Bioequivalence Studies of Itraconazole Capsules

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ABSTRACT:

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Objectives: To compare pharmaceutical properties and perform bioequivalence studies of two generic products with the innovative product, Sporal®.

Methods: The pharmaceutical properties; weight variation, content uniformity, percent labeled amount, and dissolution profile, of two itraconazole generic products (Product A and Product B) were investigated and compared with those of the innovative itraconazole capsule, Sporal®. Two bioequivalence

studies between product A or B with Sporal® were performed using 12 healthy Thai male volunteers for each study. A 200-mg single oral dose of itraconazole was administered immediately after breakfast. The study followed a double blind, two treatment, two period, two sequence randomized crossover design with at least a one-week wash out period between each formulation. Plasma concentrations of itraconazole were determined up to 36 hours after each dose using a validated high-performance liquid chromatography method.

Results: The itraconazole content of Product A was not uniform but no difference in dissolution profiles between Product A and Sporal® were shown. The dissolution profile of Product B was not similar to that of Sporal®. Statistical tests were carried out as stated in the USP 25 guidelines for bioequivalence studies and 90% confidence intervals of the log of the ratios of either C_{max} or $AUC_{0->last}$ between product A and Sporal®, and product B and Sporal® were outside the standard range 0.80 - 1.25.

Conclusion: In term of unchanged itraconazole, product A and B used in the studies was not bioequivalent to Sporal®. Bioequivalence studies with hydroxy-itraconazole, an active metabolite of itraconazole, should be performed to determine the overall therapeutic effects. Long term use in patients should also be determined to evaluate the therapeutic effects.

Key words: Itraconazole, Bioequivalence studies, Pharmaceutical properties

บทคัดย่อ:

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วัตถุประสงค์: เพื่อศึกษาสมบัติทางเภสัชกรรมและชีวสมมูลของยาไอทราโคนาโซลระหว่างยาสามัญสองชนิดกับยาต้นแบบ สปอรัล

วิธีการศึกษา: ทำการศึกษาสมบัติทางเภสัชกรรม ได้แก่ ความแปรปรวนด้านน้ำหนัก ความสม่ำเสมอในปริมาณตัวยา ปริมาณเปอร์เซ็นต์ของตัวยาเทียบกับที่ระบุบนฉลาก และรูปแบบการละลาย ของยาสามัญสองชนิด คือ ผลิตภัณฑ์ เอ และ ผลิตภัณฑ์ บี เทียบกับยาแคปซูลต้นแบบ สปอรัล และทำการศึกษาชีวสมมูล สองการทดลองระหว่างยาสามัญสองชนิดคือ ผลิตภัณฑ์ เอ หรือ ผลิตภัณฑ์ บี กับยาแคปซูลต้นแบบ สปอรัล โดยศึกษาใน

อาสาสมัครชายไทยสุขภาพดี การทดลองละ 12 คน ขนาดของยาที่ใช้คือให้รับประทานครั้งเดียวพร้อมอาหารในขนาด 200 มิลลิกรัม การทดลองออกแบบเป็นชนิดปกปิดสองด้าน ยารักษาสองชนิด สองช่วงเวลา สองลำดับแบบสุ่มไขว้สลับ โดยเว้นช่วงชำระอย่างน้อยหนึ่งสัปดาห์ วิเคราะห์หาความเข้มข้นของตัวยา ไอทราโคนาโซลในตัวอย่างพลาสมาที่เก็บตลอดช่วง 36 ชั่วโมงหลังรับประทานยาโดยวิธีไฮเพอร์ฟอร์มมานลิควิดโครมาโตกราฟีที่ผ่านการประเมินความถูกต้องแล้ว

