Stereoselectivity in Pharmacokinetics of Rivoglitazone, A Novel Peroxisome Proliferator-Activated Receptor γ Agonist, in Rats and Monkeys: Model-Based Pharmacokinetic Analysis and *In Vitro–In Vivo* Extrapolation Approach

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ABSTRACT: Stereoselectivity in pharmacokinetics of rivoglitazone, a novel peroxisome proliferator-activated receptor γ agonist, in rats and monkeys was examined. The pharmacokinetic model involving chiral inversion explained well the plasma profiles of *R*-isomer and *S*-isomer after intravenous and oral administration of (*R*)-rivoglitazone or (*S*)-rivoglitazone to rats and monkeys. The high stereoselectivity was evaluated in chiral inversion clearance (*R*/*S* ratio: 7.92), metabolic clearance (5.78), and volume of distribution (4.04) in rats; however, these were low (1.73, 1.31, and 1.06) in monkeys. The stereoselectivity in chiral inversion was also observed in *in vitro* incubation studies in plasma, and the *R*/*S* ratio of chiral inversion showed high correlation with the *R*/*S* ratio of plasma unbound fraction. The metabolic clearance of the primary five metabolic pathways of rivoglitazone was evaluated from an *in vitro–in vivo* extrapolation approach using rat and monkey liver microsomes. The high stereoselectivity in metabolic clearance in rat was evaluated (*R*/*S* ratio: 5.78), which was assumed to be because of the stereoselectivity in plasma unbound fraction, on the contrary, that in monkeys exhibited low stereoselectivity (0.774). Thus, the stereoselectivity in plasma unbound fraction was estimated to be a major determinant of stereoselectivity in pharmacokinetics of rivoglitazone in rats and monkeys. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3174–3188, 2013

Keywords: pharmacokinetics; protein binding; metabolic clearance; metabolism; distribution; chiral inversion; stereoselectivity; *in vitro–in vivo* extrapolation (IVIVE); unbound fraction; intrinsic clearance

INTRODUCTION

Rivoglitazone, (RS)-5-{4-[(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methoxy]benzyl}-1,3-thiazolidine-2,4-dione monohydrochloride (Fig. 1), is a novel thiazolidinedione (TZD) that selectively activates the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ).[1] TZD-containing drugs, pioglitazone and rosiglitazone, are a clinically important new class of oral antidiabetic agents for the treatment of type 2 diabetes mellitus, which increase insulin sensitivity in target tissues through interaction with PPARγ.[2] Pharmacokinetics, metabolism, and disposition studies of rivoglitazone after intravenous and oral administration of [C]rivoglitazone to rats and monkeys have been reported.[3,4] Rivoglitazone exhibits low clearance and small volume of distribution. The clearance is mainly the result of metabolism; and on the basis of the structures of the metabolites, five primary metabolic pathways consisting of four oxidation pathways and one *N*-glucuronidation

Abbreviations used: TZD, thiazolidinedione; IVIVE, *in vitro–in vivo* extrapolation; IS, internal standard; LC–MS/MS, liquid chromatography–tandem mass spectrometry.

Additional Supporting Information may be found in the online version of this article. Supporting Information

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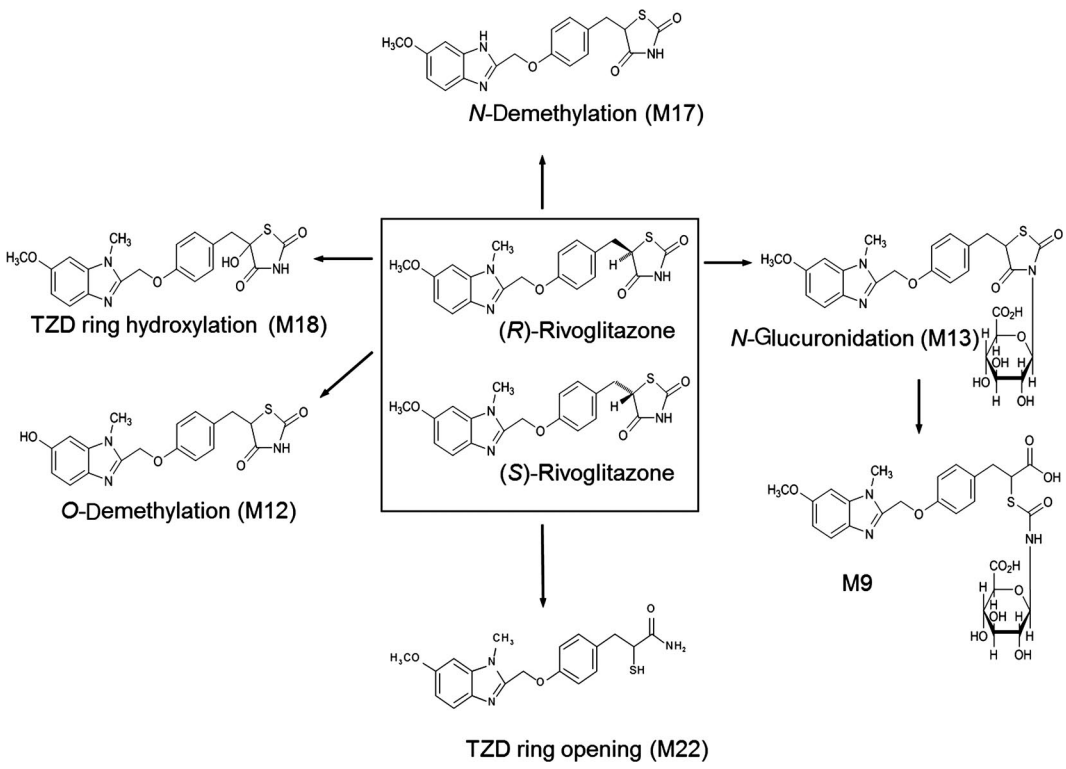

