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The determination of 2-(2-hydroxypropanamido) benzoic acid enantiomers and their corresponding prodrugs in rat plasma by UHPLC–MS/MS and application to comparative pharmacokinetic study after a single oral dose

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ABSTRACT

A simple and sensitive UHPLC–MS/MS method was developed and validated to determine the pharmacokinetic profile of 2-(2-hydroxypropanamido) benzoic acid (HPABA) enantiomers and their prodrugs in rat plasma. Separation was performed on a Thermo Syncronis C_{18} column (50 mm × 2.1 mm, 1.7 μm; Thermo, USA), which was protected by a high pressure column prefilter (2 μm) at a flow rate of 0.4 ml/min. Liquid-liquid extraction with ethyl acetate was used to process plasma samples. The separation of two enantiomers, prodrugs of (*R*)-/(*S*)-HPABA and internal standard was obtained within a cycle time of 4.5 min. The lower limit of quantification of (*R*)-/(*S*)-HPABA and prodrugs of (*R*)-/(*S*)-HPABA in plasma were 0.01 μg/ml and 0.2 μg/ml, respectively. (*S*)-HPABA showed significantly higher AUC, C_{max} and a longer $t_{1/2}$ than (*R*)-HPABA, indicating higher bioavailability of the (*S*)-HPABA. Additionally, inversion between HPABA enantiomers was not observed in rats. (*R*)-/(*S*)-HPABA showed higher C_{max} and AUC than those of their prodrugs. However, the values of $t_{1/2}$ of prodrugs were higher than those of (*R*)-/(*S*)-HPABA. Furthermore, the higher V_z values of prodrugs might improve the targeting of (*R*)-/(*S*)-HPABA in rat tissues.

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1. Introduction

As we all know, although enantiomers possess similar physicochemical properties, they may differ in absorption, distribution, metabolism, and excretion, particularly when these processes involve interaction of the drug with other chiral macromolecules, such as transporters and enzymes [1–5]. In addition, the pharmacodynamics and toxicological properties of the two enantiomers may be different *in vivo*. Therefore, it is necessary to investigate the drug enantiomers in biological fluids to keep the safety and efficacy of drug therapy.

Marine natural products, especially their metabolites or synthetic analogs, are being developed with growing intensive interest to discover abundant structurally novel and biologically active compounds. In addition, a lot of structurally and pharmacologically important substances have been isolated and investigated with a wide range of activities [6–9]. (*R*)-/(*S*)-2-(2-hydroxypropanamido) benzoic acid ((*R*)-/(*S*)-HPABA, Fig. 1B) was initially isolated from the fermentation broth of a marine fungus *Penicillium chrysogenum*. Initial investigations demonstrated that (*R*)-/(*S*)-HPABA presented remarkable analgesic and anti-inflammatory activities, but it exhibits no ulcerogenic effects compared to aspirin [10,11]. A UHPLC–MS/MS method had been developed to assay the pharmacokinetic properties of HPABA in rats [12]. To research further on HPABA, the metabolic profile of it was determined by UHPLC-FT-ICR-MS method [13].

Prodrug is a kind of less active or inactive compound *in vitro* and has pharmacological activities after the active substance is released under the action of enzymes or non-enzymes *in vivo*. The design of prodrugs could improve the selectivity of drugs to the target, reduce side effects and extend action time [14]. Accordingly, (*R*)-/(*S*)-methyl 2-(2-Hydroxypropanamido) benzoate (prodrugs of (*R*)-/(*S*)-HPABA) were also synthesized. Moreover, we are going to carry out a comparative study on (*R*)-/(*S*)-HPABA and their prodrugs.

As far as we know, however, no research has been reported on the comparison of the chiral pharmacokinetics of (*R*)-/(*S*)-HPABA and their prodrugs (Fig. 1C) which may provide potential way to improve oral bioavailability of (*R*)-/(*S*)-HPABA. Therefore, the aim of this study is to develop a simple and sensitive UHPLC–MS/MS method to determine and compare the pharmacokinetic profile of enantiomers of HPABA and their prodrugs in rat plasma.

