33	40.7

the medicine at the hospital pharmacy or one of five neighboring community pharmacies, where they were informed of the objective of the present study. They were provided with the questionnaire about the incidence of gastrointestinal side effects and the convenience of intake. As shown in Table 1, AZ-SR was dispensed most frequently at Phain pharmacy (24.7%), followed by the Gifu University hospital pharmacy (18.5%), the community pharmaceutics of Gifu Pharmaceutical University (18.5%), Tanpopo pharmacy (16.0%), Kirara pharmacy (12.3%), and Ain pharmacy (9.9%). Among 81 patients, 33 patients (40.7%) sent back the questionnaire by mail, in which the recovery rate was the highest (69.2%) in Tanpopo pharmacy and the lowest (26.7%) in the Gifu University hospital pharmacy. The characteristics of 33 patients are shown in Table 2.

As shown in Table 3, diarrhea appeared in 18 (54.5%) of 33 patients. The symptom occurred in most cases within 2 days (61.1% in the first day and 27.8% in the second day) and disappeared within 1–2 days, in which the duration was one day in 50% and two days in 44.4%. The symptom was in most cases mild, in which grade 1 was most frequent (77.8%), grade 2 appeared in 11.1%, and grade 3 in 5.6%. The shape of stool was muddy (44.4%), softened (27.8%) and watery (27.8%).

With regards to the convenience of intake, 63.6% of patients reported "easy", but 36.4% replied as "hard" or "a bit hard" (Table 4). The amount of the formulation was suitable in 57.6%, but many or too many in 42.5%. Azithromycin is a bitter powder, but 63.6% of patients reported that the taste was acceptable, although 36.4% of patients answered as slightly acceptable or hard to accept.

Table 3: Incidence, onset, grade and duration of diarrhea, and shape of stool in patients with oral ingestion of AZ-SR formulation as assessed by the questionnaire

	Number of patients	%
Incidence	18	54.5
Onset		
day 1	11	61.1
day 2	5	27.8
day 3 and later	2	11.1
Grade		
grade 1	14	77.8
grade 2	2	11.1
grade 3	1	5.6
no reply	1	
Duration		
one day	9	50.0
two dyas	8	44.4
3 days and more	1	5.6
Shape of stool		
loose	5	27.8
muddy	8	44.4
watery	5	27.8

3. Discussion

In the present study, we surveyed the incidence of diarrhea associated with AZ-SR and convenience of intake, AZ-SR was approved in Japan in March 2009 and introduced in our hospital in June 2009. During a period between July 1, 2009 and February 28, 81, outpatients received the medicine at the hospital pharmacy or a neighboring community pharmacy.

The predominant ADRs of AZ-SR are gastrointestinal ADRs (Hopkins 1991), including diarrhea, nausea, vomiting, abdominal distention, abdominal pain, abnormal increase in transaminases (Higa and Saito 2000), and sensorineural hearing loss (Mick and Westerberg 2007). Among them, diarrhea occurs

Table 2: Characteristics of patients

Age (years)	59.5 ± 17.0
Gender (male/female)	21/12
Albumin (g/dL)	4.1 ± 0.5
Aspartate transaminase (U/L)	27.1 ± 16.2
Alanin transaminase (U/L)	26.0 ± 18.4
Serum creatinine (mg/dL)	0.79 ± 0.30
Blood nitrogen urea (mg/dL)	16.5 ± 9.0
Treatment department	
Oral surgery	15 (45.5)
Respiratory internal medicine	4 (12.1)
Hematological medicine	4 (12.1)
Cerebral surgery	2 (6.1)
Others	8 (24.2)

Values represent number of patients or mean ± SD.

Table 4: Patients' impression on taking AZ-SR formulation

	Number of patients (N = 33)	%
Intake		
easy	21	63.6
A bit hard	9	27.3
hard	3	9.1
Amount of dose		
appropriate	19	57.6
much	12	36.4
too much	2	6.1
Taste		
no problem	21	63.6
a little bitter	7	21.2
quite bitter	5	15.2

Questionnaire about Zithromac® SR dry syrup

(Please check the relevant box)

1) Did you have diarrhea during 7 days after taking Zithromac® SR dry syrup?

☐ yes ☐ no

2) If you had diarrhea, please answer the following questions:

i) What was the shape of stool?

☐ soft ☐ muddy ☐ watery

ii) When did the (first) diarrhea occur?

☐ day 1 ☐ day 2 ☐ day 3 ☐ day 4 or later

iii) What was the maximal stool frequency in a day?

☐ ≦3 times/day ☐ 4-6 times/day ☐ ≧7 times/day

iv) How long did diarrhea last?

☐ 1 day ☐ 2 days ☐ 3 days ☐ 4 days or more

v) Did you take antidiarrheal or antiflatulent drugs, when you had diarrhea?

