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Original

A Retrospective Study of Injection Site Pain from Azithromycin Injection in Japanese Patient

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Abstract: Azithromycin (AZM) injection tends to increase injection site pain when administered in excess of 2 mg / ml. As AZM is frequently used in combination therapies, it is expected to be administered at a high concentration in clinical use due to fluid restrictions. Therefore, in this study, the relation between AZM concentration and injection site pain was examined. From January 2012 to July 2017, we retrospectively investigated the medical records of patients who were administered AZM by injection at Showa University Fujigaoka Hospital. Vascular pain was related to intensive care unit (ICU) administration (P=0.003) compared with that in general wards and a long duration of administration (P=0.002). The number of days of AZM injection should be kept as short as possible. Given that the risk of injection site pain is increased in the ICU, we recommend switching to oral administration. Further collection of safety data in patients on fluid restriction is necessary, and high concentration AZM administration should be considered.

Key words: azithromycin (AZM) injection, injection site pain, safety, high concentration

Background

Azithromycin (AZM) injection was approved in Japan in 2011. Outside of Japan, the use of AZM is recognized in treating community-acquired pneumonia[1, 2)] and acute lung injury[3)]. In a Japanese phase I trial, when AZM administration exceeded 2 mg / ml, the frequency of adverse events related to injection site pain tended to increase.

In Japan, it is recommended to strictly observe an injection concentration of 1 mg / ml and an administration time of 2 h to avoid pain at the injection site. However, in the aforementioned trial, the number of cases evaluated was as few as 10 patients, and the administration time was over 1 h. Furthermore, tolerability has been confirmed for intravenous administration at

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2 mg / ml / h in the United States[4]. It was also reported that injection site pain increases at concentrations above 4 mg / ml[5]. In Japan, a prospective trial in which concentrations of AZM of 2 mg / ml were injected was reported, but it included only 12 cases[6].

In recent years, AZM has been administered to patients in the intensive care unit (ICU) in Japan[7], and no cases of phlebitis were reported. However, 20%–70% of patients receiving peripheral infusions have been reported to develop phlebitis[8, 9], and antimicrobial drugs themselves are regarded as a risk for phlebitis[8–11].

Among antibiotics, erythromycin, a macrolide antibacterial drug, tends to cause phlebitis[11]. Factors related to the occurrence of phlebitis include diabetes, female sex, work experience, catheter material, hemoglobin, drug pH, and osmotic pressure[8–12].

As AZM is frequently used in combination with a beta-lactam agent, it is expected to be administered at a high concentration in clinical use due to restrictions on infusion volume. Therefore, in this study, we investigated the relation between AZM concentration and vascular pain during injection in our hospital.

Methods

From January 2012 to July 2017, we retrospectively investigated the medical records of patients who were administered AZM by injection at Showa University Fujigaoka Hospital. Patients under 18 years of age and those in whom AZM was administered via central venous catheter were excluded.

The survey items were as follows: age, sex, body weight, ward (intensive care or general), cardiac disease, electrocardiographic monitoring, administration time, number of administration days, AZM concentration administered by injection, laboratory data, vascular pain, and concurrent medications. It was confirmed that the infusion time of AZM as administered by the pharmacist took over 2 h.

For comparison between the two groups, Fisher's direct stochastic method and t-test were used, and a significant difference was assumed at a 5 % risk rate. The odds ratio and 95% confidence interval were calculated as the expression rate of each factor. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[13]. This study was approved by the Institutional Review Board of Showa University Fujigaoka Hospital (Approval No. F2017C50).