ผลการศึกษา: ปริมาณตัวยาไอทราโคนาโซลในผลิตภัณฑ์ เอ ไม่เท่ากันในแต่ละแคปซูล แม้ว่าไม่พบความแตกต่างกับยาต้นแบบ สปอรัล ในรูปแบบการละลาย สำหรับผลิตภัณฑ์ บี พบว่ามีรูปแบบการละลายไม่เหมือนกับยาต้นแบบ สปอรัล สำหรับการศึกษาชีวสมมูลพบว่า ช่วงความเชื่อมั่น 90 เปอร์เซ็นต์ของลอการิทึมของสัดส่วนของ C_{max} หรือ $AUC_{0->last}$ ระหว่างผลิตภัณฑ์ เอ กับ สปอรัล และ ผลิตภัณฑ์ บี กับ สปอรัล ไม่อยู่ในช่วงมาตรฐาน 0.80–1.25

สรุปผลการศึกษา: สามารถระบุได้ว่า เมื่อพิจารณาเฉพาะยาไอทราโคนาโซลในรูปที่ไม่เปลี่ยนแปลง ผลิตภัณฑ์ เอ และ ผลิตภัณฑ์ บี ที่ใช้ในการศึกษาครั้งนี้ไม่แสดงชีวสมมูลกับ สปอรัล ควรมีการศึกษาชีวสมมูลของไฮดรอกซี อิตร้าโคนาโซลซึ่งเป็นเมตาบอไลท์ที่มีฤทธิ์ในการรักษาประกอบด้วยเพื่อประเมินฤทธิ์ในการรักษาทั้งหมด นอกจากนี้ควรคำนึงถึงผลการรักษาเมื่อใช้ในคนไข้ระยะยาวด้วย

คำสำคัญ: ไอทราโคนาโซล, การศึกษาชีวสมมูล, สมบัติทางเภสัชกรรม

Introduction

Itraconazole is a triazole antifungal agent that has a broad spectrum of activity and is well tolerated in humans[1]. It acts primarily by inhibiting biosynthesis of ergosterol, an essential component of fungal membranes. The drug binds more avidly to fungal cytochrome P450 than does ketoconazole and has little effect on mammalian cytochrome P450 enzyme systems[2]. The pharmacokinetics of itraconazole in man are characterized by; a good oral absorption, an extensive tissue distribution with tissue concentrations many times higher than in plasma, a relatively long elimination half-life of about one day and a biotransformation into a large number of metabolites[3,4,5]. The major metabolite, hydroxy-itraconazole, reaches higher plasma concentrations than the parent compound and has comparable antifungal activity to itraconazole.

Itraconazole is an extremely weak base (pKa=3.7) and is only ionized at low pH, such as found in gastric juice[5]. The log partition coefficient of itraconazole in a system of n-octanol and an aqueous buffer solution of pH 8.1 is 5.66 which indicates very high lipophilicity. Itraconazole is almost insoluble in water and in dilute acidic solution (less than 5 ug/mL). Early formulations contained itraconazole dissolved in a matrix of acidified high-molecular PEGs (PEG capsules).

Later, the formulation was replaced by capsules with itraconazole coated pellets (pellet capsules)[5,6].

Generic products of itraconazole capsules require sophisticated formulation techniques in order to achieve similar dissolution properties otherwise bioequivalence may not be obtained. Bioequivalence study is a tool to investigate the efficiency of a generic product compare with that of the reference product by looking at drug concentration in plasma of volunteers. An area under the concentration-time curve (AUC) and a maximum concentration (C_{max}), the pharmacokinetics parameters which represent the extent of drug that reach the blood circulation, are used as the comparing factors. The bioequivalence between the two products is able to be stated if 90% confidence interval of the ratio of the logarithm transformation of these factors is required to be in a range of 0.80 –1.25. This paper discussed the results of two bioequivalence studies performed in healthy Thai male volunteers between the innovative product, Sporal® capsule (Janssen-Cilag) with any of two generic itraconazole products made in Thailand.

Materials and Methods

Drug products:

The following itraconazole 100 mg capsules were used: Sporal® (Janssen Cilag, Batch No. 143007, MFD 14/6/2001, EXP. 14/6/2004, Janssen-Cilag), Product A (Lot No. C12028, MFD 9/3/2001, EXP. 9/3/2003, Company A) and Product B (Lot No. 911022, MFD 02/2001, EXP. 02/2003, Company B)

Pharmaceutical properties

The pharmaceutical properties, i.e. weight variation, content uniformity, % labeled amount, and dissolution profile, of these three products were investigated.

