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Note

Intestinal glucuronidation metabolism may have a greater impact on oral bioavailability than hepatic glucuronidation metabolism in humans: A study with raloxifene, substrate for UGT1A1, 1A8, 1A9, and 1A10

Takashi Mizuma*

Department of Drug Absorption and Pharmacokinetics, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

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ABSTRACT

The kinetic impact of intestinal glucuronidation metabolism on oral bioavailability (*F*) was assessed using reported human data of raloxifene, of which oral bioavailability was only 2%. Kinetic analysis showed that presystemic intestinal availability (Fpg) was 5.4%, whereas fraction absorbed (Ff) and hepatic availability (Fh) were 63% and 59.3%, respectively. Thus, Fpg was the lowest among factors, which affect oral bioavailability. In addition, Fpg was much lower than Fh, suggesting that intestinal glucuronidation metabolism has a greater impact on oral bioavailability than hepatic glucuronidation metabolism. It has been reported that UDP-glucuronosyltransferase (UGT) 1A1, UGT1A8, UGT1A9, and UGT1A10 are enzymes for raloxifene glucuronidation, and UGT1A8 and UGT1A10 are absent in the human liver, whereas UGT1A1, UGT1A8, UGT1A9, and UGT1A10 are present in the human intestine. Therefore, it is also suggested that intestinal glucuronidation catalyzed by UGTs, particularly UGT1A8 and UGT1A10, may play important roles in the first-pass metabolism, causing low oral bioavailability.

Oral administration of drugs is a simple, easy, and widely used method, but the pharmacological action of orally administered drugs is influenced by oral bioavailability. Oral bioavailability is determined by the fraction entering intestinal tissue, intestinal availability, and hepatic availability. For many years hepatic metabolism has been recognized as the primary organ impacting oral bioavailability, but other organ availabilities are now starting to be recognized as important contributors to oral bioavailability. For example, studies have shown that intestinal phase I oxidative metabolism, catalyzed by CYP3A4, impacts oral bioavailability (Wu et al., 1995), and the author has reported the quantitative impact of intestinal sulfotransferase activity, SULT1A3, on the oral bioavailability of salbutamol (Mizuma, 2008). Presystemic intestinal availability is lower than presystemic hepatic availability for salbutamol, indicating that intestinal SULT1A3-catalyzed sulfation impacts oral bioavailability the most among factors affecting oral bioavailability.

Raloxifene is a selective estrogen receptor modulator (SERM) used to treat osteoporosis and prevent breast cancer. Glucuronide metabolites of raloxifene have been detected in plasma following oral administration of raloxifene, and oral bioavailability (*F*) was only 2% (U.S. Food and Drug Administration, 1999a). Nevertheless, the reason for low oral bioavailability has yet to be fully elucidated. Since the intestine is anatomically and physiologically different from other organs, such as the liver, the first-pass process of a drug through the intestine, which dominates presystemic intestinal availability, is different from that of the liver, and membrane permeability has been reported to significantly affect presystemic intestinal availability (Mizuma, 2002; Mizuma et al., 2004). Therefore, the author hypothesizes that presystemic intestinal glucuronidation metabolism has more of an impact on the oral bioavailability of raloxifene than presystemic hepatic glucuronidation metabolism even if the intrinsic clearance of the intestine is lower than that of the liver. Thus, the goal of the present study is to analyze pharmacokinetic data to determine if intestinal glucuronidation metabolism can significantly affect the bioavailability of raloxifene.

Presystemic hepatic availability can be assessed by a kinetic equation based on the well-stirred model. In contrast, a kinetic equation to estimate presystemic intestinal availability, by using in vitro intrinsic clearance (metabolic enzyme activity data) has not been established, although an in vitro study of raloxifene has been reported by Kemp et al., 2002. Therefore, in the present paper, the kinetic impact of intestinal glucuronidation metabolism on oral bioavailability of raloxifene is assessed using reported in vivo data from humans.

Oral bioavailability (*F*) is calculated by

$$F = \mathrm{Ff} \times \mathrm{Fpg} \times \mathrm{Fh} \quad (1)$$

* Tel.: +81 426 76 3181; fax: +81 426 76 3142.
E-mail address: mizuma@ps.toyaku.ac.jp.

