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Diagnostic Microbiology and Infectious Disease 70 (2011) 101–111

DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE

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Pharmacology

Evaluation of the pharmacokinetics–pharmacodynamics of fusidic acid against *Staphylococcus aureus* and *Streptococcus pyogenes* using in vitro infection models: implications for dose selection☆

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Received 15 February 2011; accepted 3 March 2011

Abstract

The pharmacokinetics–pharmacodynamics (PK-PD) of fusidic acid were investigated against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pyogenes* using in vitro infection models. Front-loaded and non–front-loaded fusidic acid dosing regimens were evaluated over 48 h using a 1-compartment infection model and over 240 h using a hollow fiber infection model (HFIM). All dosing regimens demonstrated initial decreases in bacterial density against both isolates in both in vitro models. A mechanism-based PK-PD model was developed to describe the effect of the concentration–time course of fusidic acid on the time course of MRSA in the in vitro infection model. With the use of this model and Monte Carlo simulation to evaluate the effect of different dosing regimens against MRSA, front-loaded [≥1200 mg every 12 h (Q12) × 2 doses followed by ≥600 mg Q12 h] compared to non–front-loaded (600 mg Q12 h) dosing regimens demonstrated better activity. HFIM data confirmed the effect of the front-loaded dosing regimens over 48 h and also demonstrated the suppression of growth of the total population and resistant subpopulations for MRSA over 96 and 120 h, respectively, associated with these dosing regimens.
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Keywords: Fusidic acid; *Staphylococcus aureus*; *Streptococcus pyogenes*; Mechanism-based pharmacokinetic–pharmacodynamic model; In vitro infection model

1. Introduction

Fusidic acid, administered as sodium fusidate, is an oral antibiotic with in vitro activity against *Staphylococcus aureus* and *Streptococcus pyogenes* (Castanheira et al., 2010; Rhomberg et al., 2009), the primary pathogens associated with skin and skin-structure infections. It is currently being developed in the United States for the treatment of acute bacterial skin and skin-structure infections (ABSSSI).

In vitro infection models, such as the 1-compartment and hollow fiber infection models (HFIM), can provide valuable information regarding the pharmacokinetics–pharmacodynamics (PK-PD) of antimicrobial agents. These models are especially useful in discriminating among candidate dosing regimens, particularly in the circumstance where the pharmacokinetic (PK) profile in patients is difficult to mimic in an animal infection model. Such is the case with fusidic acid, where the apparent half-life after an oral dose of 550 mg in healthy volunteers is 14.5 h (Bulitta et al., 2009b) as compared to the very short apparent half-life in mice (i.e., less than a few minutes) (Degenhardt et al., 2009). This magnitude of difference in half-life, which would require the administration of multiple doses per hour in mice to mimic exposures in patients, is logistically challenging. In such cases, the use of in vitro infection models, which allow for any concentration–time profile of interest to be mimicked,

☆ This work was supported by Cempra Pharmaceuticals.
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0732-8893/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.diagmicrobio.2011.03.001

provides the opportunity to effectively evaluate the PK-PD of an antibacterial agent. PK-PD targets associated with efficacy can then be identified based on analyses of such data. With the use of Monte Carlo simulation (MCS), together with PK-PD targets from non-clinical infection models and PK parameters from a population PK model based on data from healthy subjects, potential dosing regimens for future clinical trials can be evaluated (Bhavnani et al., 2005; Drusano et al., 2001). This process, which is described in the Food and Drug Administration (FDA) draft guidance for industry for the development of drugs for the treatment of patients with ABSSSI (US Department of Health and Human Services, Food and Drug Administration & Center for Drug Evaluation and Research (CDER), 2010), represents the current paradigm for supporting clinical trial dose selection for antibacterial agents.

The objectives of this study were 3-fold. The first objective was to evaluate the PK-PD of fusidic acid against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pyogenes* over 48 h using data from a 1-compartment infection model. As part of this objective and using the data for MRSA, a mechanism-based PK-PD model to describe the relationship between the concentration–time course of fusidic acid and bacterial growth and death was developed. The second objective was to use this mechanism-based PK-PD model, a previously developed population PK model and MCS to evaluate the effect of several different fusidic acid dosing regimens on the bacterial density of MRSA to support phase 2 dose selection. The last objective of this study was to use a HFIM to confirm the effect of selected fusidic acid dosing regimens over a 10-day period of study. The impact of fusidic acid on the change in bacterial burden and suppression of resistance of MRSA and *Streptococcus pyogenes* was evaluated in this system.

