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Research Paper

pH-Dependent Dissolution *in Vitro* and Absorption *in Vivo* of Weakly Basic Drugs: Development of a Canine Model

Rong Zhou,[1] Paul Moench,[1] Christopher Heran,[1] Xujin Lu,[1] Neil Mathias,[1] Teresa N. Faria,[1] Doris A. Wall,[1] Munir A. Hussain,[1] Ronald L. Smith,[1] and Duxin Sun[1,2,3]

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Purpose. The aim of this research was to develop a pH-dependent canine absorption model for studying pH effect on both dissolution *in vitro* and pharmacokinetics *in vivo* using the weak bases ketoconazole and dipyridamole as model drugs.
Methods. Ketoconazole and dipyridamole pH-dependent dissolution profiles *in vitro* were determined by dissolution test at different pH values using USP apparatus II and an Opt-Diss Fiber Optic UV System. *In vivo* absorption studies for ketoconazole and dipyridamole were performed with crossover design in three groups of beagle dogs under control (no treatment), pentagastrin, and famotidine treatments. Ketoconazole and dipyridamole plasma concentrations were quantified by gradient high performance liquid chromatography mass spectroscopy (HPLC MS/MS). Pharmacokinetic parameters were determined from individual plasma concentration vs. time profiles.
Results. Ketoconazole and dipyridamole displayed pH-dependent dissolution. Increasing the pH of the dissolution medium from 1.2 to 6.8 reduced the extent of dissolution of ketoconazole and dipyridamole at 1 h by 96% and 92%, respectively. *In vivo* studies in dogs under control (no treatment), pentagastrin, and famotidine treatments show marked differences in systemic ketoconazole and dipyridamole exposure. Area under the concentration-time curve (AUC) increased more than 4-fold as compared to control group, whereas it increased nearly 30-fold for ketoconazole and 9-fold for dipyridamole with pentagastrin (gastric pH ~2–3) as compared to famotidine (gastric pH ~5–7.5) treatment.
Conclusions. This work demonstrates a pH-dependent dissolution *in vitro* and absorption *in vivo* for the weak bases ketoconazole and dipyridamole independent of food effects. This model is useful to examine pH-dependent effects on oral drug absorption and for screening formulations to overcome the pH dependency.

KEY WORDS: absorption; bioavailability; canine; dissolution; pH-dependence.

INTRODUCTION

Poor oral bioavailability is a growing issue in the drug development process. Although many new drugs fail due to toxicity or lack of *in vivo* efficacy, many other compounds are deemed undevelopable owing to their poor solubility/dissolution rate, undesirable pharmacokinetic profiles, and other limiting characteristics. Therefore, experimental models able to detect problems and test strategies aimed at overcoming these obstacles are essential to the development of new drug products.

The oral bioavailability of a drug is largely a function of its solubility characteristics in gastrointestinal fluids, absorption into the systemic circulation, and metabolic stability. The dissolution of a drug substance *in vivo* determines the extent to which a drug is available for absorption from the gastrointestinal tract and is dependent upon the chemical nature of the drug and on the gastrointestinal milieu in which it resides. Specifically, a drug's pK_a, pH of maximum solubility, molecular weight, partition coefficient (log P), gastrointestinal pH, and lipid content of its environment dictate that the fraction absorbed is proportional to solubility and permeability.

Prior to clinical testing, animal models play a key role in screening for the best compounds and optimal formulation for clinical development. The canine model is particularly popular for preclinical determination of oral bioavailability (1,2). However, significant differences in drug bioavailability have been reported between dog and man. For instance, for many compounds, studies have shown that oral bioavailability in dogs is not predictive of that in humans, owing to significant differences in drug absorption and first-pass metabolism (3). Additionally, physiologic factors such as gastric and intestinal transit time, blood flow rate, and gastrointestinal pH can all affect the rate and extent of drug absorption and therefore bioavailability. However, similarities between the gastrointestinal membranes of dogs and humans, suggests that the intrinsic absorption of drugs across the intestinal wall might be predictable under controlled conditions.

