

Gastroretentive, Bioadhesive Drug Delivery System for Controlled Release of Itraconazole: Pharmacokinetics of Spherazole™ CR in Healthy Human Volunteers

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ABSTRACT SUMMARY

The pharmacokinetic profiles of two formulations of Spherazole™ CR and Sporanox® were assessed after a single dose (fed) in volunteers, in order to compare the bioavailabilities of the test and reference formulations. Spherazole™ CR showed enhanced bioavailability, reduced C_{max} and reduced variability compared to the innovator drug.

KEYWORDS: itraconazole, bioavailability, pharmacokinetics, bioadhesive, poly[fumaric-co-sebacic anhydride]

INTRODUCTION

The superior bioadhesive¹ properties of polyanhydride polymers have enabled the design of controlled release delivery systems that are gastroretentive for at least 6-8 hrs in the fed state. Such systems offer important advantages: (1) less prone to gastric emptying resulting in reduced intra- and inter-subject variability in plasma drug levels; (2) effective for delivery of drugs with narrow absorption windows; (3) reduced dosing and increased patient compliance; (4) reduced C_{max} and prolonged drug levels above the minimum effective concentration; (5) improved safety profile for drugs with side-effects associated with high C_{max}.

Itraconazole is a synthetic triazole anti-fungal agent with a broad spectrum of activity against *Candida* and other yeasts, dermatophytes and pathogenic fungi. It acts by impairing the synthesis of ergosterol in fungal cell membranes. It is used in the treatment of vulvovaginal candidosis, pityriasis versicolor, dermatophytoses caused by susceptible organisms, oral candidosis, fungal keratitis, systemic mycoses and onychomycosis².

Itraconazole is a Biopharmaceutical Class 2 Drug with poor water solubility and low bioavailability (~50%). The drug is soluble only at acidic pH (pK_a 2), limiting absorption in GIT to duodenum and jejunum. The oral bioavailability of itraconazole is greatest when it is taken immediately after a full meal. Itraconazole has extremely variable and erratic absorption, limiting the usefulness of the drug. Peak plasma levels are reached 3 to 4 hours following an oral dose¹. 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 weeks². It may be given at a dose of 100 mg to 400 mg daily for periods of 1 day up to 8 months².

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 dose².

Sporanox® capsule (Janssen) consists of 100 mg of itraconazole coated onto sugar non-pareils, overlaid by a gastrosoluble, hydroxypropylmethylcellulose (HPMC) top coat².

The composition of Spherazole CR Tablet 100 mg, Type A is given in Table 1. Spherazole™ CR consists of 100 mg of itraconazole layered onto microcrystalline cellulose, NF with Eudragit E100 (Rohm America) as a binder. The granulation is then blended with spray-dried lactose, hypromellose and magnesium stearate to formulate an inner-core blend with controlled-release properties. A bioadhesive layer blend is prepared by mixing bioadhesive, poly[fumaric-co-sebacic]anhydride 20:80 (p[FA:SA] 20:80) with Eudragit RS PO and citric acid. The inner core blend is sandwiched between outer bioadhesive layer blends and directly compressed to create a bioadhesive, trilayer tablet. Formulations A and B differed in levels of rate-controlling excipients resulting in different dissolution rates in simulated gastric fluid.

Spherazole™ CR formulation is engineered to reside in the stomach for greater than 6 hrs in the fed state and release itraconazole downstream to duodenum and upper jejunum, the main absorptive sites, in a controlled manner.

EXPERIMENTAL METHODS

The clinical study was designed as a three-way, randomized crossover study. Eight healthy volunteers were dosed with 100 mg of itraconazole in the form of either Sporanox® or Spherazole™ CR, Types A and B following a light breakfast. 1 mL blood samples were collected at the following times post-dosing: 0, 1,2,3,4,5,6,8,10,12, 24,48,72,96 and 120 hrs. Plasma was collected after centrifugation for 10 min at 3,000 rpm at 4°C. Samples were stored frozen at -20°C until analyzed.

Plasma itraconazole and hydroxyitraconazole levels were determined by LC/MS/MS. Turbulent flow chromatography using a 2300 HTLCTM system (Cohesive Technologies, Franklin, MA) was coupled to tandem-mass spectrometry (MS/MS) performed on a triple stage quadrupole from Perkin Elmer SCIEX API 365 (Sciex, Concord, Ontario, Canada) with an atmospheric pressure ionization (API) chamber. The limit of detection of itraconazole and hydroxyitraconazole in human plasma was 20 ng/mL.

