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RESEARCH PAPER

Bioavailability of Itraconazole in Rats and Rabbits After Administration of Tablets Containing Solid Dispersion Particles

Sun Dong Yoo,[1,*] Sang-Heon Lee,[2] Eunhee Kang,[1] Hun Jun,[1] Jae-Young Jung,[2] Jong Woo Park,[2] and Kyu-Hyun Lee[2]

[1]*College of Pharmacy, Sungkyunkwan University, 300 Chonchon-dong, Jangan-ku, Suwon, Kyunggi-do, 440-746, Korea*
[2]*Formulation Research Laboratory, Choongwae Pharma Co., 146-141 Annyung-ri, Taean-up, Hwasung-kun, Kyunggi-do 445-970, Korea*

ABSTRACT

A tablet dosage form containing solid dispersions of itraconazole (Asd tablets) was prepared by using the spray-drying and wet granulation methods. The dissolution rate of itraconazole from Asd tablets was fast, with more than 90% released within 10 min, compared to less than 20% for a marketed product, Sporanox® capsules. The oral absorption of itraconazole from Asd tablets was determined in rats and rabbits and was compared with that for Sporanox capsules. In the rat, there was no difference between the Asd tablets and Sporanox capsules in the mean area under the curve (AUC) (3089.5 ± 4332.8 ng · hr/ml and 3653.9 ± 2348.9 ng · hr/ml, respectively) and C_{max} *(295.0 ± 344.5 and 390.5 ± 169.4 ng/ml, respectively). Also, in the rabbit, no difference was found between the two products in the mean AUC (AUMC; 19357.9 ± 5117.5 ng · hr/ml and 23382.2 ± 6236.5 ng · hr/ml, respectively) and* C_{max} *(766.4 ± 276.5 and 1127.5 ± 577.9 ng/ml, respectively). Despite the rapid in vitro release characteristics of itraconazole from the Asd tablets, the in vivo absorption of itraconazole was comparable to that of Sporanox capsules, with no difference in* T_{max} *in both animal species. Serum levels of the major active*

*To whom correspondence should be addressed. Telephone: 82-331-290-7717. Fax: 82-331-292-8800. E-mail: sdyoo@yurim.skku.ac.kr

metabolite hydroxyitraconazole were also measured. Itraconazole was rapidly converted to hydroxyitraconazole in both rats and rabbits, but there were species-specific differences in their pharmacokinetics. It is concluded that, in addition to drug solubility and dissolution characteristics, other formulation factors such as the physical state of the drug and the granulation process, may also need to be considered in the prediction of the in vivo absorption of itraconazole based on in vitro data.

INTRODUCTION

Itraconazole is an oral triazole agent that has a broad spectrum of antifungal activity. It is a weakly basic drug with high lipid solubility (*n*-octanol/water partition log $P = 5.22$) and a pK_a of 3.7 (1). Itraconazole is ionized only at low pH; therefore, on oral administration, the gastric acidity is needed for adequate dissolution. In healthy human subjects, itraconazole is well absorbed, with maximal plasma levels reached at 3.0–4.6 hr after dosing and the terminal elimination half-life ranging from 21 to 37 hr (1–3). The bioavailability of itraconazole is known to be increased after a meal as compared to that found in the fasting state (2–4). Itraconazole undergoes extensive metabolism, with hydroxyitraconazole being the major active metabolite in humans. Serum concentrations of hydroxyitraconazole are two to three times higher than the corresponding parent drug levels (2). It is generally accepted that plasma levels of itraconazole above 250 ng/ml are necessary for protection against fungal infection. Since hydroxyitraconazole also possesses an antifungal activity similar to the parent drug, combined serum concentrations of itraconazole plus hydroxyitraconazole of approximately 1 μg/ml are considered adequate for effective treatment of fungal infections (5).

The dissolution rate of poorly water soluble drugs often becomes a rate-limiting step in their absorption from the gastrointestinal tract (6,7). Various solubilization methods have been used to increase the drug solubility and dissolution properties, including the use of surfactants, water-soluble carriers, polymeric conjugates, and solid dispersions (8–11).