[1] Department of Exploratory Biopharmaceutics & Stability, Pharmaceutical Research Institute, Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903, USA.
[2] Present address: Division of Pharmaceutics, College of Pharmacy, The Ohio State University, Columbus, Ohio, USA.
[3] To whom correspondence should be addressed. (e-mail: sun.176@osu.edu)

Canine gastric pH is usually higher than that in humans. Thus, pH differences between dog and human will affect the dissolution of drugs with pH-dependent solubility. Several studies have shown inconsistent results for canine gastric pH ranging from 0.9 to 8.3 (1,2,4). Weakly basic drugs with pH-dependent solubility might have a 100- to 1000-fold solubility difference in this pH range. In practice, most formulation efforts focus on how to improve drug absorption. Therefore, we hypothesize that a canine model of drug absorption, if controlled for gastric pH, can be used to predict formulation performance in humans.

Ketoconazole and dipyridamole are Biopharmaceutical classification system (BCS) class II drugs that display pH-dependent dissolution and absorption. Ketoconazole is an oral antifungal agent (5–8), and dipyridamole is a platelet adhesion inhibitor commonly used to prevent postoperative thromboembolic complications (9). Both ketoconazole and dipyridamole are weak bases with pK_a values of (2.94, 6.15) and 6.4, respectively (10,11). Both are poorly soluble in water at or above neutral pH (less than 4–6.7 μg/ml), whereas they are readily soluble in water at acidic pH (<3). Therefore, sufficient gastric acidity is a prerequisite for adequate dissolution and absorption *in vivo*. Studies assessing the bioavailability of ketoconazole and dipyridamole have demonstrated that absorption is variable and pH-dependent in humans (12–15).

In the current work, we describe a pH-dependent drug absorption model in dogs for assessing and optimizing oral formulations of weakly basic drug candidates. Two weak bases, ketoconazole and dipyridamole, that display pH-dependent solubility were chosen as model compounds. Although the effect(s) of food and antacids on the bioavailability of weak bases in man have been studied, this model is designed to isolate the pH-dependent aspect of drug solubility and absorption. Assessing the effect(s) of gastric pH on the solubility/dissolution and absorption of potential drug candidates will aid in the design, selection, and optimization of formulations that enhance oral bioavailability and reduce the effect of gastrointestinal pH on oral absorption.

MATERIALS AND METHODS

Chemicals

Ketoconazole tablets USP (200 mg) were purchased from Mylan Pharmaceuticals Inc. (Morgantown, WV, USA). Dipyridamole tablets USP (75 mg) were supplied by Barr Laboratories Inc. (Pomona, NY, USA). Famotidine tablets (Pepsid AC, 10 mg) were purchased over the counter (OTC). Pentagastrin (cat. no. B1636) was obtained from Sigma-Aldrich (St. Louis, MO, USA).

In Vitro Dissolution Studies

pH-dependent ketoconazole and dipyridamole release profiles were evaluated *in vitro* using USP apparatus II utilizing a dissolution bath Disteck 5100 and an Opt-Diss Fiber Optic UV System (Leap Technologies Inc., Carrboro, NC, USA). The dissolution test was performed on six tablets of ketoconazole and dipyridamole in 1000 ml of 0.1 N HCl (pH 1.2), 0.05 M acetate buffer (pH 4.5), and 0.05 M phosphate buffer (pH 6.8), maintained at 37°C at a paddle rotation speed of 50 rpm for 1 h. For the ketoconazole dissolution test, the concentration of ketoconazole at each time point was measured at 270 nm, 285 nm, and 240 nm in 0.1 N HCl, 0.05 M acetate buffer, and 0.05 M phosphate buffer, respectively. For the dipyridamole dissolution test, the concentration of dipyridamole at each time point was measured at 320 nm, 260 nm, and 290 nm in 0.1 N HCl, 0.05 M acetate buffer, and 0.05 M phosphate buffer, respectively. During each dissolution test, all of the measurements were calculated with a baseline correction at 350 nm by the Opt-Diss Fiber Optic UV system. This UV fiberoptic system is equipped with a multichannel CCD spectrometer (205–410 nm). Fiberoptic arch probes, which connected individually to the CCD spectrometer, were inserted directly into the dissolution vessels to measure real-time dissolution. Cumulative percentage of drug release was calculated in real-time with the Opt-Diss software, version 1.13.0. The mean of six determinations was used in data analysis.

