

Single-Dose Pharmacokinetics of Bioadhesive Itraconazole Tablets (Spherazole™) in Healthy Volunteers

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ABSTRACT SUMMARY

Itraconazole bioadhesive tablets (Spherazole™), 100mg, were compared to 100mg Sporanox® capsules in a single dose pharmacokinetic study in 16 healthy volunteers. Spherazole™ tablets demonstrated improved bioavailability and reduced inter-subject variability compared to Sporanox® capsules.

KEYWORDS: itraconazole, bioavailability, pharmacokinetics, bioadhesive polymer, poly[adipic anhydride]

INTRODUCTION

Itraconazole is a synthetic triazole anti-fungal agent with a broad spectrum of activity against *Candida* and other yeasts, dermatophytes and pathogenic fungi and is widely used for the treatment of local and systemic fungal infections. It acts by impairing the synthesis of ergosterol in fungal cell membranes¹.

As per Biopharmaceutics Classification System, itraconazole is classified as a class II drug due to its poor water solubility ($S < 1 \mu\text{g/mL}$) and low bioavailability (~50%). As a consequence, oral absorption is erratic and highly variable². The oral bioavailability of itraconazole is highest when it is taken immediately after a full meal. Peak plasma levels are reached 3 to 4 hours following an oral dose. Elimination from plasma is biphasic with a terminal half-life of 1 to 1.5 days. During chronic administration, steady-state is reached after 1-2 weeks. It may be given at a dose of 100 mg to 400 mg daily for periods of 1 day up to 8 months³.

Itraconazole is extensively metabolised by the liver to a large number of metabolites, including the major active metabolite, Hydroxyitraconazole. Together, the metabolites constitute 40% of the excreted dose³.

Sporanox® capsules (Janssen Pharmaceutica Products LP) consists of 100 mg of itraconazole coated onto sugar non-pareils, overlaid by a gastro-soluble top coat³. Spherazole™ formulation comprises of 100 mg of itraconazole encapsulated within spray-dried bioadhesive polymer, blended with common tableting excipients and compressed into tablets.

The bioadhesive formulation was designed to increase the residence time of the drug particles at the target absorption site for longer duration and thereby improve bioavailability. Spherics' formulation utilized poly (adipic anhydride), p[AA], as a bioadhesive polymer. p[AA] is a surface-eroding polymer belonging to the polyanhydride family of bioerodable and biocompatible polymers.

EXPERIMENTAL METHODS

A single-dose, randomized, two-way crossover study in sixteen healthy volunteers was conducted at the Shandon Clinic, Ireland. Volunteers were dosed either with 100mg Sporanox® capsules or Spherazole™ Tablets 20 minutes after a standard breakfast. A seven day washout period was used between studies. Plasma samples were collected for 120 hours post dose and stored at -20°C until analyzed.

Plasma itraconazole and hydroxyitraconazole levels were determined by liquid chromatography with MS/MS detection (LC-MS/MS). The LC-MS/MS assay was validated over the range of 10ng/mL to 500 ng/mL for both analytes.

For each subject the following pharmacokinetic parameters were calculated: maximum observed concentration (C_{max}), time at which C_{max} was observed (t_{max}), terminal elimination half-life ($t_{1/2}$) and area under the plasma concentration versus time curve (AUC) carried out to 120 hrs (AUC_{0-t}) and extrapolated to infinity ($\text{AUC}_{0-\infty}$).

Pharmacokinetic parameter calculations were conducted using Kinetic 2000® Version 4.2 (Innaphase Clinical Information Engineering). Statistical analyses were performed using SAS® Version 8.1 (SAS® Institute, Cary, N.C., U.S.A.).