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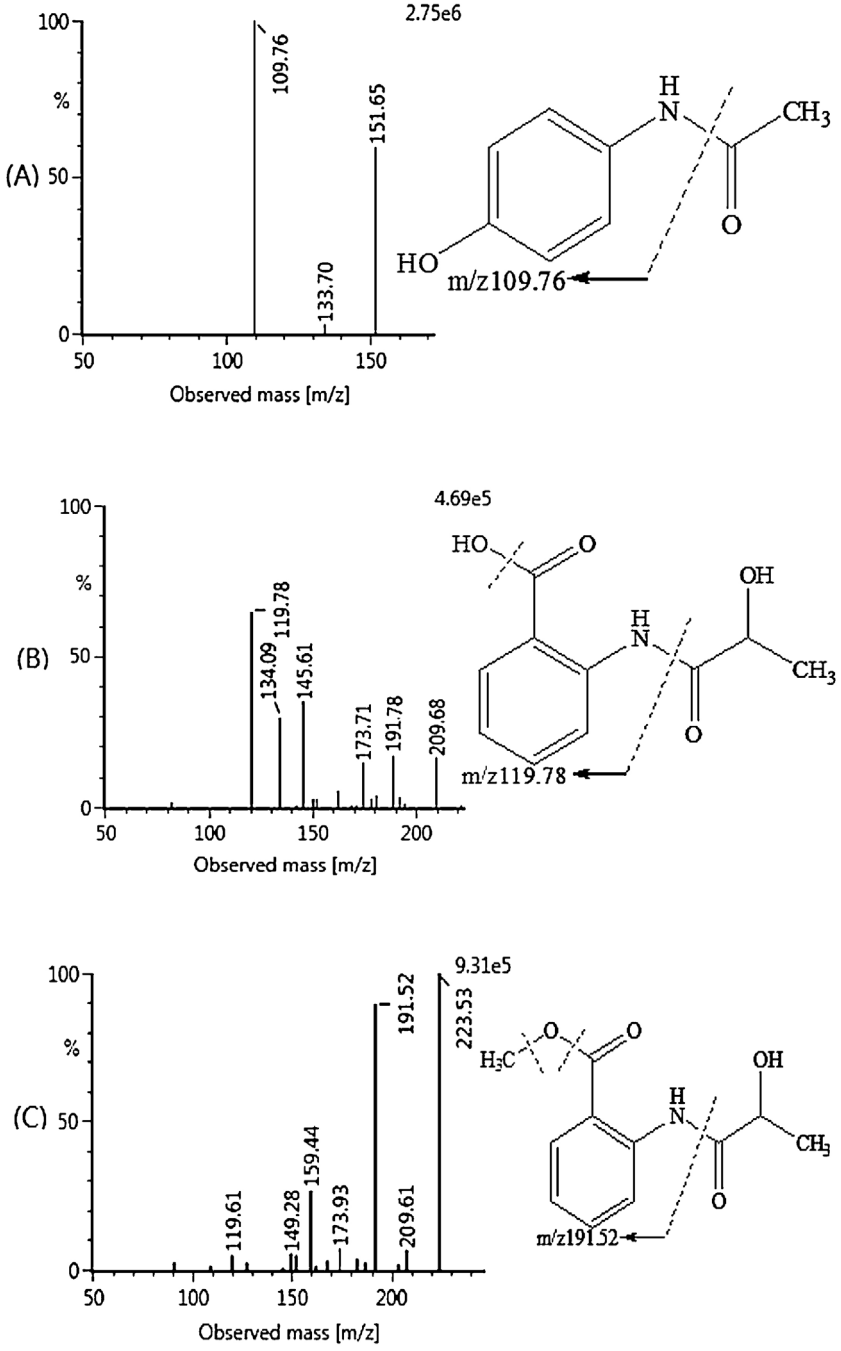

Fig 1. Full-scan product ion spectra of $[M+H]^+$ ions of IS (A), (*R*)-/(*S*)-HPABA (B) and prodrugs of (*R*)-/(*S*)-HPABA (C) in positive ionization mode.

In present study, the method was successfully applied to a pharmacokinetic study of (*R*)-/(*S*)-HPABA and prodrugs of (*R*)-/(*S*)-HPABA after full validation. Pharmacokinetic characteristics of (*R*)-/(*S*)-HPABA and corresponding prodrugs were compared, which could facilitate a further research and development of (*R*)-/(*S*)-HPABA.

2. Experimental

2.1. Materials, reagents and animals

(*R*)-HPABA (optical purity > 99.3%), (*S*)-HPABA (optical purity > 98.8%), prodrug of (*R*)-HPABA (optical purity > 99.1%) and prodrug of (*S*)-HPABA (optical purity > 99.0%) were synthesized in School of Pharmacy, Shenyang Pharmaceutical University (Shenyang, China). Paracetamol (IS, purity > 99.0%, Fig. 1A) was purchased from National Institute for Food and Drug Control (Beijing, China). Methanol of HPLC grade was purchased from Fisher Scientific (Fair Lawn, NJ, USA). All the other reagents were of analytical grade. Deionized water was purified using a Milli-Q system (Millipore, Milford, MA, USA).

Sprague-Dawley male rats (220–250 g) were obtained from Experimental Animal Center of Shenyang Pharmaceutical University. Animals were housed under good laboratory conditions (temperature 22 ± 2 °C, relative humidity 50 ± 10%). Before experiment, rats were fasted with only access to water for 12 h. Animal experiment was carried out according to the Guideline for Animal Experimentation of Shenyang Pharmaceutical University, and

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