For each volunteer, the following pharmacokinetic parameters were calculated for the parent drug, itraconazole and the active metabolite,

hydroxyitraconazole: maximum observed concentration (C_{max}), time at which C_{max} was observed (t_{max}), and area under the plasma concentration versus time curve (AUC) carried out to 120 hrs (AUC_{0-t}).

RESULTS AND DISCUSSION

In previous beagle studies³, Spherazole™ CR tablets resided in the stomach for a minimum of 6-8 hrs and had equivalent or superior AUC with reduced variability compared to Sporanox®.

In the current study, formulations of Spherazole™ CR with different release rates, Type A and B, were compared to the immediate release product, Sporanox®. Clearly the AUC for the Spherazole™ CR type A and B formulations were superior to the Sporanox® reference product (Fig 1). For both Type A and B there was an 18% improvement in AUC compared to Sporanox®. C_{max} was greatly reduced for the CR products, which is an important advantage because of the C_{max} related side-effects associated with Sporanox®. T_{max} of the CR formulations was elongated compared to Sporanox®, which is typical of CR formulations and indicative of gastroretention.

The bioadhesive CR versions had considerably reduced variability in C_{max} and AUC compared to the reference product (Fig. 2). CR formulation Type A had a 48% reduction in variability for C_{max} and 35% reduction in variability for AUC_{0-t} compared to Sporanox®. Similarly, CR Type B had a 12.2% reduction in variability for C_{max} and 27% reduction in variability for AUC_{0-t} compared to Sporanox®. Reduction in variability is an important endpoint in product development for a controlled release version of itraconazole, because the reference drug is known to have wide intersubject variability⁴.

CONCLUSION

Trilayer tablets with outer layers composed of bioadhesive, polyanhydride polymers were previously shown to be gastroretentive for at least 6-8 hrs in the fed state in beagle dogs. In humans, the dosage form resisted gastric emptying resulting in reduced variability in AUC and C_{max} compared to Sporanox®. Spherazole™ CR Types A and B had superior AUC to Sporanox® and reduced C_{max}, offering important safety advantages for use of itraconazole, a drug with C_{max}-related side effects.

REFERENCES

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Ingredient	% w/w
Itraconazole, BP	8.4
Emcocel 90 M, NF	8.4
Eudragit E100	8.4
Lactose Fast Flo 316 Spray Dried, NF	8.3
Methocel Premium LV E5, NF	18.3
Hypromellose 2208, 100 cps, NF	6.1
p[FA:SA] 20:80	29.9
Eudragit RS PO	9.6
Citric Acid, anhydrous, USP	2.1
Magnesium Stearate, NF	0.6
Total	100.0

Table 1. Composition of Spherazole CR Tablets, 100 mg Type A.

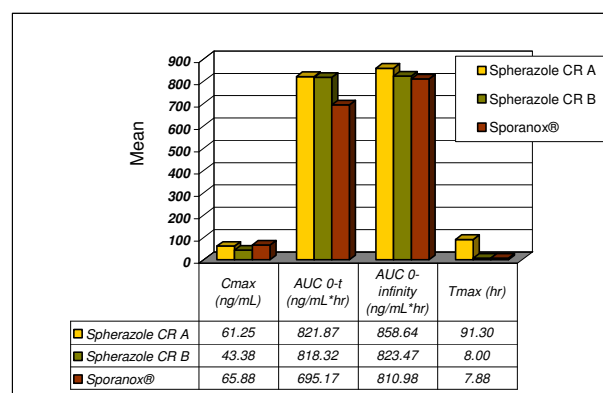


Figure 1. Pharmacokinetic parameters for Spherazole CR Types A and B, 100 mg, compared to Sporanox®.

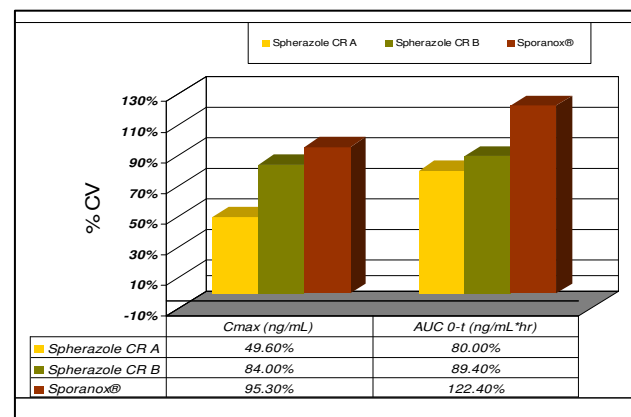


Figure 2. Calculation of % Coefficient of Variation (%CV) of C_{max} and AUC_{0-t} for Spherazole CR Types A and B, 100 mg, compared to Sporanox®.