In Vivo Absorption Study

Beagle dogs (male and female) were fasted overnight, with no water intake 1 h before and after dosing, and no food intake 4 h after dosing. Studies were performed with crossover design in three groups including no treatment, pentagastrin treatment, and famotidine treatment. In the pentagastrin treatment group, gastric pH was maintained at 2–3 by pentagastrin (6 μg/kg) administered intramuscularly 30 min before dosing (1). In the famotidine treatment group, gastric pH was maintained at 5–7.5 by giving famotidine tablets (40 mg/dog) orally 3 h before dosing. Ketoconazole (200 mg/dog) or dipyridamole (75 mg/dog) was administered orally and followed by 50 ml water gavage. Blood samples (2 ml), using heparin as anticoagulant, were collected at 0.25, 0.5, 1, 2, 4, 6, and 24 h Studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH Publication No. 85-23, revised 1985).

HPLC MS/MS Analysis

Plasma concentration was quantified by gradient HPLC mass spectroscopy (HPLC MS/MS) using a Waters 2790 Separations Module (Milford, MA, USA) connected to a Waters 2487 Dual Wavelength UV Detector (231 nm for ketoconazole, 285 nm for dipyridamole) and a ThermoQuest Finnigan LCQ Duo Mass Spectrometer (San Jose, CA, USA). Dog plasma was spiked with ketoconazole in EtOH to yield concentrations for a standard curve. To 100 μl of plasma standard and unknowns, 100 μl of acidified (0.1% acetic acid) acetonitrile was added. Samples were vortexed for 30 s and spun at 14,000 rpm for 15 min. The supernatant fluid was analyzed by HPLC. The stationary phase was a YMC ODS-AQ C18, 3 μm, 120 A, 2.0 × 50 mm held at 40°C (Waters Corp.). The mobile phase consisted of 0.1% acetic acid in H_2O and acetonitrile delivered at a flow rate of 0.3 ml/min for ketoconazole and 0.5 ml/min for dipyridamole. The injection volume was 10 μl. Ketoconazole had a retention time of ~5.02 min. MS/MS settings were as follows: positive ion mode ESI, 200°C, isolate 531.2 *m*/*z*, collision energy 40%, isolation width 3.0 *m*/*z*, quantitate 489.2 *m*/*z*. Dipyridamole had a retention time of ~4.07 min. MS/MS settings were as follows: positive ion mode ESI, 200°C, isolate 505.6 *m*/*z*, collision energy 54%, isolation width 3.0 *m*/*z*, quantitate 385.4 *m*/*z*.

Pharmacokinetics

Pharmacokinetic parameters were determined using Kinetica software 4.0.2 (Innaphase Corp, Philadelphia, PA, USA) from individual plasma concentration vs. time profiles. AUC was computed using the log trapezoid rule. All values are presented as mean ± SEM with the exception of T_{max}, which is median and range. Statistical analysis was by one-way analysis of variance (ANOVA) and Tukey's *post hoc* test.

RESULTS

Dissolution Study

The rate and extent of ketoconazole and dipyridamole dissolution are strongly pH dependent. Dissolution of ketoconazole at pH 1.2 reaches 90% within 20 min and 100% after 40 min. In contrast, dissolution after 1 h at pH 4.5 and 6.8 was only 43% and 4%, respectively (Fig. 1). Dissolution of dipyridamole at pH 1.2 reaches 100% within 7 min. Maximum 1-h dissolution of dipyridamole in pH 4.5 and 6.8 is only 79% and 8%, respectively (Fig. 2).

