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Supersaturation and Precipitation of Posaconazole Upon Entry in the Upper Small Intestine in Humans

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ABSTRACT

The purpose of this study was to explore gastrointestinal dissolution, supersaturation and precipitation of the weakly basic drug posaconazole in humans, and to assess the impact of formulation pH and type on these processes. In a cross-over study, two posaconazole suspensions (40 mg dispersed in 240 mL water at pH 1.6 and pH 7.1, respectively) were intragastrically administered; subsequently, gastric and duodenal fluids were aspirated. In parallel, blood samples were collected. Additionally, posaconazole was intragastrically administered as a solution (20 mg in 240 mL water, pH 1.6). When posaconazole was administered as an acidified suspension, supersaturated duodenal concentrations of posaconazole were observed for approximately 45 min. However, extensive intestinal precipitation was observed. Administration of the neutral suspension resulted in subsaturated concentrations with a mean duodenal $AUC_{0\text{-}120\ min}$ and C_{max} being approximately twofold lower than for the acidified suspension. The mean plasma $AUC_{0\text{-}8\ h}$ of posaconazole was also twofold higher following administration of the acidified suspension. Similar to the acidified suspension, significant intestinal precipitation (up to 92%) was observed following intragastric administration of the posaconazole solution. This study demonstrated for the first time the gastrointestinal behavior of a weakly basic drug administered in different conditions, and its impact on systemic exposure.

Introduction

Exploring gastrointestinal drug and formulation behavior and its eventual effect on drug absorption is extremely challenging in terms of various simultaneously ongoing processes, including dissolution, degradation, precipitation, and permeation. Understanding these processes is very important in order to improve the value of predictive *in vitro* biopharmaceutical tools, or to define relevant input parameters for physiologically based pharmacokinetic modeling. In the present study, we specifically focused on the characterization of intestinal precipitation of a poorly soluble weak base by comparing the intraluminal behavior of a drug solution versus 2 drug suspensions in humans.

Posaconazole was selected as basic model compound. For almost 10 years, posaconazole is registered as one of the most potent triazole antifungal agents. Its antifungal activity against *Zygomyces* spp. has been reported to be more pronounced *in vitro* compared with itraconazole.[1] Moreover, by inhibiting the fungal cytochrome P450-dependent enzyme 14α-demethylase, its antimycotic activity can be expanded to other fungi, including *Aspergillus* spp. as such, *Blastomyces* spp., *Coccidiomyces* spp., *Candida* spp., *Fusarium* spp., *Histoplasma* spp., and *Cryptococcus* spp.[2-7] With respect to *in vivo* disposition of posaconazole, several reports indicate extensive distribution in the body after oral intake of the marketed suspension Noxafil® (40 mg/mL), resulting in 40-fold higher tissue levels compared with serum levels.[8,9]

Complete recovery from invasive fungal infections depends on the extent of intestinal absorption of posaconazole. In fasting conditions, fluctuations in systemic exposure after oral administration have warranted therapeutic drug monitoring in immunocompetent patients.[10,11] Characterized by a low aqueous solubility but high intestinal permeability, posaconazole (molecular weight = 700.78 g/mol; cLog *P* 4.6) can be classified as a BCS 2 compound.[12,13]

This work is dedicated to the memory of my father, Patrick Hens (1957-2015), and to the memory of Dr. Marcus Brewster (1957-2014).

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Although no specific solubilization technology is being used for the suspension, relatively high gastric posaconazole concentrations are achieved after oral administration because of its weakly basic properties (p*Ka* 3.6 and 4.6) and the acidic environment of the stomach in fasting conditions (pH 1–2). Simulating different intragastric scenarios, literature data clearly indicate that higher gastric concentrations of posaconazole are accompanied by higher systemic exposure.[14-16] Therefore, inter-subject variability in systemic exposure may be attributed to differences in gastric residence time and alternating gastric pH levels between patients, whether or not related to a disease condition or the use of other medication. For instance, coadministration of drugs that reduce acid production (e.g., proton pump inhibitors or H_2-antagonists) resulted in lower systemic exposure of posaconazole because of the elevated pH in the stomach. On the contrary, coadministration of Coca Cola® prolonged gastric residence time, resulting in higher gastric concentrations and improved systemic exposure.[15,16] Despite the beneficial effect of Coca Cola®, however, the oral bioavailability of posaconazole remains limited in fasting conditions.

