MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

Effect of single-dose extended-release oral azithromycin on anticoagulation status in warfarinized patients

Yuji Kusafuka, DDS,[a] Hiroshi Kurita, DDS, PhD,[b] Shinichi Sakurai, DDS,[c] Shigeru Suzuki, DDS, PhD,[a] Yoshitaka Nakanishi, DDS, PhD,[a] Yoshihiko Katsuyama, PhC, PhD,[d] and Shigeru Ohmori, PhC, PhD,[e] Matsumoto, Japan
SHINSHU UNIVERSITY SCHOOL OF MEDICINE AND SHINSHU UNIVERSITY HOSPITAL

Objective. The aim of this study was to investigate the possible influence of single-dose 2.0-g azithromycin (AZ-ER) on anticoagulation in patients taking warfarin.
Study Design. Eighteen consecutive patients receiving long-term stable warfarin therapy were enrolled in this study. AZ-ER was administered 1 hour prior to tooth extraction. The international normalized ratio (INR) value was measured prior to AZ-ER administration as well as during, 1 day after, and 7 days after the tooth extraction. Additionally, the azithromycin concentration in the extraction wound as well as in the peripheral venous blood was assessed.
Results. The changes in INR throughout the study period were not statistically significant (2-factor analysis of variance, NS). The azithromycin concentration in extraction wounds was higher than that in peripheral veins.
Conclusions. The results of this study suggest that prophylactic administration of AZ-ER to patients receiving daily warfarin therapy with a stable coagulation status has no relevant effect on the anticoagulant effect of warfarin. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:148-151)

Warfarin is the most commonly prescribed oral anticoagulant and is used in the management of thromboembolic diseases.[1] Various antibiotics have been reported to interact with warfarin. In daily practice, dentists generally use antibiotics either as prophylactic cover or in the therapeutic management of infection. Antibiotics used in dentistry also have a possible capacity to interact with warfarin, producing a clinically significant alteration in anticoagulation status.[1-3]

A novel microsphere-based azithromycin extended-release formulation (AZ-ER) allows administration of a high oral dose of azithromycin as a single-dose regimen, while maintaining tolerability.[4,5] Azithromycin is an effective antibiotic in the treatment of odontogenic infections,[6] and the administration of a single large dose of azithromycin as front-loading achieves more rapid bacterial eradication and prophylaxis of postoperative infections, including prevention of infective endocarditis.[7,8] Azithromycin is an azalide, a subclass of macrolide antibiotics.[9] Some case reports have suggested that macrolides have the potential to enhance the anticoagulation effect of warfarin.[1-3] However, no prospective study has yet evaluated the effect of AZ-ER on the anticoagulation of warfarin therapy.

The purpose of this study was to investigate the possible influence of AZ-ER on anticoagulation in patients taking warfarin.

MATERIAL AND METHODS

This study included a total of 18 consecutive patients receiving long-term stable warfarin therapy with an international normalized ratio (INR) of less than 3.0 and who required a dental extraction. Patients who had an allergic reaction for azithromycin, who had any other hemorrhagic diathesis, or who had received treat-

[a]Clinical Fellow, Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Matsumoto, Japan.
[b]Professor, Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Matsumoto, Japan.
[c]Resident, Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Matsumoto, Japan.
[d]Chief, Department of Pharmacy, Shinshu University Hospital, Matsumoto, Japan.
[e]Professor, Department of Pharmacy, Shinshu University Hospital, Matsumoto, Japan.

Statement of Clininal Relevance

Warfarin is a commonly prescribed oral anticoagulant used in the management of thromboembolic diseases. Various antibiotics have been reported to interact with warfarin. However, no prospective study has yet evaluated the effect of azithromycin on the anticoagulation of warfarin therapy.

Table I. Patient data

Sex (male:female)	13:5
Age[a]	72.5 years (44-87)
Daily dose of warfarin[a]	2.5 mg (0.25-6)
No. of teeth extracted	1 in 7 patients, 2 in 5 patients, 3 in 6 patients
Time between AZM administration and tooth extraction	70 min (60-120)
Amount of analgesic used	None in 5 patients, 1 dose in 9 patients, 2 doses in 1 patients, 3 doses in 2 patients, 6 doses in 1 patient

AZM, azithromycin.
[a]Median (range).