In the present study, Asd tablets containing itraconazole were manufactured by wet granulation of solid dispersion particles prepared by spray-drying with polyvinylacetal diethylaminoacetate. The relative bioavailability of itraconazole was determined for the Asd tablets in rats and rabbits; in addition, species-specific differences in the pharmacokinetic disposition of itraconazole and hydroxyitraconazole are discussed.

EXPERIMENTAL

Chemicals and Reagents

Itraconazole, hydroxyitraconazole, and ketoconazole were synthesized at Choongwae Pharma Company (Kyunggi-do, Korea) and were used without further purification (purity > 99.2%). Acetonitrile, methanol, and methylene chloride (all high-performance liquid chromatography [HPLC] grade) were purchased from J. T. Baker (Phillipsburg, NJ). Ketamine, xylazine, diethylamine, *t*-butyl methyl ether, and acetic acid were obtained from Sigma Chemical Company (St. Louis, MO). Polyvinylacetal diethylaminoacetate (AEA®) was purchased from Sankyo Company, Limited (Tokyo, Japan). All other chemicals used were analytical grade.

Preparation of Solid Dispersion Particles and Tableting

Itraconazole and AEA (1:1 w/w) were dissolved in an appropriate volume of methylene chloride, and the solution was used in the preparation of solid dispersions of itraconazole by a spray-drying method (B-190 Mini-spray dryer, Büchi Labortechnik AG, Flawil, Switzerland). The spray-drying conditions were as follows: pump speed, 5 ml/min; airflow rate, 800 Nl/hr; aspirator level, 10–15; inlet air temperature, 45°C; outlet air temperature, 38°C. Spray-dried solid dispersions of itraconazole were added with 10% lactose solution and granulated by passing through a 35-mesh screen. The granules were dried in an oven at 40°C for 16 hr and were mixed with lactose (1:1 w/w) and Explotab® (5% w/w). This mixture was lubricated using 0.5% w/w magnesium stearate and compressed on an IR press (Carver Laboratory Press-C, Fred S. Carver, Inc., Mississauga, Ontario, Canada). The content of itraconazole was maintained at 5.03 ± 0.28 mg and 50.13 ± 0.34 mg ($n = 4$ each) for the tablets used in the rat and rabbit studies, respectively.

Dissolution Testing

The dissolution profiles of itraconazole from Asd tablets and Sporanox® capsules were determined at 37 ± 0.5°C at a stirring rate of 100 rpm using the paddle method (USP 23). The dissolution media used in the study were pH 1.2 simulated gastric juice and pH 2.0, 3.0, and 4.0 buffer solutions. In each dissolution test, a weighed quantity (5 or 50 mg itraconazole) was placed in 900 ml of the dissolution medium (n = 3–4). At 5, 10, 30, and 60 min, aliquots (2 ml each) were withdrawn through a filtering rod (10 μm) and were immediately centrifuged at 14,000 rpm for 5 min. At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted and assayed for drug concentration by HPLC.

Animals

Male Sprague Dawley rats (7–8 weeks of age, 250–280 g, SPF) and New Zealand white rabbits (4–5 months of age, 3.0–3.5 kg) were purchased from Japan SLC, Incorporated (Shizuoka, Japan). The rats and rabbits were placed in plastic rat cages and stainless steel rabbit cages, respectively, and were housed in a temperature-controlled (23° ± 2°C) animal facility with a light/dark cycle of 12/12 hr and relative humidity of 50 ± 10%. The animals had free access to standard rat and rabbit diet (DaeJong Co., Seoul, Korea) and water throughout the study.