RESULTS AND DISCUSSION

Pharmacokinetic results for the Spherazole™ tablets and Sporanox® capsules are shown in Figure 1. Spherics' bioadhesive formulation resulted in greater bioavailability than the Sporanox® capsules both in terms of C_{max} and AUC for both itraconazole (parent compounds) and hydroxyl-itraconazole (active metabolite). Analysis of the log transformed data demonstrated a 17% reduction in C_{max} variability and 37% reduction in AUC variability based on coefficient of variation for Spherazole™ compared to Sporanox® capsules (Figure 2). An improvement in bioavailability and reduced inter-subject variability of itraconazole may be attributable to the bioadhesive polymer, p[AA]. As demonstrated previously, an improvement in bioavailability in rats and pigs was observed for BCS class II drug dicumarol when encapsulated in polyanhydride bioadhesive polymers^{4,5}. Encapsulation of itraconazole in p[AA] spray-dried complex increased its absorption by improving dissolution of the drug via micronization, and increasing residence time through contact of drug/ p[AA] complex with the GI mucosa.

No significant adverse events were reported during the course of the study. The overall evaluation of

laboratory results showed no significant changes or trends between screening and final examination. The vital signs of all the volunteers recorded during the study were satisfactory. Spherazole™ tablet formulation was safe and well tolerated in healthy volunteers at the dose given.

CONCLUSION

A bioadhesive polymer based formulation was developed for a challenging drug like itraconazole. The data showed an improved bioavailability and reduced inter-subject variability compared to the Sporanox® capsules, hence demonstrating the usefulness of Spherics' bioadhesive polymers in the designing of novel dosage forms.

REFERENCES

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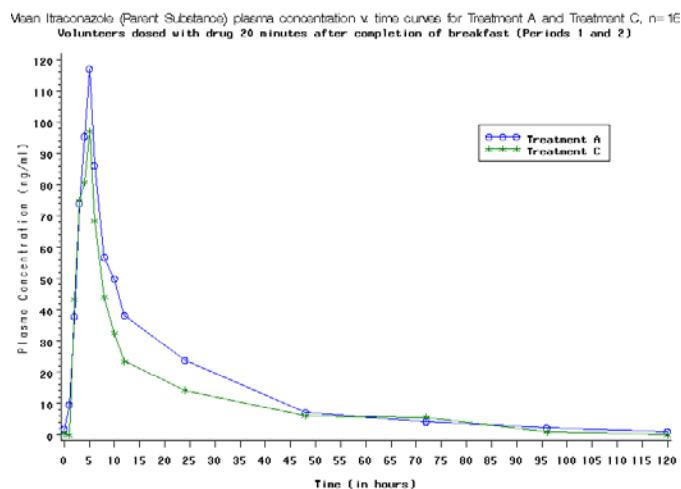


Figure 1. Mean Itraconazole plasma concentration versus time profiles following a single dose of “Treatment A” - 100 mg Spherazole™ Tablet (Spherics Inc., USA) or “Treatment C” - Sporanox® 100 mg Capsule (Janssen Pharmaceutica Products L.P., USA) 20 minutes after completion of breakfast, n=16.

Parameter	Arithmetic Mean ± SD	
	Spherazole™	Sporanox®
C _{max} (ng/mL)*	115.6	100
AUC _{0-∞} (ng/mL.h)*	120.04	100
t _{max} (h)	4.81 ± 2.17	4.75 ± 1.24
t _{1/2} (h)	23.37 ± 19.10	23.01 ± 18.78

* C_{max} and AUC_{0-∞} relative to Sporanox® capsules

Table 1. Summary of pharmacokinetic parameters for Spherazole™ tablets and Sporanox® capsules after testing in the fed state.

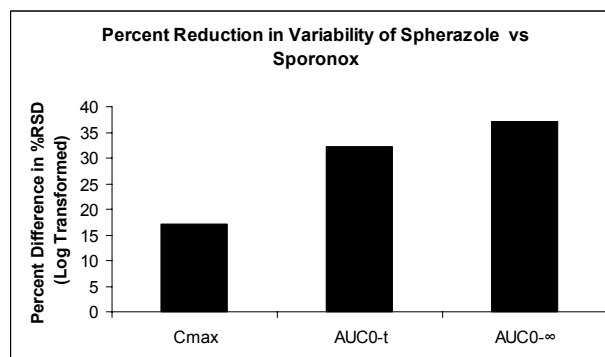


Figure 2. Percent reduction in inter-subject variability in C_{max} and AUC for Spherazole™ compared to Sporanox® capsule