2. Methods

2.1. Bacteria, susceptibility testing, media, and drug preparation

The organisms used in both the 1-compartment and hollow fiber infections experiments included an MRSA strain, pulse field gel electrophoresis–type USA300, and a *Streptococcus pyogenes* isolate (JMI isolate number 991), both provided by JMI Laboratories (North Liberty, IA, USA). The MIC of fusidic acid for both isolates was determined in triplicate by broth microdilution methods outlined by the Clinical and Laboratory Standards Institute (2009a, 2009b).

For all experiments with MRSA, Mueller-Hinton broth (Difco, Detroit, MI, USA) supplemented with calcium titrated to physiologic levels (1.1 to 1.3 mmol/L) and 12.5 μg/mL of magnesium (CAMHB) was used for all in vitro models. Given that unbound fusidic acid is the main determinate of fusidic acid activity (Munckhof & Turnidge, 1997), 4 g/dL of free fatty acid–containing human albumin (Sigma, St. Louis, MO, USA) was also added to the CAMHB to approximate protein binding in human serum. All albumin-supplemented CAMHB was titrated with calcium as needed to maintain physiological levels and account for decreases in calcium concentrations that result from binding to albumin (Tsuji & Rybak, 2005). For all experiments with *Streptococcus pyogenes*, the CAMHB was supplemented with 5% lysed horse blood to ensure adequate bacterial growth.

Colony counts were determined using trypticase soy agar plates (TSA) with 5% sheep blood (BD Biosciences, Franklin Lakes, NJ, USA). Given that pH changes have previously been found to be associated with fusidic acid MIC decreases for MRSA (Lemaire et al., 2009), the pH of broth samples was monitored throughout the experiment. Fusidic acid powder was provided by Cempra Pharmaceuticals (Morrisville, NC, USA) and fresh stock solutions were prepared daily.

2.2. One-compartment infection model and sample processing

A 1-compartment infection model (500-mL glass chamber; working model volume, 270 mL), similar to that previously described by Akins and Rybak (2000) and Harigaya et al. (2009), was used to evaluate the PK-PD of fusidic acid against MRSA and *Streptococcus pyogenes*. The experiments were conducted in duplicate over 48 h with a simultaneously run drug-free growth control.

Dosing regimens evaluated against MRSA and *Streptococcus pyogenes* included sodium fusidate doses that were in multiples of 275 and 300 mg, respectively. Since MRSA experiments were the first to be conducted, these experiments involved the use of 275-mg dose increments, which represented an early formulation of sodium fusidate. Subsequent experiments for *Streptococcus pyogenes* were conducted using dose increments of 300 mg. The following fusidic acid dosing regimens were evaluated against MRSA: 550 mg administered every 12 h (Q12 h); 1100 mg administered every 24 h (Q24 h); front-loaded 550 mg Q12 h; 1100 mg Q12 h; front-loaded 1100 mg Q12 h; and 2200 mg Q24 h. The front-loaded 550 mg and 1100 mg dosing regimens were designed such that the loading dose was 2.3 and 4.4 times the maintenance dose, respectively. The following dosing regimens were evaluated against *Streptococcus pyogenes*: 600 mg Q12 h, 1200 mg Q24 h; 1200 mg Q12 h × 2 doses followed by 600 mg Q12 h; 1500 mg Q12 h × 2 doses followed by 600 mg Q12 h; 1200 mg Q12 h; and 2400 mg Q24 h.

All dosing regimens were administered in a manner to achieve similar total-drug area under the concentration–time curve (AUC) values over 48 h that would be expected in healthy subjects. An apparent half-life for fusidic acid of 14.5 h, which had been observed after the administration of an oral 550 mg dose to healthy subjects (Bulitta et al., 2009b), was used for these experiments.

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