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The Effect of Food on the Intraluminal Behavior of Abiraterone Acetate in Man

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ABSTRACT

To relate the reported positive effect of food on the oral bioavailability of abiraterone to the intraluminal behavior of abiraterone acetate, an *in vivo* experiment was performed, in which duodenal fluids and plasma samples were collected from healthy volunteers after the administration of abiraterone acetate in fasted and postprandial conditions. The plasma concentration-time profiles confirmed the positive food effect. Nevertheless, intraduodenal concentrations of abiraterone acetate and abiraterone did not fully reflect this observation. This apparent discrepancy was explored by performing several *in vitro* experiments including solubility, dissolution, and transfer studies. Gastrointestinal transfer studies illustrated a positive impact of gastric processing of the abiraterone acetate formulation on the duodenal concentrations in the fasted state, which could not be observed in the postprandial condition. As the influence of gastric dissolution on the intraluminal concentrations in the small intestine declines aborally, it is most likely the superior solubility of abiraterone acetate and abiraterone in intestinal fluids of the fed state which dictates the food effect. Furthermore, N-oxide abiraterone sulfate and abiraterone sulfate appeared in the duodenum at significantly later time points than abiraterone, suggesting biliary excretion of these abiraterone metabolites; this was confirmed by *in situ* biliary excretion experiments in rats.

Introduction

It has been shown that the oral bioavailability of drugs can be modified when coadministered with food.[1,2] Several mechanisms have been described by which food can influence the intestinal absorption of a compound including an increased solubility, a delayed gastric emptying, as well as an increase in the intestinal stability of the compound.[3-6] The influence of food on the bioavailability of different ester prodrugs has been demonstrated in several studies.[7-9] Premature chemical or enzymatic hydrolysis in the intestine can indeed jeopardize the intended increased absorption of the ester.[10,11]

Abiraterone is commercialized as abiraterone acetate (Zytiga®, Janssen-Cilag International NV) and exhibits a low solubility and low permeability, resulting in limited oral bioavailability of abiraterone[12] (Fig. 1).

Abiraterone is a CYP17 inhibitor which is used for the treatment of metastatic castration-resistant prostate cancer.[13] The oral bioavailability of abiraterone is significantly increased when abiraterone acetate is taken in the fed state.[14] Despite this positive food effect, the Zytiga® leaflet states that abiraterone acetate should be taken on an empty stomach which is in keeping with the rationale of preventing excessive variability in plasma exposure. Using a unique sampling technique in which intraluminal fluids can be collected after the administration of a drug, Stappaerts et al. have recently investigated the fasted-state intraluminal behavior of abiraterone acetate in more detail and demonstrated that abiraterone acetate is rapidly hydrolyzed to abiraterone in human intestinal fluids of the fasted state, resulting in intraluminal supersaturation of abiraterone.[1,6,15] These supersaturated concentrations of abiraterone were shown to be a strong driving force for its intestinal absorption.[16] Nevertheless, mass balance studies report that large proportions of the administered dose were

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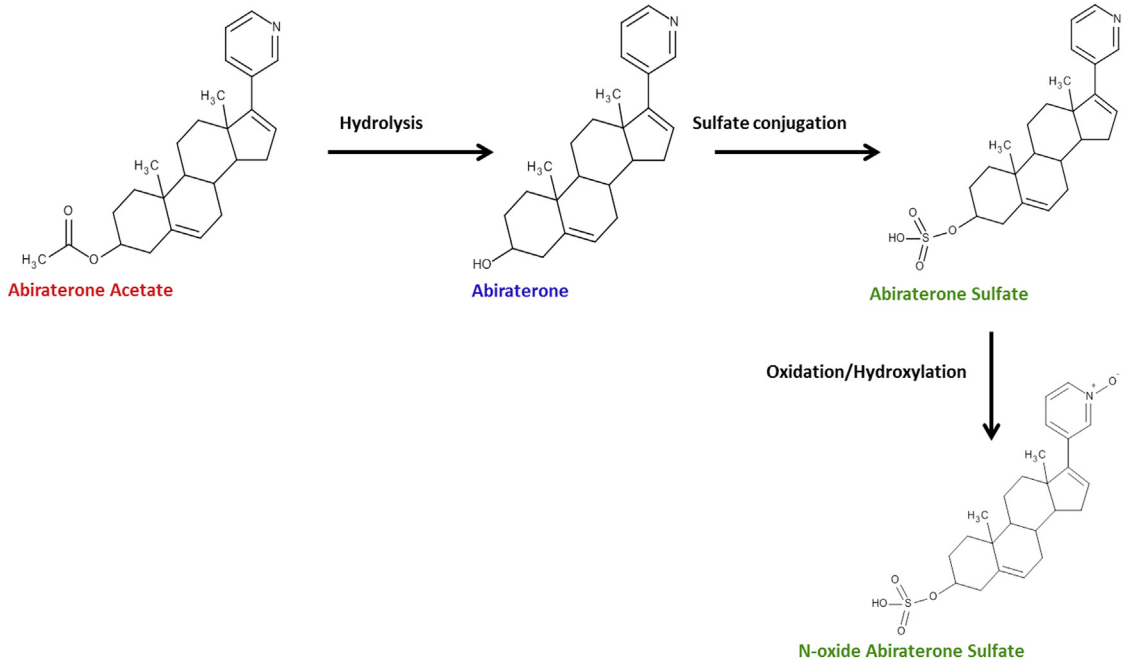

