

**Effect of single-dose extended-release oral azithromycin on anti-coagulation status  
in warfarinized patients**

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## Abstract

**Objective:** 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, during, one-day after, and seven-days after the tooth extraction. Additionally, the azithromycin concentration in the extraction wound as well as in peripheral venous blood was assessed.

**Results:** The changes in INR throughout the study period were not statistically significant (two-factor ANOVA, N.S.). The azithromycin concentration in extraction wounds was higher than that in peripheral veins.

**Conclusion:** 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.

## **Introduction**

Warfarin is the most commonly-prescribed oral anticoagulant and is used in the management of thromboembolic diseases<sup>1)</sup>. Various antibiotics have been reported to interact with warfarin. In daily practice, the dentist usually uses 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<sup>1-3)</sup>.

A novel microsphere-based azithromycin extended-release formulation (AZ-ER) allows administration of a high oral dose of azithromycin as single dose regimen, while maintaining tolerability<sup>4, 5)</sup>. Azithromycin is known as an effective antibiotic in the treatment of odontogenic infections,<sup>6)</sup> 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<sup>7, 8)</sup>. Azithromycin is an azalide, a subclass of macrolide antibiotics<sup>9)</sup>. Some case reports have suggested that macrolides have the potential to enhance the anticoagulation effect of warfarin<sup>1-3)</sup>. 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.

## **Materials 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 treatment 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 the tooth extraction. Dental extractions were performed under local anesthesia using 2% (20 mg/ml) lignocaine hydrochloride with 1/80,000 (12.5µg/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 was recorded as immediate postoperative bleeding. Loxoprofen 60 mg, 8-hourly depending on the presence of pain was prescribed and patients were advised not to use 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 modified Shepard's high-performance liquid chromatography (HPLC). 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) prior to AZ-ER administration, during, one-day after, and seven-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 1. The time period between AZ-ERM administration and extraction varied between 60 to 120 minutes. Tooth extractions were carried out by trained oral surgeons and no remarkable troubles were noted. Five patients did not request a pain-killer and 9 patients took a single dose of loxoprofen, 1 patient two doses, 2 patients three doses, and 1 patient six doses. All analgesics were taken on the day of and the day after the extraction. No additional pain-killers were administered on or after the third day from extraction.

The azithromycin concentration distributions are shown in Figure 1. The concentration in extraction wounds varied from 0.16  $\mu\text{g/ml}$  to 4.34  $\mu\text{g/ml}$  with a median concentration of 0.85  $\mu\text{g/ml}$ , while the concentration in venous blood varied from 0.05  $\mu\text{g/ml}$  to 2.13  $\mu\text{g/ml}$  with a median concentration of 0.54  $\mu\text{g/ml}$ . 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, and 1.4 (0.00) at 7-days after extraction, respectively. These changes in INR through the study period were not statistically significant (two-factor ANOVA, N.S.).

The relationship between change of INR value (difference between pre-administration and 7 days after extraction) and dose of analgesics is shown in Figure 3. Although INR tended to increase with increasing use of analgesics, there was no statistically-significant correlation between them ( $R^2=0.261$ , Spearman's rank correlation test, N.S.).

Immediate postoperative bleeding was observed in one patient and the bleeding was easily stopped with an additional suture and direct pressure. Neither delayed bleeding, infection, nor adverse effects related to AZ-ER were observed through the study.

## **Discussion**

To date, various antibiotics have been used in dental practice<sup>8</sup>). In this study, we used single-dose 2.0 g azithromycin, which is a persistent extended-release formulation<sup>5</sup>). The safety of massive doses of azithromycin is confirmed, and a single-dose of 2.0g of azithromycin can yield a high blood concentration<sup>4, 5</sup>). AZ-ER is thought to show high penetration into inflammation tissue<sup>4-6, 9, 10</sup>). We therefore measured the azithromycin concentration in tooth extraction sites and compared with that in venous blood during a period between 60 and 120 minutes after AZ-ER administration. The results of this

study showed that the concentration level in extraction sites was higher than that in the peripheral veins. Lai et al. measured steady-state levels of azithromycin in gingival crevicular fluid (GCF) and reported that the concentrations in GCF were higher and more sustained than those in serum. They suggested that the pharmacokinetic profiles of azithromycin are different in GCF and serum<sup>6)</sup>. It was also reported that azithromycin attenuates acute and chronic tissue inflammation<sup>4, 5, 9, 10)</sup>. A higher concentration of azithromycin into the tooth extraction site is considered beneficial for preventing infection after tooth extraction.