Rat Study

After at least a 1-week acclimatization period, the rats were anesthetized with an intramuscular (i.m.) injection of ketamine and xylazine (90/10 mg/kg) and cannulated with PE tubing (0.58 mm id and 0.96 mm od, Natume Co., Tokyo, Japan) in the right jugular vein. The animals were kept in metabolic cages until the drug dosing study was completed. After surgery, at least 2 days of recovery was allowed prior to drug administration. One Asd tablet (5 mg itraconazole per tablet) or two minicapsules filled with the content of Sporanox capsules (2.5 mg itraconazole per minicapsule) were administered separately to two groups of rats (n = 6 each). The minicapsules had a cap with an external diameter of 2.55 mm, a length of 7.3 mm, and a minimum capacity of 30 mm^2 (Natume Co.). Asd tablets were manufactured so that their external size was the same as that of the minicapsules and so that they fit a minicapsule injector (model KN-346, Natume Co.). Immediately after dosing, approximately 0.4 ml of distilled water was given to help facilitate swallowing the capsules and tablets. Serial blood samples (approximately 0.3 ml each) were taken via the jugular vein catheter at 0, 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 4, 8, 12, 24, 36, and 48 hr after dosing. Equal volumes of saline were replaced after each sampling. Serum samples were harvested by centrifugation at 1500g for 10 min and were kept at −20°C until drug analysis.

Rabbit Study

Asd tablets and Sporanox capsules were administered orally to two groups of rabbits in 50 mg doses (n = 4–5). Serial blood samples (approximately 0.5 ml each) were taken from the marginal ear vein at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hr after dosing. Serum was harvested by centrifugation at 1500g for 10 min and was kept at −20°C until analysis.

Drug Analysis

The chromatographic system used in the study was a Hewlett Packard 1100 series with a model G1311A quaternary pump, model G1313A autosampler, model G1315A diode array detector, model G1316A column compartment, and model G1322A degasser and HP Chem Station (ver. 4.02) chromatography manager software (Hewlett Packard, Santa Clara, CA). Chromatographic separations were achieved using a Lichrospher 100 RP 8 (Merck, 4.0 mm × 250 mm, 5 μm, Darmstadt, Germany) and a guard column (HP, 4.0 mm × 4.0 mm, 5 μm, Santa Clara, CA).

The mobile phase consisted of acetonitrile:0.05% diethylamine in deionized water (6:4, v/v) (Milli Q Plus System, Millipore, Milford, MA). The mobile phase was adjusted to pH 6.0 by dropwise addition of 30% acetic acid passed through a 0.22-μm membrane filter and degassed by ultrasonication under vacuum before use.

Itraconazole and its major active metabolite hydroxyitraconazole were extracted by a single liquid-liquid extraction using *t*-butyl methyl ether. Briefly, to 100 μml of the rat or rabbit serum in borosilicate tubes were added 10 μl of the internal standard solution (ketoconazole 15 μg/ml in mobile phase) and 100 μl of 1 M carbonate buffer (pH 10), and the mixture was mixed on a vortex mixer for 10 sec. The mixture was then extracted with 2 ml of *t*-butyl methyl ether on a vortex mixer for 70 sec and centrifuged at 4000g for 10 min. The resulting supernatant was transferred into a fresh tube and dried at 45°C under nitrogen gas. The residue was reconstituted with 125 μl of the mobile phase on a vortex mixer for 90 sec.

The reconstituted solution was centrifuged at 1500*g* for 30 sec, and a portion (40 μl) was injected onto the chromatograph.

The flow rate of the mobile phase was maintained at 2.0 ml/min at ambient temperature, and the effluent was monitored at an ultraviolet (UV) detection wavelength of 263 nm. Itraconazole, hydroxyitraconazole, and ketoconazole (internal standard) were well resolved, with the retention times of 2.8, 3.3, and 5.4 min, respectively. The standard curve was linear over the concentration range 10–2000 ng/ml, with a typical correlation coefficient of $r = .9995$. The extraction recovery of itraconazole and hydroxyitraconazole was more than 87% and more than 93%, respectively, in the rat and rabbit plasma. The intra- and interday assay variabilities were less than 5.0% and less than 2.1%, respectively, for both itraconazole and hydroxyitraconazole over the dose range studied ($n = 4$ each for rat and rabbit serum).

Data Analysis

Data for serum itraconazole and hydroxyitraconazole concentration versus time were analyzed by a noncompartmental method using the nonlinear least-squares regression program WinNonlin (Scientific Consulting, Inc., Cary, NC). Statistical differences were tested by the unpaired Student *t* test for the area under the curve (AUC), C_{max}, T_{max}, MRT (mean residence time), and the mean area under the curve (AUMC) values between the two oral dosage forms. The significance level was set at $p < .05$.