Weight variation

Ten 100 mg itraconazole oral hard gelatin capsules of each brand were used in the study. Each capsule with its contents was weighed using an analytical balance and then the empty capsule was weighed after washing with acetone. Weights of the contents in each capsule were then calculated. Means and coefficient of variations (CV) for 10 capsules of each brand were also determined.

Percent Labeled Amount

The itraconazole content of ten pooled 100 mg itraconazole oral hard gelatin capsules of each brand was triplicately determined using HPLC method with 20 μL of injection volume. HPLC system was the same as that in the topic "Plasma itraconazole content analysis method".

Content Uniformity

Each of 10 capsules were analysed for itraconazole content. The analytical protocol was similar to that of % labeled amount analysis, except the content was from a particular capsule.

Means, standard deviations and coefficient of variations were calculated. The itraconazole content of every capsule should be in the range of 85-115 % and % CV should be less than 6 %.

Dissolution Profile

The dissolution profiles of itraconazole hard gelatin capsules from generic products (A or B) were compared with the dissolution profile of Sporal®. Dissolution apparatus II (paddle method) was used. The dissolution medium consisted of 1% polysorbate 20 in simulated gastric fluid without pepsin[8]. A volume of 900 mL was controlled at 37.0 ± 0.5 °C. The rotation speed was 100 rpm. Samples (5 mL) of dissolution medium were withdrawn after 10, 20, 30, 45, and 60 minutes without replacement. Twelve capsules of each product were used. Each time, 3 capsules of either Product A, Product B or Sporal® were randomly placed in the vessels of a 6 hole dissolution apparatus. After 4 times of study, each hole was 2 times placed with either Product A, Product B or Sporal®. The itraconazole content for each sample was quantified using a validated UV spectroscopic assay at 255 nm. The percentage itraconazole dissolved at each sampling time was calculated.

Difference factor (f1) was then calculated from the equation[7]

$$f1 = [\{ \sum_{t=1}^{n} R_t - T_t \} / \{ \sum_{t=1}^{n} R_t \}] \times 100$$

and similarity factor (f2) was calculated from

$$f2 = 50 \times \log[\{1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2\}^{-0.5} \times 100$$

Where n is the number of a sampling time, R_t is the amount of dissolved drug from the reference product at time t and T_t is the amount of dissolved drug from the test or generic product at time t.

If the difference factor (f1) has a value outside the range 0 – 15, a difference in the dissolution profiles could be concluded. While if a similarity between dissolution profiles is obtained when the similarity factor (f2) are in the range of 50 – 100[7].

Bioequivalence studies

Two separate bioequivalence studies comparing Sporal® capsule with two generic products (A or B) were approved by the Ethical Review Committee, Faculty of Pharmacy, Chiang Mai University. Twelve healthy Thai male volunteers, aged between 20-24 years old and having a Body Mass Index between 19 - 24 kg/m^2, participated in each study.

A double blind, single dose, two treatment, two period, two sequence, randomized cross over design study with at least one week washout period

between each formulation was used. Two 100 mg itraconazole capsules were administered immediately after breakfast with 240 mL water. Blood samples (5 mL) were taken at times 0, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, and 36 h after drug administration. Plasma was separated and kept at -40 °C before analysis for itraconazole content.

Plasma itraconazole content analysis method

Itraconazole content in plasma samples were analysed by validated High Performance Liquid Chromatography. Briefly, 500 μL of plasma sample was mixed with 50 μL of 0.3 N $Ba(OH)_2.8H_2O$ and then 50 μL of 0.4 N $ZnSO_4$ was added. A 1 ml quantify of acetonitrile fortified with 0.25 ug/ml internal standard (celecoxib, lot no. OCC021, Cadila Healthcare Ltd., India) was subsequently added and the contents were vortex-mixed for 10 minutes and centrifuged at 10,800 rpm for 10 minutes. The supernate was decanted to a clean test tube (16 x 100 mm, Kimax®, USA) and evaporated to dryness under reduced pressure at 60 °C. The residue in the tubes were reconstituted using 250 μL of mobile phase, vortex-mixed and centrifuged at 10,800 rpm for 5 minutes. The clear solution was then transferred to an injection vial and 50 μL of the solution was injected onto a reverse phase Hypersil® ODS column (C18, 125x4 mm, 5 μm) connecting with a Hewlett Packard Series 1100 HPLC system (G1356AA, Germany) equipped with UV detecter. The mobile phase was Acetonitrile : 0.05% Diethylamine pH 6.0 : Methanol (50:49:1) using with a flow rate of 1.0 mL/min. The UV detection was performed at 261 nm.