☐ yes ☐ no

3) Please fill out other side effects than diarrhea, and their onset and duration, if you experienced after taking Zithromac SR dry syrup.

side effects	onset	duration

[Question about convenience of intake]

4) How did you feel about intake the drug?

☐ easy ☐ a bit hard ☐ hard

5) How about the amount of dose?

☐ appropriate ☐ much ☐ too much

6) How about the taste of the drug?

☐ no problem ☐ a little bitter ☐ quite bitter

7) Please enumerate, if you had any inconvenience in taking the medicine.

Fig.: Questionnaire

most frequently, and the incidence is reported to be 11%–12% (Drehobl et al. 2005; Marple et al. 2007) or 16.4% (Zithromac® SR dry syrup package insert). In the present study, the incidence of patients-reported diarrhea (54.5%) was much higher than those reported earlier. However, the symptom of diarrhea was mild in most cases. At present, we do not know why the incidence of diarrhea was markedly different between our data and those reported earlier. Differences in the race or the method of the survey may cause such a discrepancy. In the present study, the incidence of diarrhea was assessed by a patient-reported questionnaire, which was only returned by 41% of patients. Therefore, the data may be overestimated if most of the patients who experienced diarrhea sent the questionnaire. In contrast, the incidence of ADRs was assessed by the telephone interviews in the reports by Drehobl et al. (2005) and Marple et al. (2007). A further study should be carried out to determine the incidence of diarrhea associated with AZ-SR in Asian populations because of the limited number of patients in the present study.

The recovery rate of the questionnaire was different among pharmacies, ranging from 26.7% to 69.2%. We cannot explain why such a difference in the rate existed, since the patients' education was similar among pharmacies and the questionnaire was the same.

Antibiotic therapy often causes alterations in the intestinal microflora, which may lead to *Clostridium difficile* toxin diarrhea (CDAD) (Bignardi 1998), although CDAD occurs mostly in inpatients with long hospital stay and prolonged antibiotic therapy. In the present study, AZ-SR-associated diarrhea appeared mostly within 2 days and was short-lasting. Therefore, it is unlikely that the diarrhea results from changes in microflora. It has been demonstrated that erythromycin and a variety of macrolide compounds activate directly the motilin receptor

(Marple et al. 2007). Motilin is a polypeptide showing a strong contractile action on the gastrointestinal tract. Thus, the acute and transient diarrhea induced by AZ-SR may result partly from a stimulation of the motilin receptor. It has been reported that the initial 24-h AUC ($AUC_{0\text{-}24}$) and the maximum plasma concentration after administration of AZ-SR are 5.2-fold and 3.3-fold, respectively, as those obtained from a 500-mg azithromycin tablet (Fang et al. 2009). The higher incidence of diarrhea in AZ-SR than in the tablet formulation may be due to such differences in the pharmacokinetic parameters. Therefore, pharmacists have the responsibility to provide information about the incidence of mild and transient diarrhea to patients who receive AZ-SR.

On the other hand, macrolide antibiotics have an unpleasant bitter taste in common, and the bitterness is intensified under acidic condition (Zgoulli et al. 1999). Several attempts have been made to reduce the bitterness of microlides, including mixing with chocolate jelly (Zgoulli et al. 1999) and microencapsulation (Amrol 2007). In AZ-SR formulation, azithromycin is incorporated into sustained-release microspheres (200 μm in diameter), thus the bitterness is masked and the effect is long-lasting (Amrol 2007). Nevertheless, in the present survey, approximately one third of patients reported inconvenience in taking the formulation for reasons of difficulty in taking, large amount of dose, and bitter taste. Further approaches are required to mask the unpleasant bitterness of the formulation.

In conclusion, the incidence and severity of diarrhea associated with AZ-SR and convenience of intake were surveyed in collaboration with the hospital pharmacy and the community pharmacy. The incidence of diarrhea was unexpectedly high (54.5%) as compared with results reported earlier or that indicated by the manufacturer's package insert, although the symptom was mostly mild and transient. In addition, some patients reported the inconvenience of intake in respect of the amount and taste. However, small number of patients and the low recovery rate of questionnaire reported by patients were the main limitations to the current study addressing the frequency and severity of diarrhea associated with AZ-SR.