RESULTS AND DISCUSSION

The dissolution data for itraconazole from Asd tablets and Sporanox capsules as a function of the medium pH are shown in Table 1. The solubility of itraconazole from the solid dispersion particles was found to be significantly increased (130.4-fold) over that of the pure material (238.7 ± 3.86 μg/ml versus 1.83 ± 0.03 μg/ml, $n = 4$ each) as determined at pH 1. 2. As the pH of the test medium was increased, the drug solubility for the solid dispersions was drastically reduced, although it still was higher (8.48 ± 2.21 μg/ml at pH 2.0 and 6.04 ± 2.96 μg/ml at pH 3.0) than determined for the pure material. The drug dissolution rate was also higher for Asd tablets, with more than 90% released within 10 min as compared to less than 20% for Sporanox capsules (Table 1). Within 60 min, 97.5 ± 3.03% of the drug was released from Asd tablets, whereas 86.5 ± 1.80% was released from Sporanox capsules.

Figure 1 shows the average serum concentration-time curves of itraconazole and hydroxyitraconazole after administration of Asd tablets and Sporanox capsules in the rat. Despite the rapid in vitro release characteristics of itraconazole from Asd tablets, the mean T_{max} values between Asd tablets and Sporanox capsules were comparable (2.9 ± 1.8 hr versus 3.5 ± 0.5 hr, respectively). There was no difference between Asd tablets and Sporanox capsules in the mean AUC (3089.5 ± 4332.8 ng · hr/ml and 3653.9 ± 2348.9 ng · hr/ml, respectively) and C_{max} (295.0 ± 344.5 and 390.5 ± 169.4 ng/ml, respectively). As reported in humans (12–15), there was a large interindividual variability in the pharmacokinetics of itraconazole in the rat. The formation of hydroxyitraconazole was rapid, with the time to the maximum concentration being 4.3 ± 0.8 hr and 4.9 ± 1.4 hr for Asd tablets and Sporanox capsules, respectively. The mean C_{max} of hydroxyitraconazole was significantly higher than for the parent drug (Table 2). In humans, the elimination of hydroxyitraconazole is faster than that of itraconazole (2,12). In contrast, in the rat, the elimination of hydroxyitraconazole was slower than for the parent drug. The terminal elimination half-life of hydroxyitraconazole and itraconazole was, respectively, 7.7 ± 2.2 hr and 4.3 ± 1.5 hr for Asd tablets and 10.5 ± 2.6 hr versus 4.5 ± 2.1 for Sporanox capsules.

Figure 2 shows the average serum concentration-time curves of itraconazole and hydroxyitraconazole after administration of Asd tablets and Sporanox capsules in the rabbit. Again, despite the rapid in vitro release characteristics, the rate of drug absorption from Asd tablets was comparable to that of Sporanox, with a mean T_{max} of 10.4 ± 2.9 hr and 12.4 ± 6.8 hr for Asd tablets and Sporanox capsules, respectively (Table 3). There were no differences between Asd tablets and Sporanox capsules in the mean AUC (19357.9 ± 5117.5 ng · hr/ml and 23382.2 ± 6236.5 ng · hr/ml, respectively) and C_{max} (766.4 ± 276.5 and 1127.5 ± 577.9 ng/ml, respectively). As in the rat, the formation of hydroxyitraconazole was rapid in the rabbit, and the time to C_{max} was similar for both itraconazole and hydroxyitraconazole (Table 3).

