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Study on pharmacokinetics and bioequivalence of Vonoprazan pyroglutamate in rats by liquid chromatography with tandem mass spectrometry

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ABSTRACT

Vonoprazan Fumarate (TAK-438 F) is a new and effective drug approved in Japan in 2014 for treatment and prevention of acid-related diseases (ARDs), which exhibits many advantages compared with traditional proton-pump inhibitors (PPIs). However, the clinical applications of TAK0-438 F suffers limitation due to the lack of injection dosage form. Efforts to overcome this limitation lead to the systhesis of Vonoprazan pyroglutamate (TAK-438 P) for its high water solubility and more potent antisecretory effect. This was the first report to establish and validate a reliable and sensitive LC–MS/MS method for the quantification of TAK-438 P in rat plasma and tissues (heart, liver, spleen, liver, kidney, rain, stomach and small intestine). All the features of the developed method suggested it was within bioanalytical criteria recommended by regulatory authorities. Furthermore, the developed method was applied to the exploration of the bioequivalence between TAK-438 P and TAK-438 F, as well as the pharmacokinetics and tissue distribution of TAK-438 P. The results showed that there was no significant differences between TAK-438 P and TAK-438 F after oral administration of the same dose. Besides, TAK-438 P was rapidly absorbed and eliminated in rat plasma. And it was widely distributed and there was no long-term accumulation in most tissues. Notably, more than 2000 ng/mL was observed in stomach 12 h after oral administration. The high accumulation revealed that stomach was likely to be the target organs of TAK-438 P.

1. Introduction

Vonoprazan Fumarate (TAK-438 F) is an orally bioavailable potassium-competitive acid blocker (P-CAB) approved in Japan for the treatment and prevention of acid-related diseases (ARDs) in 2014 [1]. Compared with the traditional proton-pump inhibitors (PPIs) used for ARDs, TAK-438 F exhibits advantages such as a fast onset of action [2], high accumulation, slow clearance [3], better control of night-time acid secretion [4], does not require acid protection so they don't exhibit acid-dependent activation like PPIs [5]. Additionally, TAK-438 F shows limited CYP polymorphism [6,7] and thus is less affected by CYP inhibitors or inducers [8]. Meanwhile, there are many reports with respect to efficacy of TAK-438 F showing longer and higher antisecretory effect compared with that of classical PPIs [9–12]. So TAK-438 F soon attracts worldwide attention, most efforts is focused on pharmacodynamics and the clinical efficacy [13–21].

However, poor water solubility (< 1 mg/mL) and low bioavailability (only 10%) [22] of TAK-438 F limit its clinical applications. For example, TAK-438 F is only commercially available in form of tablet, which keeps out those patients who suffer loss of consciousness or fast or have difficulty in swallowing, or need intravenous therapy in acute and severe case[23]. Hence, a series of TAK-438-based derivatives were synthesized with the aim to improve the solubility, and eventually vonoprazan pyroglutamate (TAK-438 P Fig. 1) was identified in screening for ARDs with higher water solubility (> 1 g/ml, 1000 times higher than TAK-438 F) and more potent antisecretory effect (the patent

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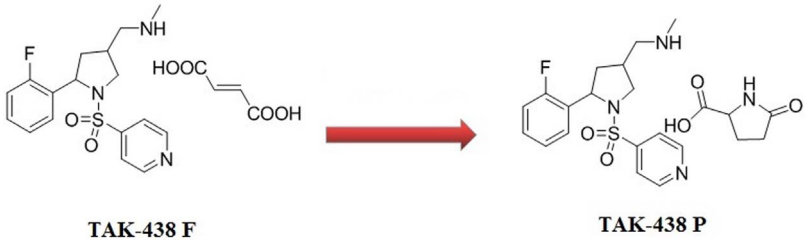

Fig. 1. The structures of TAK-438F and TAK-438 P.

number was ZL201410154778.8). So TAK-438 P was expected to be prepared not only in oral dosage but also injection form, which might overcome the aforementioned issues of TAK-438 F and provide an alternative for some patients. However, changes on the physicochemical property and dosage forms of compounds may influence the pharmacokinetic properties [24], so it was necessary to study the pharmacokinetics of TAK-438 P. In this study a sensitive LC–MS/MS method for TAK-438 P quantification in biological samples was established and validated for the first time. Then the developed method was further applied to validating the clinic feasibility of TAK-438 P by investigating the bioequivalence between TAK-438 P and TAK-438 F, as well as intravenous administration and tissue distribution of TAK-438 P from the perspective of pharmacokinetics.