Results

Patient characteristics

Patient characteristics are shown in Table 1. The average age of the patients was 68.3 years, and 72% were male. AZM was administered in the ICU in 40.6% of the patients, 19.8% had a history of cardiovascular disease, and the electrocardiogram of 86.8% of the patients was monitored. AZM was administered at 1 mg / ml in 71.7% of the patients and at a concentration

Table 1. Patient's characteristics (n = 106)

	n(%), mean ± SD
Age (years)	68.3 ± 16.4
Sex (male / female)	76 / 30
Body weight (kg)	57.4 ± 14.1
Clinical departments	
Intensive care unit	43 (40.6)
General wards	63 (59.4)
Cardiac disease	21 (19.8)
Electrocardiographic monitoring	92 (86.8)
Concentration of azithromycin	
1 mg / ml	76 (71.7)
2 mg / ml	21 (19.8)
5 mg / ml	9 (8.5)
Duration of azithromycin administration (days)	4.2 ± 2.2
Over duration of 5 days	44 (41.5)
30-day mortality	26 (24.5)
WBC (×103 / ml)	11.4 ± 5.8
Hgb (g / dl)	12.0 ± 2.1
AST (IU / l)	59.8 ± 106.8
ALT (IU / l)	40.7 ± 56.9
BUN (mg / dl)	28.6 ± 27.4
Cr (mg / dl)	1.3 ± 1.4
Alb (g / dl)	3.1 ± 0.7
CRP (mg / dl)	15.5 ± 11.3
Corticosteroids	42 (39.6)
Analgesic drug	28 (26.4)
Anticoagulant treatment	
Heparin or warfarin	21 (19.8)
Combination of antibiotics	
AZM only	4 (3.8)
Combination	
Penicillins	46 (43.4)
Cephems	18 (17.0)
Carbapenems	34 (32.1)
Quinolones	1 (0.9)
Others	3 (2.8)
Risk factors for erythema	
Gender (female)	30 (28.3)
Age (over 61)	77 (72.6)
Diabetes	30 (28.3)
Cancer	13 (12.3)
Immunocompromised	11 (10.4)
Injection site pain or erythema	9 (8.5)

Background of patients receiving azithromycin (AZM) infusion. 71.7% of patients were administered AZM at the concentration indicated on the package insert.

exceeding the package insert directions in 28.3%. The average number of treatment days was 4.2, but 41.5% of the patients underwent administration exceeding 5 days. AZM alone was administered in 3.8% of the patients.

Endpoint

A total of nine patients (8.5%) were found to have vascular pain during AZM administration. All of them were administered AZM at an injection concentration of 1 mg / ml. No medications were administered to hypersensitive patients who may have experienced skin disorders related to AZM injection. The vascular pain in these nine patients was not judged to be caused by allergic reaction.

Univariate analysis

Table 2 shows the results of univariate analysis depending on the presence or absence of vascular pain. Factors found to be related to vascular pain were administration in the ICU (P=0.003) versus that in general wards and long duration of administration (P=0.002). Hemoglobin, female sex, age ≥ 61 years, diabetes, cancer, immunological disorder, and administration concentration have been reported as factors causing vascular pain[10]. However, none of these factors was considered to be relevant in the vascular pain observed in the present study.

Discussion

In this study, AZM administration at a high concentration over that recommended on the package insert was performed in 28.3% of the patients. Injection site pain was experienced in 8.5% of all treated patients. Similar to that in the present study, 5.9% of patients with pneumonia who were administered AZM at a concentration of 1 mg / ml by injection in a Japanese phase III trial experienced mild injection site pain[14].

In the present study, no correlation between AZM concentration and injection site pain was found. The only risk factors for injection site pain were administration in the ICU and duration of administration. Compared with erythromycin, AZM is reported to be more neutral in pH, its osmotic pressure is close to 1, and less vascular pain is reported[15]. However, there is also a report suggesting problems of tolerability due to the influence of macrolides on endothelial cells, even at normal concentrations[16]. Various drugs are administered in the ICU[17, 18], and the use of antibiotics is ten times higher than in general wards[18]. Antibiotics that are prone to causing vascular pain are frequently used in combination. During the study period, the pharmacist audited all orders for AZM administration, and adherence to injection over 2 h was strictly observed. This strict observance of administration time was not mainly for the prevention of vascular pain but because slow administration does not cause QT prolongation that is observed with the rapid administration of macrolides. When it is necessary to administer AZM at a high concentration, as in the previous reports[7], it may be possible to suppress injection site pain by setting the intravenous drip time to 2 h or more.