Table II. Extraction region data

No.	Extraction region*	Cause	PT-INR[a] 1.75 (1.08-2.91)	Level of extraction
1	34, 35	Periodontitis	2.13	Easy
2	15, 17	Periodontitis	1.64	Easy
3	22, 23, 27	Periodontitis, deep caries	1.64	Easy
4	14, 15, 17	Periodontitis, deep caries	1.08	Easy
5	22, 41, 42	Periodontitis	1.53	Easy
6	31, 33	Periodontitis	2.07	Easy
7	33, 37, 43	Periodontitis	2.0	Easy
8	26, 27, 38	Periodontitis, deep caries	1.6	Easy
9	46	Periodontitis	1.14	Easy
10	37, 44, 45	Periodontitis, deep caries	1.41	Easy
11	15, 33	Periodontitis	2.01	Easy
12	36	Periodontitis	1.1	Easy
13	13	Fractured tooth	1.38	Easy
14	38	Perico	2.1	Surgical
15	36	Periodontitis	1.97	Easy
16	24, 45	Periodontitis	1.78	Easy
17	36	Deep caries	2.91	Easy
18	14	Periodontitis	1.96	Easy

[a]Two-digit system, median (range).

ment with any systemic antibiotic within the previous 7 days were excluded from the study.

AZ-ER (a single 2.0-g dose of azithromycin) was administered orally on an empty stomach and more than 1 hour prior to tooth extraction. Dental extractions were performed under local anesthesia using 2% (20 mg/mL) lignocaine hydrochloride with 1/80,000 (12.5 μg/mL) adrenaline. Dental extractions were conducted using forceps and elevators as atraumatically as possible. Each extraction socket was packed with oxycellulose dressing (Surgicel) and sutured with 3-0 nonabsorbable nylon surgical sutures (Surgiron). Patients were then given a gauze swab to bite on for 20 minutes. If hemostasis was not achieved after biting on the gauze swab, this result was recorded as immediate postoperative bleeding. In case of pain, 60 mg loxoprofen was prescribed. The patients were advised to wait more than 8 hours between intake of tablets and not to take any other analgesics.

The azithromycin concentration of dental alveolar blood in extraction wounds as well as in peripheral venous blood at the same time was assessed by high-performance liquid chromatography.[10] Immediately after each tooth extraction, blood from extraction wounds was collected directly into a sterile syringe while avoiding contamination with saliva by using dental cotton rolls.

The INR value was measured using the CoaguChek XS system (Roche Diagnostics, Indianapolis, IN) prior to AZ-ER administration as well as during, 1 day after, and 7 days after the tooth extraction using capillary blood from a fingertip or untreated venous whole blood.

This study was approved by the institutional review board and all participants gave written informed consent.

RESULTS

A total of 18 patients (13 men and 5 women, with a median age of 72.5 years) were available for the study. The patient data are summarized in Table I.

Additional information on the details of extracted teeth is summarized in Table II. The time period between AZ-ER administration and extraction varied between 60 and 120 minutes. Tooth extractions were carried out by trained oral surgeons and no remarkable troubles were noted. Five patients did not request a painkiller; 9 patients took a single dose of loxoprofen, 1 patient took 2 doses, 2 patients took 3 doses, and 1 patient took 6 doses. All analgesics were taken on the day of and the day after the extraction. No additional painkillers were administered on or after the 3rd day from extraction.

The azithromycin concentration distributions are shown in Figure 1. The concentration in extraction wounds varied from 0.16 to 4.34 μg/mL with a median concentration of 0.85 μg/mL, whereas the concentration in venous blood varied from 0.05 to 2.13 μg/mL with a median concentration of 0.54 μg/mL. Linear approximation showed a gentle increase of azithromycin concentrations during the period between 60 and 120 minutes after AZ-ER administration, and the concentration level in extraction sites was higher than that in the peripheral veins.

The changes of INR values over time are shown in Figure 2. The maximum increase of INR was 0.17 (median increase, −0.01) at the time of extraction, 0.77 (0.08) at 1 day after extraction, and 1.4 (0.00) at 7 days after extraction. These changes in INR throughout the study period were not statistically significant (2-factor analysis of variance, NS).