Precipitation of Posaconazole upon Entry in the Upper Small Intestine in Man
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**Purpose**
The purpose of this study was to explore dissolution, supersaturation and precipitation of the weakly basic drug posaconazole (cLogP 4.6; pKa 3.6 and 4.6) in humans, following intragastric administration of posaconazole in tap water at pH 1.6 and 7.

**Methods**
In a cross-over study, posaconazole (40 mg) was dispersed in tap water (i) at pH 1.6 and (ii) 7 and intragastrically administered to five healthy volunteers; subsequently, gastric and duodenal fluids were aspirated in parallel with the collection of blood samples. Besides dissolved concentrations, solubility and total concentrations of posaconazole were determined in all aspirates, enabling the assessment of supersaturation and precipitation.

**Results**
Following administration of the posaconazole at pH 1.6, significant intestinal precipitation (up to 85%) was observed in the duodenal aspirates. Still, limited but metastable intestinal posaconazole supersaturation was maintained for about 45 min. Mean duodenal concentrations (AUC0-120 min and Cmax) were approximately two-fold lower for the condition at pH 7. As a result, the mean systemic exposure to posaconazole (plasma AUC0-8h) was also two-fold higher following administration at pH 1.6 versus pH 7.

**Conclusion**
For the first time, precipitation of a weakly basic drug in humans was investigated in parallel with the impact on its systemic exposure. The results demonstrated that significant precipitation may occur for weakly basic drugs upon entry in the human small intestine. Still, limited but metastable intestinal supersaturation may suffice to enhance the oral bioavailability.