Pharmacokinetic Study

Ketoconazole plasma concentration-time profiles in dogs under control (no treatment), pentagastrin, and famotidine treatments show marked differences in systemic ketoconazole exposure with altered pH (Fig. 3). C_{max} values for control, pentagastrin, and famotidine treatment groups were 20.2 ± 19.3, 90.7 ± 25.7, and 6.9 ± 2.3 ng/ml (mean ± SEM, n = 4), respectively. This represents an approximate 4-fold increase in C_{max} under pentagastrin treatment as compared to control ($p < 0.05$). Similarly, the AUC in pentagastrin treatment group is more than 4-fold higher than that of the control group ($p < 0.05$). Although famotidine treatment seemed to reduce the C_{max} and AUC of ketoconazole, no statistically significant differences in C_{max} and AUC were observed under famotidine treatment as compared to control ($p > 0.05$). This may be due to the large variability in the control group (Table I), which could reflect gastric pH variability and in turn dissolution. Indeed, it has been reported that canine gastric pH in the fasted state can be in the range of 0.9 to 8.3 (1,2,4). A comparison of pentagastrin- to famotidine-treated groups

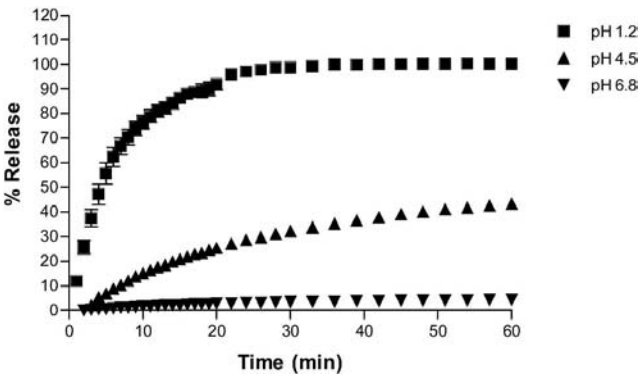

Fig. 1. Ketoconazole pH-dependent dissolution release profile. Test was performed on ketoconozole tablets in 1000 ml of 0.1 N HCl, 0.05 M acetate buffer, and 0.05 M phosphate buffer, maintained at 37°C at a paddle rotation speed of 50 rpm for 1 h. Results are plotted as mean ± SD (n = 6).

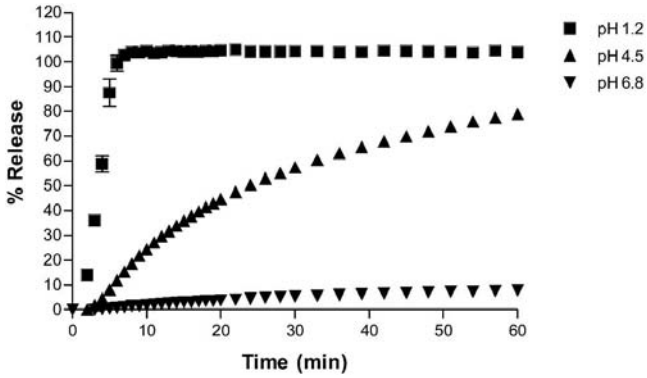

Fig. 2. Dipyridamole pH-dependent dissolution release profile. Test was performed on dipyridamole tablets in 1000 ml of 0.1 N HCl, 0.05 M acetate buffer, and 0.05 M phosphate buffer, maintained at 37°C at a paddle rotation speed of 50 rpm for 1 h. Results are plotted as mean ± SD (n = 6).

yielded a 13-fold increase in C_{max} with pentagastrin treatment ($p < 0.01$). AUC increased nearly 30-fold with pentagastrin, 617.7 ± 21.7 ng/ml·h as compared to famotidine treatment, 20.5 ± 6.6 ng/ml·h.