Figure 1. Proposed primary metabolic pathways of rivoglitazone in rats and monkeys.

pathway for rivoglitazone have been proposed: (1) *O*-demethylation to form *O*-demethyl rivoglitazone (M12); (2) TZD ring opening to form TZD ring-opened mercapto amide (M22); (3) *N*-demethylation to form *N*-demethyl rivoglitazone (M17); (4) TZD ring hydroxylation to form TZD ring 5-hydroxy rivoglitazone (M18); and (5) *N*-glucuronidation to form *N*-glucuronide (M13; Fig. 1).

Rivoglitazone is an equal mixture of two stereoisomers, arising from asymmetric carbons at the fifth position of the TZD ring (Fig. 1). (*S*)-rivoglitazone has been shown to bind PPARγ with greater than 50-fold higher affinity than (*R*)-rivoglitazone.[5] This high stereoselectivity in the pharmacological effect has also been reported for rosiglitazone.[6] On the contrary, the TZD-containing drugs have been observed as the chiral inversion at fifth position of TZD ring *in vivo*.[6–9]

In this study, the stereoselectivity in pharmacokinetics of rivoglitazone was investigated from *in vivo* and *in vitro* studies in rats and monkeys, which were used in safety and pharmacology assessment. For *in vivo* studies, the pharmacokinetic model involving chiral inversion was applied to the plasma profiles after intravenous and oral dosing of each stereoisomer. For *in vitro studies*, protein binding studies, chiral inversion studies in plasma, and drug metabolism studies for the five metabolic pathways have been examined using liver microsomes for each stereoisomer. On the basis of the metabolism data, the stereoselectivity in drug metabolism was evaluated using the *in vitro–in vivo* extrapolation (IVIVE) method and was compared with the *in vivo* data. Finally, we evaluated the predominant factors for the stereoselecivity in pharmacokinetics of rivoglitazone in rats and monkeys.

MATERIALS AND METHODS

Materials

(*R*)-rivoglitazone, (*S*)-rivoglitazone, its internal standard (IS; R-121171), its metabolites (racemate): M12 (R-239457), M22 (R-130712), M17 (R-125804), M18 (R-14526), M13 (R-417680), and M9 (A200-8132), and IS for metabolites (R-252121, R-252122, and A203-5426) were synthesized by Daiichi Sankyo Company, Ltd. or Daiichi Sankyo RD Associe Company, Ltd. (Tokyo, Japan).[3] Hydroxypropyl-β-cyclodextrin (HP-β-CD) was purchased from Nihon Shokuhin Kako Co., Ltd. (Tokyo, Japan). β-Nicotinamide adenine dinucleotide phosphate (β-NADP) sodium salt, D-Glucose-6-phosphate (G-6-P) disodium salt hydrate, Glucose-6-phosphate dehydrogenase (G-6-PDH), and L-glutathione reduced (GSH), uridine 5-diphosphoglucuronic acid trisodium salt (UDPGA), and *D*-saccharic acid 1,4-lactone monohydrate (*D*-saccharolactone) were purchased from Sigma–Aldrich (St. Louis, Missouri). UDP-glucuronosyltransferase (UGT) Reaction Mix