Table 2. Univariate analysis of risk factor in the injection site pain or erythema

	Injection site pain or erythema Yesn=9	Non=97	*p* value
Age (years)	65.1 ± 16.0	68.6 ± 16.5	0.335
Sex (male / female)	6 / 3	70 / 27	0.710
Body weight (kg)	64.1 ± 16.7	56.8 ± 13.7	0.165
Hgb (g / dl)	12.5 ± 2.5	12.0 ± 2.1	0.511
Clinical department:			
Intensive care unit	8 (88.9)	35 (36.1)	0.003
General wards	1 (11.1)	62 (63.9)	
Cardiac disease	4 (44.4)	17 (17.5)	0.074
Concentration of azithromycin			
1 mg / ml	9 (100)	67 (69.1)	0.230
2 mg / ml	0 (0)	21 (21.6)	
5 mg / ml	0 (0)	9 (9.3)	
Duration of azithromycin administration (days)	6.2 ± 2.4	4.0 ± 2.1	0.002
Over duration of 5 days	7 (77.8)	37 (38.1)	0.032
Corticosteroids	1 (11.1)	41 (42.3)	0.084
Analgesic drug	3 (33.3)	25 (25.8)	0.696
Anticoagulant treatment			
Heparin or warfarin	3 (33.3)	18 (18.6)	0.377
Risk factors for erythema			
Gender (female)	3 (33.3)	27 (27.8)	0.703
Age (over 61)	7 (77.8)	70 (72.2)	1.000
Diabetes	3 (33.3)	27 (27.8)	0.710
Cancer	0 (0)	13 (13.4)	0.597
Immunocompromised	2 (22.2)	9 (9.3)	0.235
Combination of antibiotics			
AZM only	0 (0)	4 (4.1)	
Combination			
Penicillins	3 (33.3)	43 (44.3)	
Cephems	0 (0)	18 (18.6)	
Carbapenems	6 (66.7)	28 (28.9)	
Quinolones	0 (0)	1 (1.0)	
Others	0 (0)	3 (3.1)	

Univariate analysis of risk factor in the injection site pain or erythema.

Patients who complained of vascular pain tended to have an ICU stay and longer AZM administration days.

As a limitation of this research, various other factors causing vascular pain other than drug administration concentration (such as the location of blood vessels in which the drug is administered, length of the administration route, and nurse's years of experience) were not confirmed. Although AZM administered in the ICU can be affected by various other drugs, we think that there should be no objection to the necessity for caution. In the ICU, patients are often managed in a sedated state, which may cause delay in their complaints of vascular pain[19]. Therefore, we consider the results of this study to be reasonable. As a serious side effect of

AZM, eosinophilic pneumonia can develop, which may increase hypersensitivity. Detailed data on hypersensitivity, such as the presence or absence of an elevated eosinophil level, were not examined, and thus, the possibility of an allergic potential for vascular pain cannot be denied. In the patients who did not develop vascular pain, it may have been masked by steroid administration. Steroids are frequently administered to patients with severe pneumonia, so vasculitis may be suppressed.

The number of days of AZM injection should be kept as short as possible. It is recommended that doses over 5 days be administered under adequate observation, as there is little experience with dosing in Japan over 5 days. Furthermore, this study suggested that administration for 5 days or more is a risk factor for vascular pain. Confirmation of the reason for AZM administration is necessary to ensure that administration for indeterminate reasons is not performed. Understanding that the risk of vascular pain increases in the ICU and considering the risks and benefits, we recommend switching to oral administration of AZM if possible. Although injection site pain can be caused by various factors, it is still significant to consider patients with fluid volume restriction, and in such patients, AZM can be administered at a high concentration. In this study as well, we believe that it is necessary to administer AZM more carefully as a large proportion of the patients in the high concentration group had a history of cardiovascular disease. The results of this study showed that the AZM concentration was not a risk factor for injection site pain, but high concentration administration is not recommended in all cases. In this study, all patients with vascular pain were dosed at 1 mg / ml. Although high concentrations are not recommended, AZM should be administered more carefully even at concentrations as per the package insert. High concentration administration of AZM is, in fact, performed in Japan, and considering the previous reports, we need to collect additional safety data and reconsider the administration of AZM at a high concentration.

Conflicts of interest disclosure

The authors of this paper have no conflicts of interest to disclose.

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