Standard curves were performed by preparing standard itraconazole (Janssen Pharmaceutica N.V., Lot no. ZR051211PUJ221, MFG. 10-06-2002, Exp. Date 10-06-2008) in plasma with a concentration over the range of 12.5 – 2000 ng/ml. The previously described sample preparation process was performed and the samples were injected into the HPLC system.

Linearities of the standard curves were found in the range of 12.5 – 2000 ng/ml (r^2>0.999). Specificity, accuracy, precision of the analysis method and stability of itraconazole were validated. The lower limit of quantification was 12.5 ng/ml.

Data Analysis

Blood concentration-time curves were plotted. Pharmacokinetic parameters were determined. C_{max} and T_{max} (time of maximum concentration) were taken from the raw data. AUC was determined using the trapezoidal rule and the 90% confidence intervals were calculated as follows :

90% confidence interval=$\Delta \pm t_{0.10,v}\sqrt{EMS(2/n)}$

Where Δ is the difference in means of log transformed pharmacokinetic parameters (C_{max} or AUC) between the test product and the reference,

$t_{0.10, \nu}$ is the tabulated two-tail t value for a 90 % confidence interval, V is the degree of freedom of the error mean square obtained from the ANOVA table, EMS is the error mean square from the ANOVA table and n is the number of subjects. Antilogarithm of the calculated confidence interval will yield an exact confidence interval for the ratio.

Bioequivalence between the test and reference products could be stated if the 90% confidence intervals of the ratio of the log transform of the pharmacokinetic parameters, i.e. C_{max} and AUC, were in the range of 0.80 –1.25 (USP25)[8]

Table 1 Weight variation of Sporal® and two itraconazole generic products

Products	Powder weight (mg)	
	Mean ± SD	CV (%)
Sporal®	467.98 ± 5.39	1.2
Product A	456.13 ± 2.52	0.55
Product B	457.22 ± 6.53	1.4

CV = Coefficient of variation

Table 2 Mean itraconazole content of Sporal® and two itraconazole generic products

Products	Content (mg)	
	Mean ± SD	CV (%)
Sporal®	94.70 ± 1.89	2.0
Product A	105.60 ± 7.01	6.6
Product B	99.91 ± 4.38	4.4

CV = Coefficient of variation

Table 3 Percent labeled amount of Sporal® and two itraconazole generic products

Products	Percent labelled amount	
	Mean ± SD	CV (%)
Sporal®	104.74 ± 3.58	3.4
Product A	99.25 ± 1.91	1.9
Product B	100.03 ± 1.65	1.7

CV = Coefficient of variation

Table 4 Difference factor (f1) and similarity factor (f2) for Sporal® compared with Product A and with Product B

Products	Product A and Sporal®	Product B and Sporal®	Standard Value
Difference factor (f1)	5.75	8.68	0 - 15
Similarity factor (f2)	50.56	48.82	50 - 100

Results

Pharmaceutical Properties

The weight variations of Sporal® and the two itraconazole generic products were acceptable since the relative standard deviation (%) of 10 capsules was very low (less than 2 %) (Table 1). The mean itraconazole content in each capsule of each product was 94.70 ± 1.89, 105.60 ± 7.01, and 99.91 ± 4.38 mg for Sporal®, Product A and Product B, respectively (Table 2). However, 1 of 10 capsules of Product A used had an itraconazole content over 115 % (data not shown). In addition, the relative standard deviation was over 6.0 %. Therefore, content uniformity of Product A is inadequate. The percent labeled amount of Sporal®, Product A and Product B were 104.74 ± 3.58, 99.25 ± 1.91 and 100.03 ± 1.65 %, respectively (Table 3). They were in the range of 85 – 115 %.