2. Experiment

2.1. Materials

Vonoprazan pyroglutamate (TAK-438 P, 99.0%, FT150416003W) and Fumarate (TAK-438 F, 98.9%, FT1512181001W) were provided from School of Pharmaceutical Sciences, Shandong University (Shandong, China). Carbamazepine (purity 99.7%, 100142–201505) was acquired from National Institutes for Food and Drug Control (Beijing, China) as the internal standards (IS). Methanol was secured from Fisher Scientific (Fair Lawn, NJ, USA). Ethyl acetate (EA) was purchased from TEDIA Company (Ohio, USA). A water purification system (Millipore, Milford, MA, USA) was used to produce ultra pure water. T10 B homogenizer was bought from IKA corporate (Staufer, Germany)

2.2. Animals

Adult male Sprague-Dawley rats (220 ± 20 g) were obtained from Laboratory Animals Center of the Fourth Military Medical University (Shaanxi, China). The rats were raised at a suitable humidity and temperature of 22–26 °C for one week. Then they were fasted for 12 h with only access to water prior to experiment.

2.3. Instrumentation and chromatographic conditions

Separation of the analytes was achieved by a Shimadzu liquid chromatography system (Shimadzu, Japan) with an Agelient C18 analytical column (4.6 × 150 mm, 3.5 μm). A isocratic elution was adopted with phase A (10 mM ammonium acetate and 0.1% formic acid) and phase B (Methanol) in the ratio of 15:85, at a flow rate of 0.6 mL/min. The total run time was 5 min and the sample volume injected was 5 μL.

Detection was performed on an API 4000 tandem mass spectrometer (Applied Biosystems/MDSSCIEX, USA) equipped with an Electrospray Ionization (ESI) source. TAK-438 P or TAK-438 F and IS were all determined in positive mode and the optimal parameters were as follows: Multiple reaction monitoring (MRM) were selected with the transitions of *m/z* 346.2–315.2 for TAK-438 P and *m/z* 237.2–194 for IS (Fig. 2); The declustering potential and collision energy values were set at 49 V and 15 eV, respectively, for TAK-438 P. 83 V and 28 eV was likewise chosen for IS. All data were gained and analyzed by version 1.6 Analyst software (Applied Biosystems/MDSSCIEX).

2.4. Preparation of standard solutions

The stock solutions of TAK-438 P and TAK-438 F were prepared in methanol and diluted with methanol to a series of concentrations, which were as follows: 10, 20, 50, 100, 200, 500, 1000, 2000, 5000, 10000, 20000, 40000, 80000, 120000 ng/mL. Meanwhile, Carbamazepine (IS) was prepared in methanol to a concentration of 800 ng/mL.

Standard solutions for different matrixes were prepared as follows: First of all, 10 μL aforementioned diluted series of TAK-438 P (The diluted series from 10 to 20000 ng/mL in aforementioned increments was for blank plasma matrix, 20–40000 ng/mL for blank heart, liver, spleen, liver, kidney, brain, and small intestine tissus matrix, 50–120000 ng/mL for blank stomach matrix) or TAK-438 F (from 10 to 10000 ng/mL for blank plasma matrix) and 10 μL IS was added into 100 μL different matrix. Afterwards 10 μL sodium hydroxide solution (NaOH,1 mM) was spiked to adjust pH value. Then1.00 mL of ethyl acetate was used to extract TAK-438 P (or TAK-438 F) by vortex agitation for 10 min, followed by centrifuged at 12,000 rpm for 10 min. The supernatants were transferred to another tube and evaporated to dryness under a stream of nitrogen. In the following step, the residues were dissolved in 100 μL of methanol-water (85:15,v/v) and vortex mixed for 10 min. After centrifugation, 5 μL supernatants of each sample was injected into the LC–MS/MS. Thus, the final series concentrations of TAK-438 P (or TAK-438 F) and IS solutions were diluted 10 times (added 10 μL solutions and redissolution with 100 μL methanol-water).

2.5. Method validation

To validate the developed method, four concentrations corresponding to the lower limit of quantification (LLOQ), low quality control (LQC), medium quality control (MQC) and high quality control (HQC) were prepared for each matrix.

2.5.1. Specificity

The specificity was assessed by analyzing blank biological samples (plasma and various tissue homogenates), blank biological samples spiked with TAK-438 P (or TAK-438 F) and IS, the biological samples collected after oral administration of TAK-438 P (or TAK-438 F) to conform the presence or absence of interference.

2.5.2. Linearity and sensitivity, accuracy and precision

Calibration curves were established by plotting the ratios (Y-axis) of analyte peak area to that of IS versus the concentration of standards (X-axis) through weighted regression (1/x) method analysis. LLOQ was defined as the lowest concentration on the calibration curve with S/N > 10, Accuracy and precision were evaluated in terms of the relative error (RE%) and the relative standard deviation (RSD%) with six replicates at the four concentrations on the same day and on three consecutive day respectively.