# Pharmacokinetic/Pharmacodynamic Modeling for Concentration-Dependent Bactericidal Activity of a Bicyclolide, Modithromycin

**TAKAYUKI KATSUBE,[1] TOSHIHIRO WAJIMA,[1] YOSHINORI YAMANO,[2] YOSHITAKA YANO[3]**

[1]Clinical Research Department, Shionogi and Company, Ltd., Shibata 1–1–4, Kita-ku, Osaka 530-0012, Japan
[2]Medicinal Research Laboratories, Shionogi and Company, Ltd., Futaba-cho 3–1–1, Toyonaka, Osaka 561-0825, Japan
[3]Education and Research Center for Clinical Pharmacy, Kyoto Pharmaceutical University, Misasagi-Nakauchicho 5, Yamashina-ku, Kyoto 607-8414, Japan

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**ABSTRACT:** The aim of this study was to develop a pharmacokinetic (PK)/pharmacodynamic (PD) model of a bicyclolide, modithromycin, to explain its concentration-dependent bactericidal activity based on the drug–bacterium interaction model that we developed. We have already reported the applicability of model to the time-dependent activity of β-lactams, and we further applied the model to the concentration-dependent activity in this study. *In vitro* time-kill data of modithromycin, telithromycin, and clarithromycin against *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* were used for the modeling. An effect compartment model was incorporated into our original model to explain the time lag between PK and PD profiles. Also, a turnover model for reversible reduction of efficacy was incorporated to explain the regrowth. The developed model well described the time-kill profiles for each drug–bacterium combination. The estimated parameter related to efficacy strongly correlated with minimum inhibitory concentration (MIC), and the simulated bacterial counts at 24 h strongly correlated with both the ratio of the area under the concentration–time curve to MIC (AUC/MIC) and the ratio of the maximum concentration to MIC ($C_{max}$/MIC). These results suggested that the proposed model can be applied to both concentration-dependent and time-dependent bactericidal kinetics, and would be useful for predicting the bactericidal activity of modithromycin. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1288–1297, 2014
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## INTRODUCTION

Pharmacokinetic (PK)/pharmacodynamic (PD) analysis plays an important role in drug development and clinical pharmacotherapy of various kinds of drugs.[1–3] For antibiotics, several PK/PD models have been proposed to explain bacterial count profiles in *in vitro* and *in vivo* experiments.[4–14] For the analyses of bactericidal kinetics in *in vitro* time-kill experiments, we developed a drug–bacterium interaction model of β-lactams[10] based on a logistic growth function[15] with two cellular compartments[9,16] and a saturable killing model.[6,7] The model has been applied to the analyses of time-kill data in *in vitro* experiments using an autosimulation system[17] and *in vivo* animal experiments using murine lung infection models.[18] Also, we succeeded in predicting the relationships between bactericidal efficacy (bacterial count at 24 h) and the time that the drug concentration exceeds the minimum inhibitory concentration (MIC) ($T_{MIC}$) for β-lactams. The predicted relationships are useful for determining the effective dosage regimens based on target values of $T_{MIC}$. We also have reported the Monte Carlo simulation approach using our PK/PD model for examining effective dosage regimens of a carbapenem, doripenem.[19]

Modithromycin (also known as S-013420) is a bicyclolide (bridged bicyclic macrolide) that shows a broad spectrum of activity against various pathogens of respiratory tract infections.[20] The mechanism of the bactericidal activity of modithromycin involves inhibition of amplification by binding to the 50S subunit of the bacterial ribosome as observed with telithromycin and clarithromycin.[20] Nonclinical studies have been conducted to characterize the bactericidal activity of modithromycin during drug development,[21,22] and *in vitro* time-kill experiments have shown that the bactericidal activity correlates with the ratio of the maximum drug concentration ($C_{max}$) to MIC ($C_{max}$/MIC) and the ratio of the area under the concentration–time curve (AUC) to MIC (AUC/MIC), indicating concentration-dependent bactericidal activity.