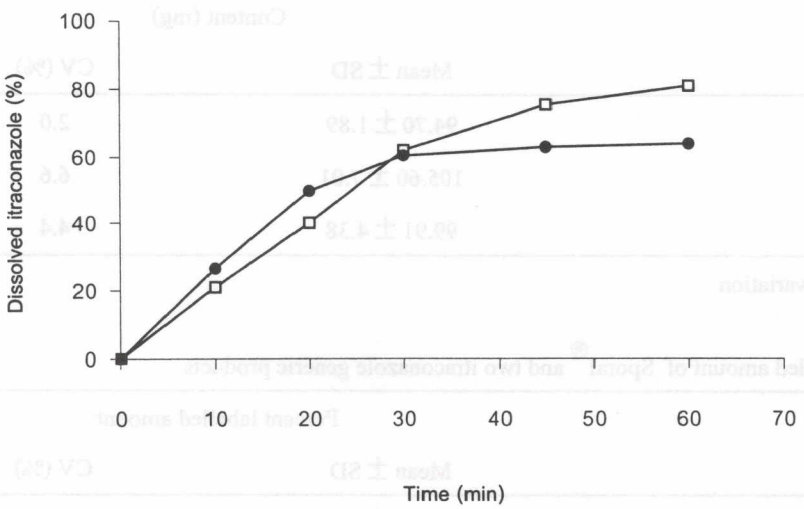


Figure 1 Dissolution profiles of Product A (●) and Sporal® (□)

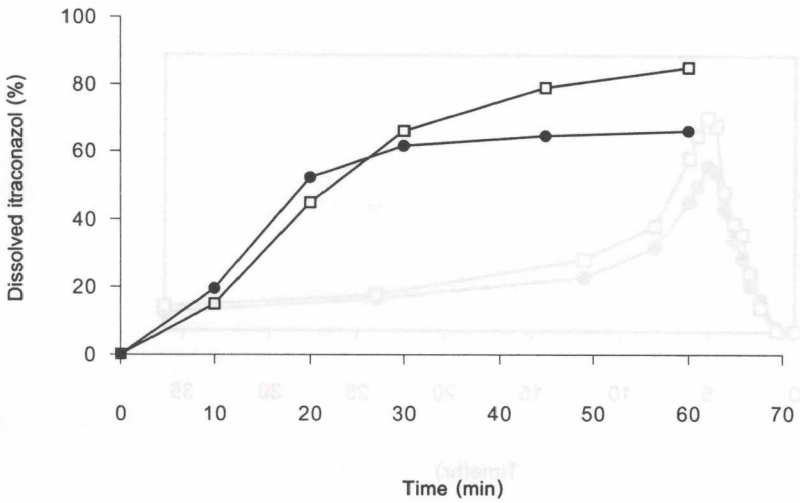


Figure 2 Dissolution profiles of Product B (●) and Sporal® (□)

The dissolution profiles for Sporal® compared with Product A and with Product B are shown in Figures 1 and 2, respectively. Itraconazole dissolved profiles up to the first 30 minutes were similar in all products. After 30 minutes the amount of itraconazole which dissolved from both Product A and Product B seemed to remain constant (about 60% at 60 minutes) while itraconazole continued to be dissolved from Sporal® (up to about 80% at 60 minutes).

Difference factor (f1) and similarity factor (f2) were calculated and the results are shown in Table 4. Difference factors were 5.75 for Product A and Sporal® and 8.68 for Product B and Sporal®. These values are in the range of 0 – 15, therefore, difference can not be stated between the dissolution profiles of either Product A and Sporal® or Product B and Sporal®. For similarity factor, the values of 50.56 were for Product A and Sporal® and 48.82 for Product B and Sporal®. Since the similarity factor of Product B and Sporal® was out of the range limit 50 – 100, it was evident that Product B and Sporal® did not have a similar dissolution profiles. However, it should be noted that the similarity factor for Product A and Sporal® was at the lower range limit.