We found no significant interaction between oral intake of AZ-ER and warfarin. Single-dose 2.0 g azithromycin with persistent extended-release formulation did not modify the anticoagulant activity (INR value) in patients receiving stable warfarin therapy. Previously, increased INR was observed in patients treated with warfarin and antibiotics used in dental practice. However, to date, there have been few prospective studies that evaluated the effect of antibiotics on the INR in patients on warfarin therapy<sup>1-3)</sup>. Recently, Zhang et al. reported the first systemic prospective evaluation of the interaction between antibiotics (amoxicillin/clavulanic acid) and warfarin, and found that it did not modify the INR in patients treated with stable warfarin therapy<sup>2)</sup>. Our study supplies additional scientific evidence that a single high dose of azithromycin (AZ-ER) does not modify INR in patients treated with stable warfarin therapy.

Antibiotics have the theoretical potential to interact with warfarin by two distinct mechanisms. Antibiotics interfere with the CYP2C9-dependent warfarin metabolism, leading to higher warfarin plasma concentrations. Separately, antibiotics alter the

normal gut flora, resulting in reduced intestinal vitamin K synthesis even if it is the case that the vitamin K produced by the colon flora (essentially K2) does not contribute significantly to the total vitamin K absorbed. Unfortunately, we could not clarify the influence of AZ-ER on either CYP2C9-dependent warfarin metabolism or the intestinal flora in this study. However, our results suggested that AZ-ER has no significant negative impact on CYP2C9-dependent warfarin metabolism or the gut flora which cause a change of anticoagulation status in patients treated with stable warfarin<sup>1-3</sup>).

Some clinicians have encountered increased INR and bleeding events in patients treated with antibiotics and warfarin. We observed increased INR at seven days after administration of AZ-ER in two patients. It is apparent that conflicts often arise between scientific studies and case reports; in the clinical situation there may be many confounding factors (vitamin K intake, food, drug, genetic factors, etc.) that alter the effect of warfarin<sup>2</sup>). Several studies have shown that CYP expression and activity may be decreased in humans during infection or inflammation, resulting in lowered drug clearance, increased toxicity and altered physiological function<sup>1,2</sup>). The infection itself (inflammatory syndrome) may alter the warfarin metabolism or hepatic clotting factor synthesis<sup>2, 3</sup>). Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to interact with the oral anticoagulant warfarin and can cause serious bleeding complications<sup>11, 12</sup>), although the results of this study failed to show significant relationship between the dose of NSAIDs and INR value.

In the current study, prophylactic administration of a single-dose 2.0 g azithromycin to patients receiving daily warfarin therapy and having a stable coagulation status had



no relevant effect on the anticoagulant effect of warfarin. However, in general, responses to warfarin therapy can be unpredictable, and we should continue to take into account the rare and sometimes serious sequelae.

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**Table 1.** Patient data

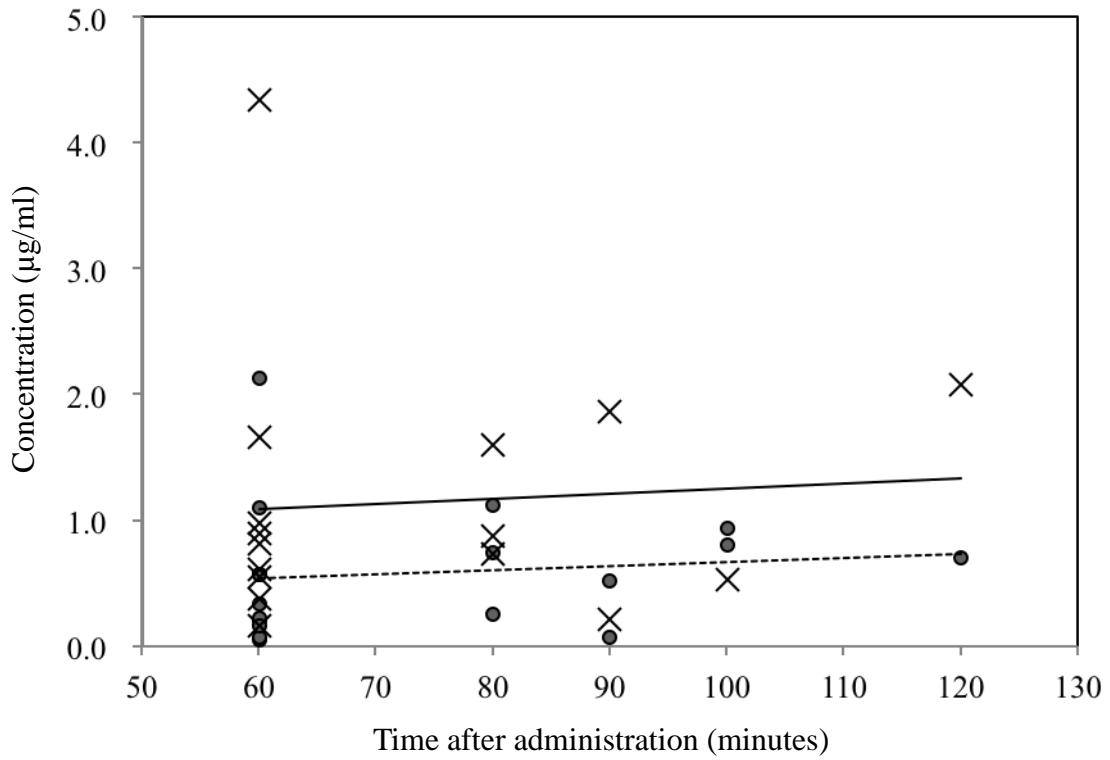
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Sex (Men : Women)	13 : 5
Age*	72.5 years (44-87)
Daily dose of warfarin*	2.5 mg (0.25-6)
No. of teeth extracted	1 in 7, 2 in 5, 3 in 6 patients
Time between AZM-administration and tooth extraction*	70 minutes (60-120)
Amount of analgesics used	None in 5, 1 dose in 9, 2 doses in 1, 3 doses in 2, 6 doses in 1 patient