There were several species-specific differences in the absorption and disposition of itraconazole and hydroxyitraconazole between the rat and the rabbit. First, the absorption of itraconazole in the rabbit was much slower than in the rat, as evidenced by the higher T_{max} values (Tables 2 and 3). Second, the elimination of hydroxyitraconazole in the rabbit was formation rate–limited, as opposed to metabolite elimination rate–limited as found in the rat (Figs. 1 and 2). The terminal elimination half-life of the parent drug was longer in the rabbit than in the rat for both Sporanox capsules (9.8 ± 3.9 hr versus 4.5 ±

Table 1

*Dissolution (%) of Itraconazole Determined at Various pH Values from the Asd Tablets and Sporanox Capsules (*n *= 3–4)*

	pH			
Time (min)	1.2	2.0	3.0	4.0
Asd				
5	68.1 ± 9.43	20.7 ± 4.63	0.55 ± 0.42	0.03 ± 0.02
10	91.2 ± 5.90	22.1 ± 4.14	1.42 ± 0.27	0.16 ± 0.07
30	97.4 ± 2.16	21.2 ± 4.16	1.76 ± 0.33	0.23 ± 0.09
60	97.5 ± 3.30	26.9 ± 15.8	1.78 ± 0.36	0.32 ± 0.05
Sporanox				
5	1.92 ± 0.42	0.61 ± 0.34	0.09 ± 0.06	0.03 ± 0.03
10	17.6 ± 1.73	1.13 ± 0.25	0.20 ± 0.12	0.06 ± 0.07
30	63.0 ± 2.57	12.9 ± 2.76	0.99 ± 0.34	0.15 ± 0.08
60	86.5 ± 1.80	18.9 ± 3.97	1.51 ± 0.35	0.43 ± 0.12

2.1 hr) and Asd tablets (10.0 ± 2.9 hr versus 4.3 ± 1.5 hr). Third, unlike in the rat, serum levels of the parent drug in the rabbit were higher than the corresponding levels of the hydroxy metabolite. Fourth, the ratios of the metabolite to the parent drug AUC (AUC_M/AUC_D) in the rabbit were less than unity (0.63 ± 0.19 and 0.57 ± 0.07 for Asd and Sporanox, respectively), whereas they were greater than unity in the rat with high variability (5.70 ± 6.71 and 3.25 ± 2.57 for Asd and Sporanox capsules, respectively). Therefore, considering the similar patterns between humans and rats in the rate of drug absorption,

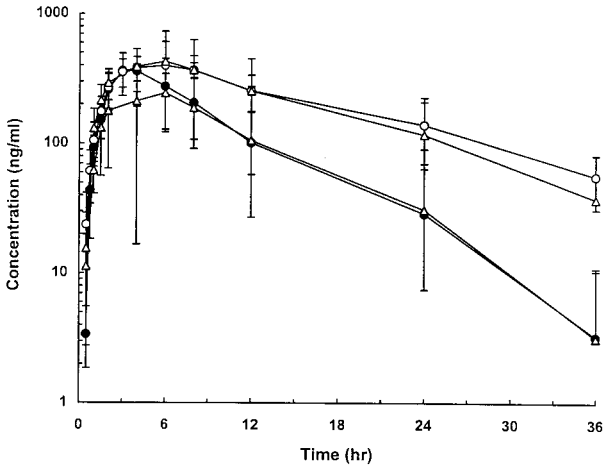

Figure 1. Average serum concentration-versus-time profiles of itraconazole (closed symbols) and hydroxyitraconazole (open symbols) after administration (5 mg itraconazole doses) of Asd tablets (triangles) and Sporanox capsules (circles) in the rat (n = 6 each).

higher serum levels of hydroxyitraconazole than the corresponding itraconazole levels, and an AUC_M/AUC_D ratio greater than unity, rats rather than rabbits may be a better animal model for studying the oral bioavailability of itraconazole. However, the longer elimination half-life of hydroxyitraconazole over that of the parent drug found in the rat needs to be taken into account in studying the pharmacodynamics of itraconazole. Figure 3 shows the relationship between the metabolite to the parent drug AUC ratios (AUC_M/AUC_D) and the apparent oral clearance of itraconazole (Cl/F). There was large variation in the oral clearance of itraconazole in rats (range 0.43–41.72 L/hr) as compared with rabbits (range 1.61–3.55 L/hr). Therefore, assuming that the systemic clearance of hydroxyitraconazole is relatively consistent across individual animals, the significant correlation within formulation indicates that the formation of this metabolite may be a contributing factor in the variations seen in the oral clearance of itraconazole in the rat, while this was not the case in the rabbit.