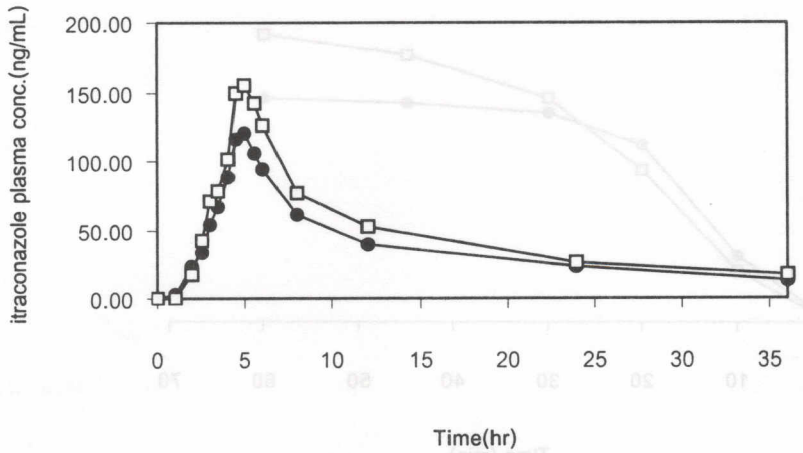


Figure 3 Itraconazole plasma concentration – time curves for Product A (●) and Sporal® (□).

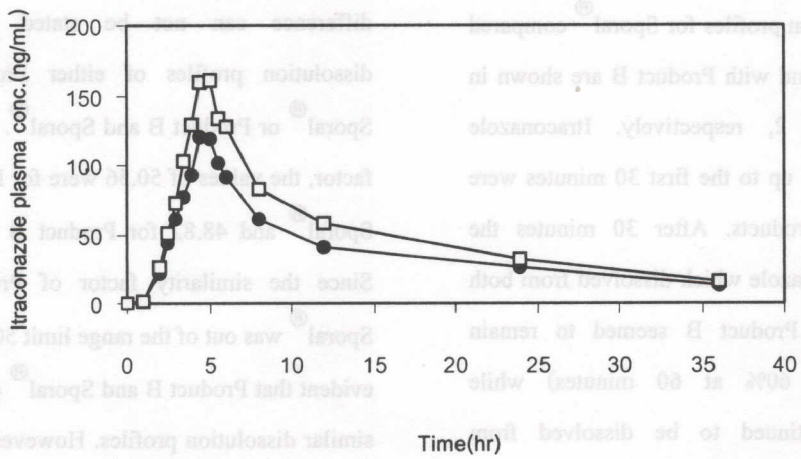


Figure 4 Itraconazole plasma concentration – time curves for Product B (●)and Sporal® (□).

Bioequivalence studies

No side effects were noticed in any of the volunteers receiving any of the itraconazole capsules. The average itraconazole concentration – time curves for Product A and Sporal® capsules, and Product B and Sporal® capsules are shown in Figures 3 and 4 respectively. Pharmacokinetic

parameters, ie. $AUC_{0\rightarrow last}$, C_{max}, T_{max}, are collated in Tables 5 and 6 respectively.

The T_{max} for volunteers who took Product A (4.75 ± 0.62 hr) was not significantly different from those who took Sporal® (4.79 ± 0.72 hr) ($p > 0.05$, t-test, Table 5). Table 6 also shows the T_{max} for volunteers who took Product B (5.04 ± 0.96 hr) was not significantly different from that of Sporal® (4.92 ± 0.47). The T_{max} at about 5 hr for Thais found in these studies was similar to that of previous reports (4.7 ± 1.4 hr)[5].

Table 5 Pharmacokinetic parameters for the bioequivalence study comparing Product A and Sporal®.

Pharmacokinetic Parameters	Product A	Sporal®	90% Confidence Interval
$AUC_{0\rightarrow last}$(ng.h/mL)	1214.15 ± 481.93	1558.04 ± 727.85	0.646 – 1.028
C_{max} (ng/mL)	139.71 ± 39.02	171.38 ± 59.69	0.690 – 1.041
t_{max}(h)	4.75 ± 0.62	4.79 ± 0.72	

Table 6 Pharmacokinetic parameters for the bioequivalence study comparing Product B and Sporal®.