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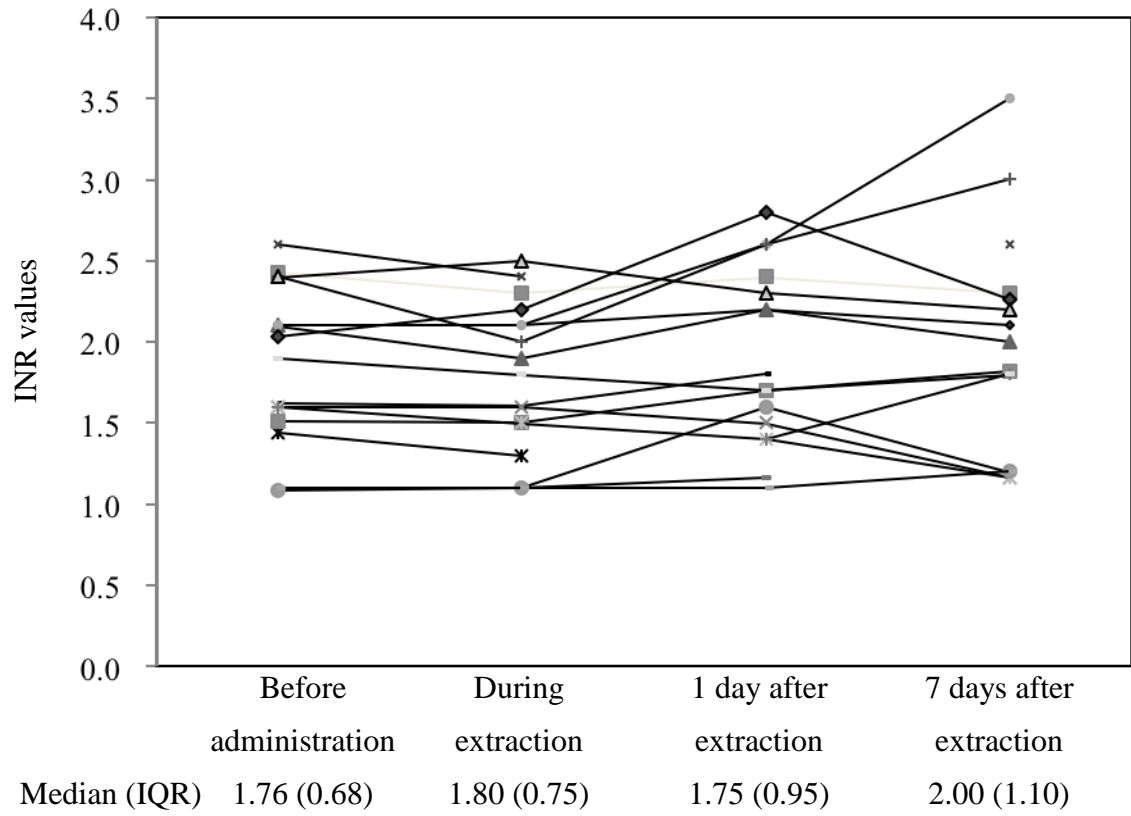
\* median (range), AZM: azithromycin