There may be several possible speculations for the poor predictability of the extent of oral drug absorption based on in vitro solubility and dissolution data. First, considering that the solubility of itraconazole was reduced drastically as the pH increased, the drug dissolved in the stomach might have been precipitated as it was passed into the small intestine. We measured the physiological pH along the gastrointestinal tract in the rat and the rabbit. The gastric pH in the rabbit was lower than in the rat (pH 1.9 versus 5.0), but the intestinal pH (5–7) was similar in both animal species. Therefore, given the comparable relative bioavailability of Asd tablets in rats and rabbits, differences in the stomach pH did not

Table 2

Pharmacokinetic Parameters of Itraconzaole After Oral Admnistration of Asd Tablets and Sporanox Capsules (Itraconazole 50-mg doses) in the Rat

Parameter	Asd (n = 6)	Sporanox (n = 6)
Itraconazole		
AUC (ng · hr/ml)	3089.5 ± 4,332.8	3653.9 ± 2,348.9
AUC (ng · hr/ml/g)	13.10 ± 21.31	14.47 ± 9.60
C_{max} (ng/ml)	295.0 ± 344.5	390.5 ± 169.4
T_{max} (hr)	2.9 ± 1.8	3.5 ± 0.5
MRT (hr)	7.6 ± 2.8	8.1 ± 2.9
AUMC (ng · hr^2/ml)	31,953.1 ± 52,028.4	34,997.3 ± 30,621.8
Hydroxyitraconazole		
AUC (ng · hr/ml)	6679.3 ± 5472.8	7883.4 ± 2503.4
AUC (ng · hr/ml/g)	26.30 ± 28.45	25.22 ± 13.96
C_{max} (ng/ml)	419.8 ± 270.9	412.1 ± 60.7
T_{max} (hr)	4.3 ± 0.82	4.9 ± 1.4
MRT (hr)	13.0 ± 3.2	17.5 ± 4.9
AUMC (ng · hr^2/ml)	98,978.9 ± 101,294.4	146,251.1 ± 71,744.6
AUC_M/AUC_D ratio	5.70 ± 6.71	3.25 ± 2.57

appear to be responsible for the poor correlation between the in vitro and in vivo data. In this regard, it may be interesting to administer smaller doses of itraconazole and examine if drug absorption becomes dose dependent. Second, it was possible that Asd tablets and minicapsules given orally somehow did not disintegrate adequately in vivo. To examine this possibility, Asd tablets and minicapsules were administered to rats; the rats were sacrificed at 30 min and 2 hr for visual inspection. However, no trace of the tablets or capsules was observed in the gastrointestinal tract. Therefore, it is unlikely that inadequate disintegration of the oral dosage form was responsible for the poor prediction. Third, it was possible that the physical state of itraconazole in solid dispersions might have been altered (i.e., from an amorphous state to a crystalline state during wet granulation prior to manufacturing the tablets), and as a result, oral absorption of itraconazole was not enhanced as expected. This aspect was examined by performing differential scanning calorimetry for the solid dispersions that had undergone the wet granulation process. Interestingly, the endothermic peak corresponding to the pure itraconazole that was absent in solid dispersions was observed for the Asd granules, indicating that the physical state of itraconazole was transformed back to a crystalline form. Further work is warranted to see if the oral drug bioavailability is increased if the amorphous form of itraconazole is maintained (i.e., by employing the dry granulation instead of the wet granulation technique).

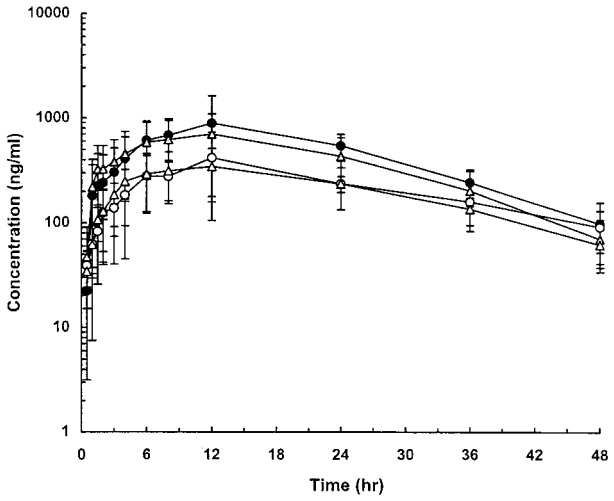

Figure 2. Average serum concentration-versus-time profiles of itraconazole (closed symbols) and hydroxyitraconazole (open symbols) after administration (50 mg itraconazole doses) of Asd tablets (triangles, n = 4) and Sporanox capsules (circles, n = 5) in the rabbit.