Pharmacokinetic Parameters	Product B	Sporal®	90% Confidence Interval
$AUC_{0\rightarrow last}$(ng.h/mL)	1275.08 ± 973.12	1687.35 ± 1067.19	0.653 – 0.893
C_{max} (ng/mL)	130.27 ± 65.50	169.23 ± 80.50	0.656 – 0.904
t_{max}(h)	5.04 ± 0.96	4.92 ± 0.47	

$AUC_{0\rightarrow last}$ values were 1214.15 ± 481.93 and 1558.04 ± 727.85 ng.hr/mL and average C_{max} values were 139.71 ± 39.02 ng/mL and 171.38 ± 59.69 ng/mL for Product A and Sporal®, respectively (Table 5). The 90 % confidence intervals of the ratio of $AUC_{0->last}$ and C_{max} for Product A and Sporal® were 0.646 – 1.028 and 0.690 –1.041 respectively.

For Product B and Sporal®, $AUC_{0\rightarrow last}$ values were 1275.08 ± 973.12 and 1687.35 ± 1067.19 ng.hr/mL and the average C_{max} values were 130.27 ± 65.50 ng/mL and 169.23 ± 80.50 ng/mL, respectively (Table 6). The 90 % confidence intervals of the ratio of $AUC_{0->last}$ and C_{max} for Product B and Sporal® were 0.653 – 0.893 and 0.656 – 0.904 respectively.

Discussion

Product A did not pass the content uniformity. Even though there was no difference in the dissolution profiles of product A and Sporal®.

However, the difference factor and the similarity factors were at the lower range limit. For Product B, it was shown that the dissolution profile for Product B was not similar to that of Sporal®. It should be noticed that the dissolution of both Product A and Product B was limited to about 60 % while itraconazole continued to dissolve up to 80% from Sporal®. In fact, the data used in the calculation of f1 and f2 should be for dissolution data of more than 85%[7]. Therefore, if the dissolution profiles were extended until 85% itraconazole had dissolved from Sporal® it is possible that f1 and f2 would be out of the range limit.

Differences in formulation technology may be the reason for the above differences since the solubility of itraconazole is very low. Reference product, Sporal®, claimed to use a pelletizing technique using a coating of itraconazole-hydroxypropyl methylcellulose on sugar core (600–700 μm) which was seal coated with polyetylene glycol 20000. The low solubility of itraconazole was thus changed. A hydrophilic itraconazole was formed with an improved solubility[6].

Results of the determination of the pharmaceutical properties agreed with the results of the bioequivalence studies. The 90 % confidence intervals of the ratio of both $AUC_{0->last}$ and C_{max} between Product A and Sporal®, and Product B and Sporal® capsules were outside the range 0.80 to 1.25 which is required by the USP 25. Therefore, bioequivalence is not indicated between Product A or Product B and Sporal® 100 mg itraconazole capsules. However, it should be noted that this finding is at present limited to the lot that was used in the study.

Although, it can be concluded that both Product A and Product B, used in these studies are not bioequivalent to Sporal® capsules, it is only in terms of unchanged itraconazole. It is important to note this since itraconazole is extensively metabolized by the liver into a major active metabolite, i.e. hydroxy-itraconazole, which has a comparable antifungal activity to itraconazole. Therefore, it is important that a bioequivalence study using hydroxy-itraconazole should be performed to determine the overall therapeutic effect.

In addition, these studies were designed as a single dose administration in healthy volunteers, therefore long term use in patients should be investigated to determine the therapeutic effect.

Conclusion

It can be concluded that Product A and Product B used in these studies are not bioequivalent to Sporal® capsules. Differences in formulation techniques for improving the dissolution of itraconazole may be the reason. This conclusion relates specifically to unchanged itraconazole.

Since itraconazole is extensively metabolited in the liver to the active metabolite, hydroxy-itraconazole, a bioequivalence study of this active metabolite should be performed to determine the overall therapeutic effects. Long term use in patients should also be investigated to determine clinical efficacy.

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