4. Experimental

The present study was carried out in accordance with the guidelines for the care for human study adopted by the ethics committee of the Gifu Graduate School of Medicine, and notified by the Japanese government (approved No. 22–37 of the institutional review board). The subjects of the present study were outpatients who were prescribed with Zithromac® SR dry syrup (Pfizer Japan Inc, Tokyo, Japan; AZ-SR) at Gifu University Hospital during a period between July 1, 2009 and February 28, 2010. The medicine was dispensed at the hospital pharmacy or one of five neighboring community pharmacies. After dispensing AZ-SR, pharmacists provided verbal instruction about the dose, efficacy, and ADRs regarding AZ-SR using a sheet prepared based on the information in the package insert. Then, a form of questionnaire Fig. that was used in common with 5 pharmacies and a hospital pharmacy was handed out after explanation about the objective of the study. Patients checked any relevant items and returned the completed form by mail to the hospital or the community pharmacy. Finally, the questionnaire was collected at the pharmacy of Gifu University Hospital. The incidence and severity of diarrhea were assessed by the patient-reported questionnaire. The severity of diarrhea was graded, according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), in which the incidence of diarrhea is 0/day (grade 0), 3 times or less/day (grade 1), 4–6 times/day (grade 2) and 7 times or more/day (grade 3). Before and during the study period, all pharmacists in charge of the present study met together once a week in the hospital and discussed the questionnaire, approach to patients' education and evaluation of ADRs. Data were analyzed at the pharmacy department of Gifu University hospital and analyzed by Statistics Program for Social Science for Windows (SPSS-X, version 10, SPSS Inc., Chicago, IL).

References

Amrol D (2007) Single-dose azithromycin microsphere formulation: a novel delivery system for antibiotics. Int J Nanomedicine 2: 9–12.

Bignardi GE (1998) Risk factors for Clostridium difficile infection. J Hosp Infect 40: 1–15.

Cooper MA, Nye K, Andrews JM, Wise R (1990) The pharmacokinetics and inflammatory fluid penetration of orally administered azithromycin. J Antimicrob Chemother 26: 533–538.

Drehobl MA, De Salvo MC, Lewis DE, Breen JD (2005) Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest 128: 2230–2237.

Fang AF, Palmer JN, Chiu AG, Blumer JL, Crownover PH, Campbell MD, Damle BD (2009) Pharmacokinetics of azithromycin in plasma and sinus mucosal tissue following administration of extended-release or immediate-release formulations in adult patients with chronic rhinosinusitis. Int J Antimicrob Agents 34: 67–71.

Handsfield HH, Dalu ZA, Martin DH, Douglas JM Jr, McCarty JM, Schlossberg D (1994) Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Azithromycin Gonorrhea Study Group. Sex Transm Dis 21:107–111.

Higa F, Saito A (2000) Clinical safety of azithromycin. Jpn J Antibiot 53 (Suppl B): 125–135.

Hooker KD, DiPiro JT (1988) Effect of antimicrobial therapy on bowel flora. Clin Pharm 7: 878–888.

Hopkins S (1991) Clinical toleration and safety of azithromycin. Am J Med 91: 40S–45S.

Jorgensen DM (2009) Single-dose extended-release oral azithromycin vs. 3-day azithromycin for the treatment of group A beta-haemolytic streptococcal pharyngitis/tonsillitis in adults and adolescents: a double-blind, double-dummy study. Clin Microbiol Infect 15: 1103–1110.

Liu P, Allaudeen H, Chandra R, Phillips K, Jungnik A, Breen JD, Sharma A (2007) Comparative pharmacokinetics of azithromycin in serum and white blood cells of healthy subjects receiving a single-dose extended-release regimen versus a 3-day immediate-release regimen. Antimicrob Agents Chemother 51: 103–109.

Lo JB, Appel LE, Herbig SM, McCray SB, Thombre AG (2009) Formulation design and pharmaceutical development of a novel controlled release form of azithromycin for single-dose therapy. Drug Dev Ind Pharm 35: 1522–1529.

Marple BF, Roberts CS, de Caprariis PJ, Reisman A (2007) Onset of symptom resolution in adults with acute bacterial rhinosinusitis treated with a single dose of azithromycin extended release compared with 10 days of levofloxacin: a retrospective analysis of a randomized, double-blind, double-dummy trial. Clin Ther 29: 2690–2698.

Mick P, Westerberg BD (2007) Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. J Otolaryngol 36: 257–263.

Oberg K, Theodorsson-Norheim E, Norheim I (1987) Motilin in plasma and tumor tissues from patients with the carcinoid syndrome. Possible involvement in the increased frequency of bowel movements. Scand J Gastroenterol 22: 1041–1048.

Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW 3rd; Macrolide Study Group (2003) Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA 290: 1749–1756.

von Rosensteil NA, Adam D (1995) Macrolide antibacterials. Drug interactions of clinical significance. Drug Saf 13: 105–122.

Whitman MS, Tunkel AR (1992) Azithromycin and clarithromycin: overview and comparison with erythromycin. Infect Control Hosp Epidemiol 13: 357–368.

Zervos M, Martinez FJ, Amsden GW, Rothermel CD, Treadway G (2007) Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. Int J Antimicrob Agents 29: 56–61.

Zgoulli S, Grek V, Barre G, Goffinet G, Thonart P, Zinner S (1999) Microencapsulation of erythromycin and clarithromycin using a spray-drying technique. J Microencapsul 16: 565–571.