**Figure 1.** Azithromycin concentrations in extraction wounds (x) and peripheral veins (.)

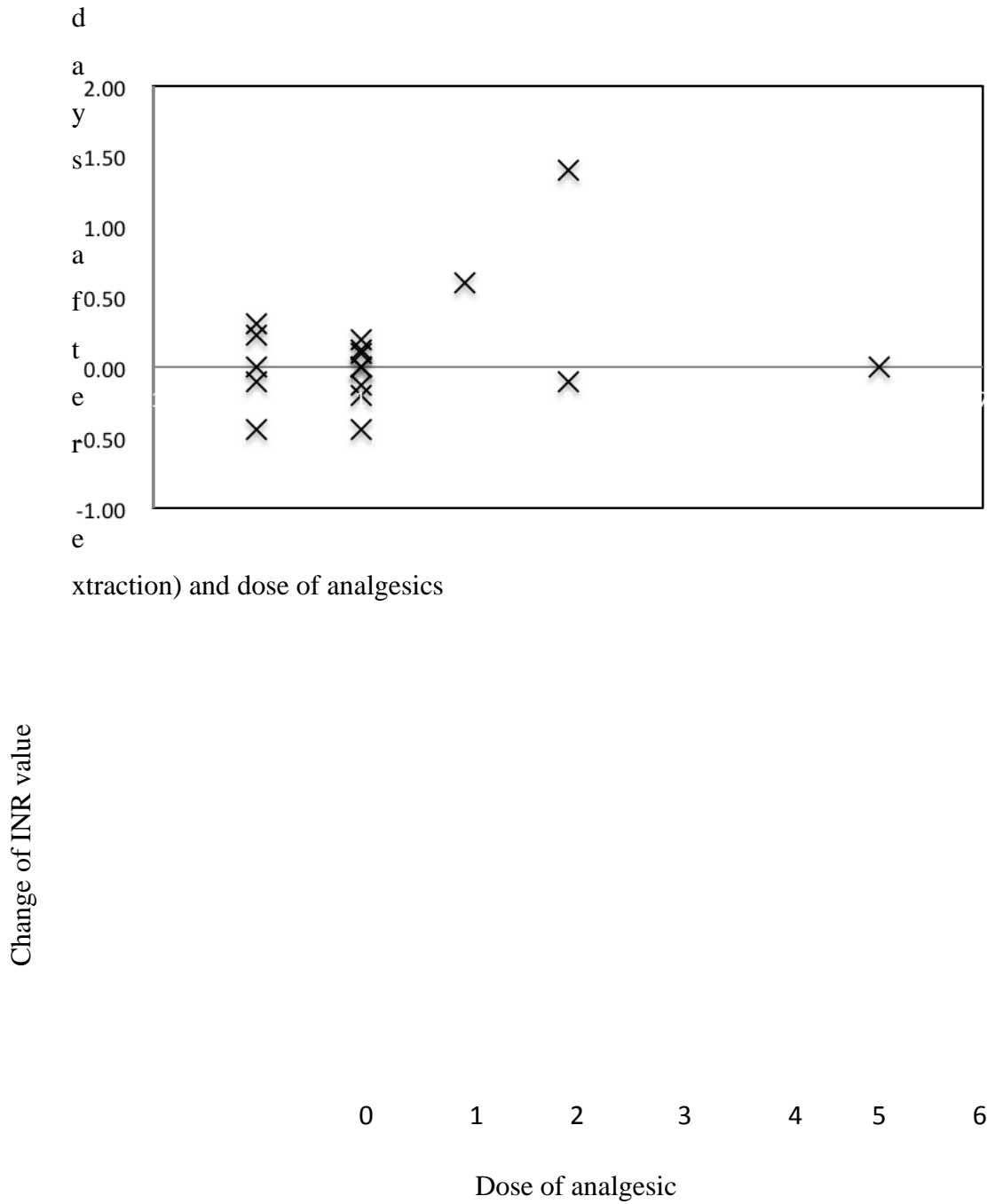


— Linear approximation of AZM concentration in extraction wounds  
- - - - - Linear approximation of AZM concentration in peripheral veins

**Figure 2.** Changes of INR values with time



**Figure 3.** Relationship between changes of INR values (difference between pre and 7



extraction) and dose of analgesics