Figure 1. The major metabolic pathways of abiraterone acetate.

detected as abiraterone acetate (50%) and abiraterone (22%) in the feces suggesting incomplete uptake of both compounds. Whereas the excreted abiraterone acetate represents unabsorbed prodrug, the detected abiraterone can originate from hydrolyzed abiraterone acetate or from biliary excreted metabolites that were subsequently hydrolyzed in more distal parts of the intestine.[17,18] The 2 major circulating metabolites detected on the oral administration of abiraterone acetate are N-oxide abiraterone sulfate and abiraterone sulfate (Fig. 1).

The aim of this research was to further expand our knowledge on the intraluminal behavior of abiraterone acetate by studying its behavior in fasted- and fed-state conditions. To reach this goal, a clinical trial was performed in which intestinal fluids were collected after the administration of 1 tablet of Zytiga® (abiraterone acetate, 250 mg) in both fasted- and fed-state conditions. In parallel, blood samples were collected to be able to relate the observed intestinal behavior to the systemic exposure of abiraterone.

Materials and Methods

Chemicals

Abiraterone, abiraterone acetate, their deuterated counter parts abiraterone-d4, abiraterone acetate-d4, N-oxide abiraterone sulfate, and abiraterone sulfate were kindly provided by Janssen Research & Development (Beerse, Belgium). Sigma Aldrich (St. Louis, MO) supplied pancreatin from porcine pancreas (powder, suitable for cell culture, 4× USP specifications). Methanol and ethanol absolute were purchased from VWR International (Leuven, Belgium). Acetonitrile and dimethyl sulfoxide were obtained from Acros-Organics (Geel, Belgium). Acetic acid was obtained from Chem-lab (Zedelgem, Belgium). Water was purified with a Maxima system (Elga Ltd., High Wycombe Bucks, UK). Methyl-tert-butyl ether was purchased from Merck (Overijse, Belgium). Ketamine (Anesketin) and xylazin (Xyl-M 2%) were obtained from Eurovet (Heusden, Belgium) and VMD (Arendonk, Belgium), respectively. Hanks' Balanced Salt Solution and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid were obtained from Lonza (Verviers, Belgium). For the measurements of the pH, a Portamess 911 pH-meter (Knick GmbH & Company, Berlin, Germany) was used. All stock solutions were prepared in dimethyl sulfoxide.

Media

Fasted- and fed-state simulated gastrointestinal fluids were developed to obtain media that are more relevant for the human gastrointestinal fluids than the formerly used plain aqueous buffers.[19,20] Fasted- (FaSSIF) and fed (FeSSIF)-state simulated intestinal fluids and fasted-state simulated gastric fluids (FaSSGF) were made according to the manufacturer's preparation protocol (Biorelevant®, Croydon, UK). FaSSIF was prepared by dissolving SIF powder (2.24 mg/mL) in a phosphate buffer (pH 6.5). For the 2-stage dissolution experiment, the pH of FaSSIF was adjusted to pH 7.5 to obtain a final pH of 6.5 after the addition of FaSSGF. FeSSIF was prepared by dissolving SIF powder (11.2 mg/mL) in an acetate buffer (pH 5.0). FaSSGF was made by dissolving SIF powder (0.06 mg/mL) in a HCl/NaCl solution (pH 1.6). Fed-state simulated gastric fluids (FeSSGF) were made by mixing FaSSGF with the nutritional drink Ensure Plus Vanilla® (Abbott Laboratories B.V., Zwolle, the Netherlands) (50:50 v/v). The pH of FeSSGF was 6.0. The pH of FeSSIF was not adjusted for the 2-stage dissolution experiment because the pH of FeSSIF on addition of FeSSGF was 5.5.[21]

The fasted- (FaHIF) and fed (FeHIF)-state human intestinal fluids used in the stability and solubility studies were aspirated from 13 healthy volunteers (8 men and 5 women) aged between 23 and 27 years. The study was approved by the Committee of Medical Ethics of the University Hospitals Leuven, Belgium, and the procedure followed the tenets of the Declaration of Helsinki (S53791). After an overnight fast (12 h), human intestinal fluids were collected from the duodenum with a double-lumen polyvinyl catheter (Salem Sump Tube 14 Ch [external diameter 4.7 mm], Sherwood Medical, Petit Rechain, Belgium). The catheter was introduced via the nose and positioned between section D2 and D3 of the duodenum. D2 is the descending part of the duodenum in which the pancreatic duct