In view of the fact that absorption takes place in the small intestine, it is obvious that the positive correlation between gastric concentrations and systemic disposition has to be linked to processes taking place upon transfer to the small intestine. One of the possibilities that has been intensively discussed in literature is the creation of supersaturation upon entry in the small intestine, possibly resulting in enhanced drug flux across the intestinal mucosa.[17,18] In general, weakly basic compounds are able to supersaturate in intestinal fluids after gastrointestinal transfer, based on a solubility gradient between stomach (higher solubility) and small intestine (lower solubility). Although supersaturation creates promising perspectives, precipitation of the drug reducing the concentration to its solubility is unavoidable from a thermodynamic point of view.[19,20] Precipitation kinetics, however, may significantly vary depending on physiological variables (e.g., pancreatic and bile secretions, gastrointestinal transfer, hydrodynamics) and physicochemical drug properties (e.g., p*Ka*, solubility, molecular structure). Regarding the fact that low intestinal concentrations were measured after oral administration of the Noxafil® suspension in humans, it was hypothesized that extensive and immediate posaconazole precipitation following gastrointestinal transfer may limit posaconazole absorption.[21]

Although supersaturation/precipitation has been explored intensively *in vitro*, *in vivo* data are rather scarce. Hence, the aim of this study was to investigate the gastrointestinal interplay between dissolution, supersaturation, and precipitation of posaconazole as such in humans. In particular, we evaluated the impact of formulation pH (acidified versus neutral) and formulation type (solution versus suspension) on these processes. To this end, intraluminal concentrations in stomach and duodenum were measured as a function of time following intragastric administration of (i) a neutral suspension of 40 mg posaconazole dispersed at pH 7.1, (ii) an acidified suspension of 40 mg posaconazole dispersed at pH 1.6, and (iii) an acidified solution of 20 mg posaconazole dissolved at pH 1.6. In case of the suspensions, blood samples were collected in parallel in order to study the impact of duodenal supersaturation and precipitation on systemic exposure.

Materials and Methods

Chemicals

Posaconazole was kindly donated by the Chemical Research Division of MSD (Whitehouse Station, New Jersey), whereas itraconazole as such was kindly provided by Janssen Research Foundation (Beerse, Belgium). The marketed suspension of posaconazole, Noxafil® (40 mg/mL), was purchased from the University Hospitals Leuven (Leuven, Belgium). Dimethyl sulfoxide (DMSO) and methanol (MeOH) were received from Acros Organics (Geel, Belgium), whereas BHD Laboratory Supplies (Poole, UK) supplied HCl and NaOH. Acetonitrile and diethylether were purchased from Fisher Scientific (Leicestershire, UK). Sodium acetate and acetic acid were purchased from VWR (Leuven, Belgium). Water was purified using a Maxima system (Elga Ltd., High Wycombe Bucks, UK).

Clinical Study

A cross-over study with two experimental conditions (involving blood sampling) was performed in five healthy volunteers (HVs; three women and two men, aged between 23 and 25 years). Exclusion criteria were checked during a medical examination and included gastrointestinal disorders, infection with hepatitis B, hepatitis C or HIV, use of medication, pregnancy and frequent X-ray exposure. All volunteers provided informed consent to participate in the clinical study. Following the tenets of the Declaration of Helsinki, the clinical study was approved by the Committee of Medical Ethics of the University Hospitals Leuven (ethical approval number ML9945), and the Federal Agency of Health and Medicines (reference number 63285). The study has been saved in the European Clinical Trials Database (EudraCT) with reference number 2013–002836–26. After an overnight fasting period of at least 12 h, volunteers were asked to come to the hospital. A double-lumen polyvinyl catheter (Argyle Salem Sump Tube, 14 Ch [external diameter 4.7 mm]; Sherwood Medical, Tullamore, Ireland) was introduced via the mouth/nose and positioned in the duodenum (D2/D3) of the small intestine. Subsequently, a second double-lumen polyvinyl catheter was positioned in the antrum of the stomach (i.e., lowest part of the stomach). Finally, in order to administer the suspensions of posaconazole intragastrically, a single-lumen polyurethane catheter (Enteral Feeding Tube Wide Bore, 10FR, 100 cm length; Eurosteriel Medical, Dronten, the Netherlands) was positioned in the body of the stomach (i.e., central part of the stomach). Positioning was checked by fluoroscopy (Fig. 1). During the entire experiment, volunteers were sitting in an upright position.

Posaconazole was administered intragastrically as 2 different suspensions:

- an acidified suspension of 40 mg posaconazole at pH 1.6;
- a neutral suspension of 40 mg posaconazole at pH 7.1.

For the acidified suspension, 1 mL of Noxafil® (40 mg posaconazole as such, which corresponds to 10% of the typical therapeutic dose) was dispersed in 240 mL of tap water acidified to pH 1.6 with HCl (70% of posaconazole in solution). For the neutral suspension, 1 mL of Noxafil® (40 mg posaconazole) was dispersed in 240 mL of tap water (pH 7.1; 2.3% of posaconazole in solution).

After intragastric administration, antral and duodenal fluids were aspirated for 3 h; samples were taken at 2, 7, 15, 25, 35, 45, 55, and 60 min during the first hour and every 15 min for the next 2 h. The sampling volume was kept as small as possible (<4 mL per time point). Immediately after aspiration of fluids, pH was measured (Hamilton Knick Portamess®, Bonaduz, Switzerland) and the determination of dissolved and total posaconazole was initiated (see below). Blood samples were collected in heparinized tubes (BD Vacutainer systems, Plymouth, UK) at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, and 24 h after intragastric administration. Blood samples were centrifuged (2880*g*, 10 min, 4°C) and the obtained plasma was stored at −26°C until analysis (see below).

In an additional condition (no blood sampling involved), posaconazole as such was intragastrically administered as a solution in