We have reported the applicability of our drug–bacterium interaction model[10] to the time-dependent bactericidal activity. The aim of the present study was to develop a PK/PD model based on our previous drug–bacterium interaction model for describing *in vitro* time-kill data of modithromycin that indicates the concentration-dependent bactericidal activity, and for predicting the relationships between efficacy and PK/PD indices. Data for telithromycin and clarithromycin were analyzed as reference data.

## MATERIALS AND METHODS

### Experimental Data

*In vitro* time-kill data in experiments using constant drug concentrations (static experiments) and experiments using time-varying drug concentrations (dynamic experiments) for modithromycin, telithromycin, and clarithromycin were

*Correspondence to*: Takayuki Katsube (Telephone: +81-6-6485-5088; Fax: +81-6-6375-5780; E-mail: takayuki.katsube@shionogi.co.jp)
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obtained from our previous nonclinical studies[21,22] during the drug development of modithromycin [unpublished data for *Staphylococcus aureus* (*S. aureus*) SR20405]. As the details of these experiments are given in the Refs.21 and22, only general information for both experiments is described here.

In the static experiments,[21] modithromycin, telithromycin, and clarithromycin were added individually to a medium with a certain amount of bacteria at the beginning of the experiment. The exponentially growing bacterial suspensions, $\leq 5 \times 10^5$ CFU/mL, were used as the initial inoculum. The bacterial suspension was incubated at 37°C in the presence of various concentrations (0.5×–16×MIC). A portion of the bacterial suspension was collected at 0, 2, 4, 6, and 24 h for *S. aureus* SR20405 and 0, 1, 2.5, 4, and 6 h for other bacteria. The number of viable bacterial cells was determined by counting the number of colonies on the agar plates. The reported bacterial count data of the following drug–bacterium combinations were used for the modeling: modithromycin against *S. aureus* SR20405; modithromycin or telithromycin against *Haemophilus influenzae* (*H. influenzae*) SR24159; modithromycin, telithromycin, or clarithromycin against *H. influenzae* SR24165; modithromycin, telithromycin, or clarithromycin against *H. influenzae* SR24169; modithromycin or telithromycin against *Streptococcus pneumoniae* (*S. pneumoniae*) SR26132. The serial numbers (Comb. #) were assigned to the drug–bacterium combinations as defined in Table 1 and shown in other tables and figures. The drug concentrations used for each combination in the static experiments were; Comb. #1: 0.25, 1, and 4 μg/mL; Comb. #2, #4, and #6: 2, 4, 8, 16, and 32 μg/mL; Comb. #3 and #5: 0.5, 1, 2, 4, and 8 μg/mL; Comb. #7 and #9: 4, 8, 16, 32, and 64 μg/mL; Comb. #8: 1, 2, 4, 8, and 16 μg/mL; Comb. #10: 0.125, 0.25. 0.5, 1, and 2 μg/mL; and Comb. #11: 0.063, 0.125, 0.25. 0.5, and 1 μg/mL.

In the dynamic experiments,[22] "autosimulation Shionogi dilution-type equipment" was used to evaluate the bactericidal activity of modithromycin by mechanically simulating *in vivo* drug concentration–time courses. The concentration–time courses were simulated by addition of the drug solution to the bacterial suspension or dilution of the bacterial suspension with adding the medium. The exponentially growing bacterial suspensions, approximately $5 \times 10^5$ CFU/mL, with 50 mL of volume were incubated in the system. The bacterial suspension was incubated at 37°C for 24 h under the simulated drug concentrations. A portion of the bacterial suspension was collected at 0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 h. *S. aureus* SR20405, *H. influenzae* SR24169, and *S. pneumoniae* SR26132 were used as the experimental bacteria in the dynamic experiments.

