Pharmacokinetics of Biochemically Active Steroidal Metabolites of Abiraterone in Healthy Volunteers

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Background: Abiraterone is a steroidal CYP17A1 inhibitor that is FDA-approved in combination with prednisone for the treatment of castration-resistant prostate cancer (CRPC). Recently, abiraterone was shown to increase survival when given to patients with castration-sensitive prostate cancer. Abiraterone is partially metabolized by steroidogenic enzymes to the more potent analog, D4A, which more effectively inhibits steroidogenic enzymes and antagonizes the androgen receptor (AR) directly. D4A may therefore contribute to the overall clinical efficacy of abiraterone. The structure of D4A allows further metabolism by steroidogenic enzymes. Six metabolites are generated from D4A metabolism: 3-keto-5α-Abi, 3α-OH-5α-Abi, 3β-OH-5α-Abi, 3-keto-5β-Abi, 3α-OH-5β-Abi and 3β-OH-5β-Abi. 3-keto-5α-Abi is an AR agonist and promotes tumor progression. Similar to abiraterone, galeterone is also metabolized by steroidogenic enzymes, suggesting that metabolism by steroidogenic enzymes is a common attribute that defines a class effect of Δ^5,3 β-hydroxyl steroidal drugs with important consequences in resultant downstream metabolites and mechanisms of drug response. However, little is known about the temporal nature of steroidal metabolite formation and elimination that would inform the timing of metabolite sampling for biomarker studies.

Methods: In this pharmacokinetic (PK) study, 15 healthy male volunteers received a single oral dose of 1000 mg abiraterone acetate plus 240 mg of the AR antagonist apalutamide under fasted conditions. Serial plasma samples were collected from each volunteer to cover the period from 0-96 hours post-dose. Aliquots of the plasma samples were subject to liquid chromatography-tandem mass spectrometry analysis to quantify the concentrations of abiraterone's seven structurally related steroidal metabolites and to assess the PK parameters for each of the metabolites. A non-compartmental analysis was performed to describe the disposition of each compound based on mechanisms of formation and degradation using Phoenix WinNonlin® 6.3.

Results: All the metabolites were detected in the volunteers. The metabolites achieved their maximum concentration between 1.9-19.3 hours. The mean Tmax was 1.9 hr for abiraterone, 2.1 hr for D4A, and 2.7 hr for 3-keto-5α-Abi, and ranged between 3.2-19.3 hrs for the other metabolites. The mean Cmax was 90 ng/ml for abiraterone, 0.91 ng/ml for D4A, and 5.5 ng/ml for 3-keto-5α-Abi. The mean AUC at 96 hrs ranged from 5.0 for 3β-OH-5α-Abi to 503.9 for abiraterone. These data suggest that abiraterone metabolism via steroidogenic enzymes takes place rapidly and that D4A and 3-keto-5α-Abi are generated in rapid succession from the first dose. Two of the 5β metabolites (3-keto-5β-Abi and 3α-OH-5β-Abi) demonstrated two possible instances of enterohepatic circulation, at 6 hr and at 24 hr.

Conclusions: This is the first study to evaluate the PK parameters of abiraterone and its seven steroidal metabolites in healthy volunteers, and these data will help in designing biomarker studies of abiraterone metabolites levels to enhance clinical treatment.

Conflict of Interest: NS and RA: Consultants for Janssen Pharmaceuticals; CC: Employee at Janssen Pharmaceuticals.

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