SPORANOX® (itraconazole) Capsules/Oral Solution
SPORANOX - Bioavailability - Effect of Food

SUMMARY

- Differences exist between the bioavailability of itraconazole (ICZ) oral capsules and ICZ oral solution.
  - The observed absolute oral bioavailability of ICZ capsules is about 55% and is maximal when the capsules are taken immediately after a full meal.[1]
  - The observed absolute oral bioavailability of ICZ oral solution under fed conditions is about 55% and increases by 30% when taken in fasting conditions.[2]
- SPORANOX Capsules Taken with Food
  - Relative to the median bioavailability of ICZ after a full meal, the median bioavailability (90% confidence interval) of ICZ was 54% (41-77%) in a fasted state and 86% (65-102%) after a light meal.[3]
  - After administration of SPORANOX in the fed state, maximum plasma concentration (C_{max}) and area under the curve (AUC) from 0 to 24 hours post-dose were higher than those in the fasted state.[4]
  - The consumption of a rice meal before the administration of ICZ caused a significant decrease in bioavailability, whereas consumption of a bread meal increased bioavailability.[5]
- Exposure of SPORANOX Capsules versus Oral Solution
  - The bioavailabilities of ICZ and hydroxy-ICZ (OH-ICZ) were 30-33% and 35-37% greater, respectively, when administered as a liquid formulation than via a capsule.[6]
- SPORANOX Oral Solution Taken in Fasted Conditions
  - The bioavailability of SPORANOX oral solution was found to be 30-43% higher when taken in fasted conditions in comparison to fed conditions.[7,8]

PUBLISHED LITERATURE

ICZ Capsules Taken with Food

Single-Dose Randomized Three-Way Crossover Study[3]

The effect of food intake on the pharmacokinetics of SPORANOX was evaluated in healthy Japanese participants (n=12 received SPORANOX). Participants were administered 100 mg SPORANOX capsules after 12 hours of fasting, within 5 minutes of finishing a light meal (estimated calorific value of 1000 kJ), or within 5 minutes of finishing a full meal (estimated calorific value of 3600 kJ), separated by a two-week washout phase. Blood samples were obtained at regular intervals through 96 hours post administration.

- The absorption of SPORANOX was impacted by stomach Ph, gastric retention time, and the fat content of meals.
- The plasma AUC and C_{max} of ICZ were significantly different between the fasting state and two fed conditions.
  - Relative to the median bioavailability of ICZ after a full meal, the median bioavailability (90% confidence interval) of ICZ was 54% (41-77%) in a fasted state and 86% (65-102%) after a light meal.
- The time to C_{max} (T_{max}) was nominally higher after consumption of a full meal.
- Inter-individual variation for SPORANOX was high; a 20-fold difference (10.3-223 ng/mL) in pre-prandial C_{max} of ICZ was observed between participants.

Open Label Study in Healthy Adult Korean Male Participants[4]

Eight participants were administered 100 mg SPORANOX in capsule formulation after either fasting overnight or eating a high-fat breakfast (total caloric value: 800-1000 cal). The two

conditions were separated by a two-week washout period. Blood samples were collected at regular intervals for 24 hours after dosing. Administration of SPORANOX in the fed state resulted in AUC_{0-24} and C_{max} values that were 2.0-fold ($P<0.05$) and 1.9-fold ($P<0.05$) higher than those in the fasted state, respectively.

Retrospective Analysis of Four Pharmacokinetic Studies[5]

The relationship between the bioavailability of SPORANOX and the type of food consumed (bread meal versus rice meal), and the effects of food consumption on the pharmacokinetics of SPORANOX following a single 100 mg oral capsule dose were evaluated in 144 healthy Korean participants. The plasma itraconazole concentration in the fasted state was measured in 144 healthy volunteers, and the plasma concentration following bread or rice meals was measured in 40 or 44 of these volunteers, respectively.

- The AUC_{∞}, C_{max}, and T_{max} in the fed state were significantly different from those in the fasted condition ($P<0.01$).
  - The bioavailability of ICZ was reduced after the rice meal compared with the fasted state.
    - AUC_{∞} and C_{max} decreased by 75.8% and 56.8%, respectively.
  - The bioavailability of ICZ was greater after the bread meal compared with the fasted state.
    - AUC_{∞} increased by 64.5% and C_{max} increased by 63.2%.
  - A significant delay in T_{max} was observed in the fed versus the fasted state ($P<0.01$); however, T_{max} was not significantly different between the bread and the rice meals.

Exposure of SPORANOX Capsules versus Oral Solution

Open-Label, Single-Dose, Crossover Study[6]

The bioavailability of a single dose of 200 mg SPORANOX administered as either a capsule (two bioequivalent capsule formulations; F05 and F12) or a liquid was evaluated in 30 healthy participants. Participants received a standard breakfast immediately before receiving the study drug. Each treatment was followed by a 2-week washout period. Blood samples were obtained before the dose and at regular intervals for 96 hours post-dose.

Pharmacokinetic results are presented in Table: Pharmacokinetics of Liquid SPORANOX versus Capsule Formulations F05 and F12.