To achieve the target values of AUC/MIC and $C_{max}$/MIC after a single dose (1–80 as AUC/MIC and 0.06–7 as $C_{max}$/MIC), certain dosages (40–1329 mg for *S. aureus* SR20405, 400–10,635 mg for *H. influenzae* SR24169, and 10–700 mg for *S. pneumoniae* SR26132), and the following parameter sets were used in the dynamic experiments:

P1: $V_d/F = 709$ L, $k_a = 1.28$ h$^{-1}$, $k_e = 0.0390$ h$^{-1}$
P2: $V_d/F = 635$ L, $k_a = 0.976$ h$^{-1}$, $k_e = 0.0780$ h$^{-1}$
P3: $V_d/F = 510$ L, $k_a = 0.679$ h$^{-1}$, $k_e = 0.156$ h$^{-1}$
P4: $V_d/F = 329$ L, $k_a = 0.403$ h$^{-1}$, $k_e = 0.312$ h$^{-1}$
P5: $V_d/F = 540$ L, $k_a = 0.947$ h$^{-1}$, $k_e = 0.0393$ h$^{-1}$

For *S. aureus* SR20405 and *H. influenzae* SR24169, PK parameter sets P1–P4, which were determined based on PK parameters estimated from plasma concentrations of modithromycin following a 400-mg single oral dose in Phase 1 study conducted in US,[23] were used. For *S. pneumoniae* SR26132, PK parameter set P5, which was determined based on PK parameters estimated from plasma concentrations of modithromycin following a 300-mg single oral dose in Phase 1 study conducted in Japan,[24] was used.

In the above time-kill experiments,[21,22] cation-adjusted Mueller Hinton broth (CAMHB) was used for *S. aureus* SR20405, Haemophilus test medium (HTM) was for *H. influenzae* strains and CAMHB supplemented with 5% lysed horse blood (CAMHB-LHB) was for *S. pneumoniae* SR26132. The number of viable bacterial cells was determined by counting the number of colonies on agar plates using brain heart infusion agar (BHIA), BHIA with 2.5% enrichment and BHIA with 5% defibrinated horse blood (DHB) for *S. aureus*, *H. influenzae*, and

**Table 1.** Summary of PK/PD Model Parameters Used for Drug–Bacterium Combinations

| Comb. # | Strain | Drug | Bacterial Parameters | Efficacy Parameters | Other Parameters | PK Parameters |
|---|---|---|---|---|---|---|
| (1) Static Experiments | | | | | | |
| 1 | *SA* SR20405 | M | β, $B_{max}$, $k_1$, $k_2$ | $K_{max}$, $KC_{50}$ | $k_{e0}$, $k_d$, $R_{max}$, $R_{50}$, $k_{out}$ | |
| 2 | *HI* SR24159 | M | β' | | $k_{e0}$, $k_d$ | |
| 3 | | T | | | | |
| 4 | *HI* SR24165 | M | β, $B_{max}$ | | $k_{e0}$, $k_d$ | |
| 5 | | T | | | | |
| 6 | | C | | | | |
| 7 | *HI* SR24169 | M | β, $B_{max}$, $k_1$, $k_2$ | | $k_d$ | |
| 8 | | T | | | | |
| 9 | | C | | | | |
| 10 | *SP* SR26132 | M | | | $k_{e0}$, $k_d$ | |
| 11 | | T | | | | |
| (2) Dynamic Experiments | | | | | | |
| 1 | *SA* SR20405 | M | β, $B_{max}$, $k_1$, $k_2$ | $K_{max}$, $KC_{50}$ | $k_{e0}$, $R_{max}$, $R_{50}$, $k_{out}$ | $V_d/F$, $k_a$, $k_e$ |
| 7 | *HI* SR24169 | | | | – | |
| 10 | *SP* SR26132 | | | | $k_{e0}$ | |

Bacterial parameters: PD parameters specific to bacteria. Efficacy parameters: PD parameters related to efficacy specific to a drug–bacterium combination. Other parameters: remaining parameters specific to a drug–bacterium combination.
–, not applied; SA, *S. aureus*; HI, *H. influenzae*; SP, *S. pneumoniae*; M, modithromycin; T, telithromycin; C, clarithromycin.