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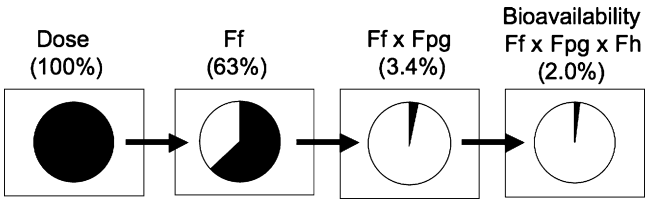

Fig. 1. Scheme showing the remaining drug fraction after oral administration of raloxifene to humans. Closed parts represent the remaining fraction of oral dose.

Table 1
Tissue distribution of UGTs catalyzing raloxifene metabolism.

UGTs[a]	Tissues[b]
UGT1A1	Liver, bile ducts, stomach, colon
UGT1A8	Esophagus, jejunum, ileum, colon
UGT1A9	Liver, colon, kidney
UGT1A10	Esophagus, stomach, bile ducts, intestine, colon

[a] Kemp et al., 2002.
[b] Tukey and Strassburg, 2000.

Ff, Fpg, and Fh are fraction absorbed, presystemic intestinal availability and presystemic hepatic availability, respectively. Thereby, Fpg is obtained by

$$\mathrm{Fpg} = \frac{\mathrm{F}}{(\mathrm{Ff} \times \mathrm{Fh})} \quad (2)$$

Fh is calculated by

$$\mathrm{Fh} = 1 - \mathrm{Eh} \quad (3)$$

$$\mathrm{Eh} = \frac{\mathrm{CLtot}}{\mathrm{Qh}} \quad (4)$$

$$\mathrm{CLtot} = \mathrm{CLpo} \times \mathrm{F} \quad (5)$$

Where Eh and CLtot are the hepatic extraction ratio and total body clearance, respectively. Hepatic blood flow rate (Qh) is 1.5 L/min (Davies and Morris, 1993). The following data of raloxifene was reported: F and Ff were 2.0% and 63%, respectively (U.S. Food and Drug Administration, 1999a). Oral clearance (CLpo) was 44.1 L/kg/h (U.S. Food and Drug Administration, 1999b).

Using this data, Ff, Fh, and Fpg can be calculated (63%, 59.3%, and 5.4%, respectively). Summarizing dose fractions remaining at each site shows that the available dose markedly decreases after passing through the intestine (Fig. 1). Data suggest that intestinal metabolism impacts oral bioavailability more than hepatic metabolism because Fpg is markedly lower than the other factors affecting oral bioavailability.

UGTs catalyzing raloxifene glucuronidation and their tissue distributions are summarized in Table 1 based on literature (Kemp et al., 2002; Tukey and Strassburg, 2000). Kemp et al., 2002 tested glucuronidation of raloxifene by expressed human UGTs (1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7, and 2B15), and reported that UGT1A1, UGT1A8, UGT1A9, and UGT1A10 were able to catalyze the formation of raloxifene glucuronide. UGT1A8 and UGT1A10 are absent in the human liver, whereas UGT1A1, UGT1A8, UGT1A9, and UGT1A10 are present in the human intestine according to a review article summarizing the expression of human UGTs mRNA in the human body (Tukey and Strassburg, 2000). Thus, there are several intestinal UGTs which may be responsible for raloxifene conjugation.

Organ availabilities, except presystemic intestinal availability, are primarily determined by intrinsic clearance derived from enzyme activity, unbound fraction in the blood, and organ blood flow rate. Whereas, presystemic intestinal availability is affected by intrinsic clearance derived from enzyme activity, unbound fraction in the blood, and membrane permeability because the drug pathway through intestinal tissues is different between presystemic metabolism and systemic metabolism (Mizuma et al., 2000, 2004: Mizuma, 2002). That is, membrane permeability significantly affects presystemic intestinal availability. Therefore, it is considered that this difference may explain low Fpg values when compared with Fh of raloxifene. These low presystemic intestinal and hepatic availabilities resulted in reducing the oral bioavailability of raloxifene.

The present study is the first that kinetically assesses the impact of presystemic intestinal glucuronidation metabolism on raloxifene oral bioavailability and illustrates the importance of evaluating presystemic intestinal glucuronidation. The raloxifene example presented in this review suggests that intestinal glucuronidation catalyzed by UGTs, particularly UGT1A8 and UGT1A10, may have a greater impact on oral bioavailability than hepatic glucuronidation. Also, it is suggested that when an orally active drug candidate is a substrate, atleast for UGT1A8 and/or UGT1A10, its presystemic intestinal glucuronidation metabolism should be evaluated early in the study of drug development.

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