The plasma concentration-time curve for dipyridamole was also significantly altered by changes in pH (Fig. 4). C_{max} values for control, pentagastrin, and famotidine treatment groups were 127.0 ± 93.6, 644.4 ± 271.8, and 64.6 ± 55.1 ng/ml (mean ± SEM, n = 4) respectively. This represents an approximate 5-fold increase in C_{max} in pentagastrin treated vs. control animals ($p < 0.05$). AUC also increased by more than 4-fold with pentagastrin treatment compared to control. Similar to the pharmacokinetics of ketoconazole, no significant difference in C_{max} and AUC of dipyridamole was observed in famotidine-treated dogs as compared to control ($p > 0.05$). AUC increased approximately 9-fold with pentagastrin, 2650.9 ± 1415.0 ng/ml·h as compared to famotidine treatment, 303.9 ± 155.4 ng/ml·h. Median T_{max} values were similar for all three treatment groups ($p > 0.05$) (Table I).

DISCUSSION

Compounds with low water solubility and high intestinal permeability are good candidates for formulation approaches aimed at enhancing bioavailability (16). However, weak bases, displaying pH-dependent solubility, may exhibit dis-

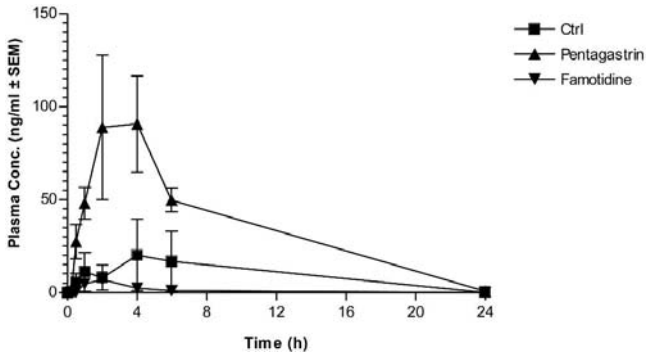

Fig. 3. Ketoconazole plasma profile in dogs, pH-dependent absorption. Results are control (no treatment), pentagastrin-, and famotidine-treated dogs shown as mean concentration (ng/ml, ± SEM, n = 4).

Table I. Pharmacokinetic Parameters for Ketoconazole and Dipyridamole Absorption in Dogs Under CTRL (No Treatment), Pentagastrin, and Famotidine Treatment Conditions

	Ketoconazole			Dipyridamole		
	CTRL	pentagastrin	Famotidine	CTRL	pentagastrin	Famotidine
C_{max} (ng/ml)	20.2 ± 19.3	90.7 ± 25.7	6.9 ± 2.3	127.0 ± 93.6	644.4 ± 271.8	64.6 ± 55.1
T_{max} (h)	3.0 (1–4)	3.00 (2–4)	2.0 (1–2)	1.0 (0.5–4)	0.5 (0.5–1)	2.0 (1.0–4.0)
$AUC_{0-\infty}$ (ng/ml.h)	147.7 ± 131.3	617.7 ± 21.7	20.5 ± 6.6	594.3 ± 224.5	2650.9 ± 1415.0	303.9 ± 155.4

C_{max}, peak concentration; T_{max}, time to peak concentration; AUC, area under the concentration-time curve. C_{max} and $AUC_{0-\infty}$ are mean ± SEM (n = 4). T_{max} is median and range (n = 4).
The number in parentheses for T_{max} indicates the range of T_{max}.

tinct absorption profiles based on different physiologic conditions even for the same formulation with similar *in vitro* dissolution.

Because human PK studies for the purpose of formulation development are impractical, the need for an alternative is clear. We choose the dog as it is an established species that is used extensively in pharmaceutical development and allows administration of clinical dosage forms. Two weak bases, ketoconazole and dipyridamole, that display pH-dependent solubility/dissolution rate were chosen as model compounds.

Gastric pH will influence drug dissolution and absorption for drugs with pH-dependent solubility. Therefore, the dissimilar gastric pH between the two species may be one of the important factors to contribute to the variability in the data taken from dogs and the reported lack of correlation to man. Many reports indicate canine gastric pH is similar to human at fasted state, which is in the range 0.9–2.5 with mean value of 1.5 ± 0.04 (1,2), whereas other report canine gastric pH is in the range 2.7–8.3 with mean value of 6.8 ± 0.2 at fasted state (3). Previous work has shown that pentagastrin treatment in dogs decreased gastric pH to 1–3 (2,4,17), which is similar to human gastric pH, whereas H_2-receptor antagonist increased the gastric pH to 7.7 (3). Thus, better control of gastric pH in the dog should allow one to more closely mimic human gastric conditions and reduce experimental variability.