CONCLUSIONS

Asd compact tablets containing itraconazole were prepared by spray-drying of solid dispersions with polyvinylacetal diethylaminoacetate, followed by wet granu-

Table 3

Pharmakonetic Parameters of Itraconzaole and Hydroxyitraconazole After Oral Admnistration of Asd Tablets and Sporanox Capsules (Itraconazole 50-mg Doses) in the Rabbit

Parameter	Asd (n = 4)	Sporanox® (n = 5)
Itraconazole		
AUC (ng · hr/ml)	19,357.9 ± 5117.5	23,382.2 ± 6236.5
AUC (ng · hr/ml/g)	5.72 ± 1.42	6.65 ± 1.57
C_{max} (ng/ml)	766.4 ± 276.5	1,127.5 ± 577.9
T_{max} (hr)	10.4 ± 2.9	12.4 ± 6.8
MRT (hr)	20.8 ± 4.6	22.0 ± 5.3
AUMC (ng · hr^2/ml)	395,211.6 ± 101,555.1	513,394.4 ± 175,562.4
Hydroxyitraconazole		
AUC (ng · hr/ml)	11,973.3 ± 2620.3	13,106.2 ± 3454.6
AUC (ng · hr/ml/g)	3.54 ± 0.70	3.75 ± 0.99
C_{max} (ng/ml)	369.2 ± 125.8	479.2 ± 277.6
T_{max} (hr)	9.4 ± 2.9	13.2 ± 6.4
MRT (hr)	32.8 ± 21.4	30.8 ± 8.9
AUMC (ng · hr^2/ml)	399,229.4 ± 286,521.9	406,184.7 ± 186,023.7
AUC_M/AUC_D ratio	0.63 ± 0.19	0.57 ± 0.07

lation. The oral absorption of itraconazole from Asd tablets was determined in rats and rabbits and was compared with a marketed product, Sporanox capsules. No differences were found in C_{max}, T_{max}, and AUC values between the two products, but there was poor correlation between the in vivo drug absorption and the in vitro solubility and dissolution characteristics. There were species-specific differences in the disposition of itraconazole and its active metabolite hydroxyitraconazole. In conclusion, in designing a solid dosage form of itraconazole with improved bioavailability, drug dissolution and other manufacturing factors, such as the granulation technique and the physical state of the drug, may need to be considered.

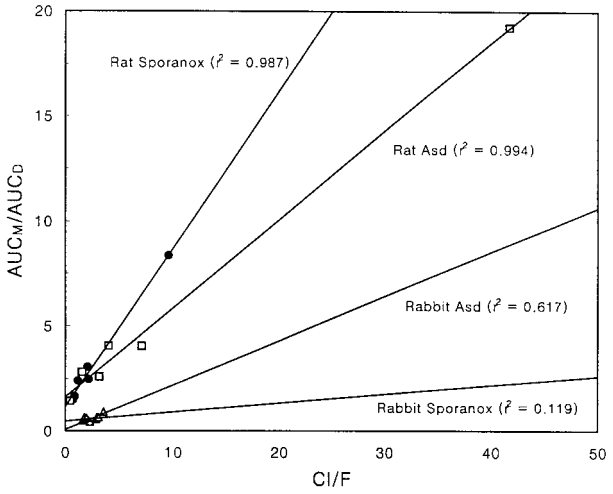

Figure 3. Relationship between the hydroxyitraconazole-to-itraconazole AUC ratios (AUC_M/AUC_D) and the oral clearance of itraconazole (Cl/F).

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