Pharmacokinetics of Liquid SPORANOX versus Capsule Formulations F05 and F12[6]

SPORANOX formulation	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-96} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)
ICZ					
Capsule (F05)	314.7	5.0	22.0	4247.5	4475.8
Capsule (F12)	301.9	4.9	22.9	4183.4	4441.3
Liquid	306.4	5.0	22.1	5550.2	5838.0
OH-ICZ					
Capsule (F05)	501.0	5.5	10.3	10847.8	10937.8
Capsule (F12)	504.3	5.3	10.7	11033.3	11148.1
Liquid	527.0	5.7	10.7	14889.3	15025.5

Abbreviations: C_{max}, the maximum concentration of the drug in plasma; T_{max}, the time to C_{max}; $t_{1/2}$, the terminal half-life; AUC_{0-96}, the area under the plasma concentration-time curve from 0 to 96 h post-dose; $AUC_{0-\infty}$, the area under the plasma concentration-time curve from 0 to ∞; ICZ, itraconazole; OH-ICZ, hydroxy-itraconazole; h, hours.
Note: Numbers are presented as least square means.

- C_{max}, T_{max}, and terminal half-life ($t_{1/2}$) for ICZ were comparable for both capsule formulations (F05 and F12) and the liquid formulation of SPORANOX.
- The bioavailabilities of ICZ and OH-ICZ were 30-33% and 35-37% greater, respectively, when administered as a liquid formulation than via a capsule (F05 and F12).

SPORANOX Oral Solution Taken in Fasting Conditions

Open-Label, Randomized, Crossover Study[8]

The pharmacokinetics of SPORANOX oral solution under fasted and fed conditions were evaluated in healthy male participants (N=30) who were randomly assigned to one of two treatment sequences: fasted-fed or fed-fasted. Participants were either fasted or fed a standard breakfast before receiving SPORANOX oral solution 200 mg/day for 15 days, followed by a 4-week washout period before the crossover phase. Blood samples were taken before the dose and at standard intervals over 24 hours. Trough samples were collected before SPORANOX dosing on days 4, 7, 12, 13, and 14. Samples were tested for ICZ and OH-ICZ. Three participants discontinued the study and were not included in the pharmacokinetic analyses.

- When single-dose SPORANOX was administered under fasted conditions, the mean bioavailabilities of ICZ and OH-ICZ were 43% and 38% higher, respectively, than when SPORANOX was administered under fed conditions.
- Steady state was achieved by day 14 with multiple dosing.
  - The bioavailabilities of ICZ and OH-ICZ were 29% and 17% higher, respectively, in the fasted state compared with the fed state.
- The $t_{1/2}$ values were similar under both fasted and fed conditions:
  - ICZ: 39.8 hours in the fasted state versus 37.5 hours in the fed state,
  - OH-ICZ: 27.3 hours in the fasted state versus 26.2 hours in the fed state.

A Randomized, Open-Label, Two-Way Crossover Study[7]

The pharmacokinetics of a single 100 mg oral dose of SPORANOX, administered as 10 mL of a 10 mg/mL SPORANOX solution, was evaluated under fasting and fed conditions in 12 healthy participants. Blood samples were taken before the dose and at standard intervals over 96 hours after each dose.

- Mean (±standard deviation) peak plasma concentrations of ICZ and OH-ICZ were significantly higher under fasting conditions than under fed conditions. The mean T_{max} was significantly shorter under fasting conditions (1.5 hours) compared to fed conditions (4 hours).
  - ICZ:
    - Fasting:
      - 83.4 ± 78.1 ng/mL at 0.5 hour
      - 345 ± 242 ng/mL at 1.5 hours (peak)
      - 5.1 ± 8.3 ng/mL at 96 hours
    - Fed:
      - 20.9 ± 13.3 ng/mL at 0.5 hour
      - 137 ± 71 ng/mL at 4 hours (peak)
      - 4.5 ± 7.5 ng/mL at 96 hours

- OH-ICZ:
  - Fasting:
    - 72 ± 52 ng/mL at 0.5 hour
    - 411 ± 150 ng/mL at 2 hours (peak)
    - Undetectable starting at 56 hours.
  - Fed:
    - 30 ± 19 ng/mL at 0.5 hour
    - 238 ± 72 ng/mL at 4 hours (peak)
    - Below the limit of detection (10 ng/mL) starting at 48 hours.

- The relative bioavailability of SPORANOX oral solution was 30% higher when administered under fasted conditions than when administered under fed conditions.
- The mean (±standard deviation) AUCs (0-∞) of ICZ and OH-ICZ were significantly higher under fasting conditions than under fed conditions.
  - ICZ: 3716 ± 2711 ng/hr/mL under fasting conditions versus 2861 ± 1914 ng/hr/mL under fed conditions (*P*=0.026).
  - OH-ICZ: 8007 ± 5185 ng/hr/mL under fasting conditions versus 6132 ± 4448 ng/hr/mL under fed conditions (*P*=0.005).
- The mean C_{max} of ICZ was 349 ± 239 ng/mL under fasting conditions and 147 ± 74 ng/mL under fed conditions (*P*=0.006).
- The mean terminal $t_{1/2}$ of ICZ was similar under fasted (24.7 ± 9.8 hours) and fed (25.9 ± 11.0 hours) conditions.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 14 February 2024.

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