In vitro dissolution tests confirmed the pH-dependent nature of ketoconazole and dipyridamole solubility, with the rate and extent of dissolution being significantly reduced with increasing pH (Figs. 1 and 2, respectively). This result agrees with previously reported findings (10,12,13,15,18) and is expected given the pK_a values for ketoconazole (2.94, 6.15) and dipyridamole (6.4). Having verified that our dissolution results using fiberoptic detection agree with those reported using traditional HPLC methods, our aim was to develop a pH-dependent canine model that agrees with both *in vitro* dissolution studies and previously reported pharmacokinetics in humans (16,19).

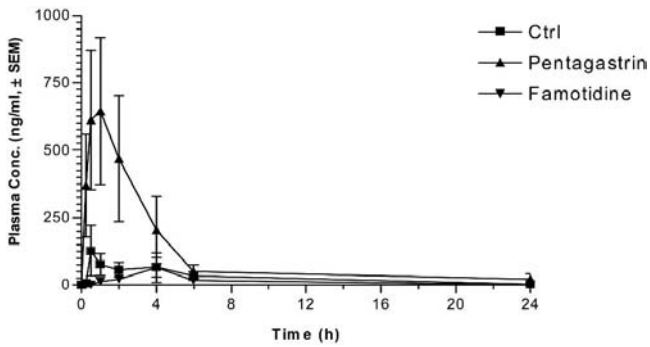

Fig. 4. Dipyridamole plasma profile in dogs, pH-dependent absorption. Results are control (no treatment), pentagastrin-, and famotidine-treated dogs shown as mean concentration (ng/ml, ± SEM, n = 4).

Correlation of *in vitro* dissolution studies with *in vivo* pharmacokinetics in man has been previously studied (16,20). A key finding is that for lipophilic poorly water-soluble drugs (BCS II compounds), a good correlation exists between *in vitro* dissolution studies using simulated intestinal fluids that mimic the fed and fasted states and *in vivo* bioavailability (21). Dietary intake and the common use of antacids become clinically important in that they can change the gastric pH and emptying time, bile salt secretion, gastrointestinal motility, and other factors affecting drug solubility/dissolution rate and absorption (22–24).

Both H_2-receptor antagonists and food are known to alter the solubility, absorption, and bioavailability of ketoconazole and dipyridamole (12–15,18). A study that assessed the effects of gastric pH on the pharmacokinetic of ketoconazole in healthy volunteers showed that acidification of the gastric content by administration of glutamic acid under fasted conditions resulted in increased $AUC_{0\text{-}24h}$ nearly 7-fold as compared to acidification followed by H_2-receptor antagonism using cimetidine (14). In addition, previous studies in man and in the rabbit have shown dipyridamole C_{max} to decrease approximately 3- to 5-fold with increased gastric pH (15,25). Our results in dogs using pentagastrin to acidify the gastric content and famotidine for H_2 blockade agree with this finding. A 30-fold increase in ketoconazole AUC was noted for pentagastrin treated dogs as compared to treatment with famotidine (Table I). Similarly, a 9-fold increase in dipyridamole AUC was observed in dogs under the same experimental conditions (Table I).

Although the magnitude of pH-dependent ketoconazole and dipyridamole absorption in our dog model is considerably greater than is reported for humans, a qualitative comparison can be made. Thus, the relative bioavailability of different formulations can be evaluated using this model. A possible explanation for the more significant increases in ketoconazole and dipyridamole absorption in the dog as compared to the human is the higher dose to gastric volume ratio in dogs. Therefore, dose adjustment should be considered when using a canine model in predicting formulation performance in humans.

In conclusion, we report a pH-dependent canine model of oral drug absorption using the weak bases ketoconazole and dipyridamole as reference compounds. This model is intended for use as a tool to direct formulation efforts aimed at overcoming problems associated with pH-dependent absorption prior to clinical studies.

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