Differentiation of Organ Availability by Sequential and Simultaneous Analyses: Intestinal Conjugative Metabolism Impacts on Intestinal Availability in Humans

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ABSTRACT: The impact of intestinal conjugative metabolism on oral bioavailability was assessed by sequential and simultaneous analyses of the reported data in humans. The data were retrieved from reports on drugs that are metabolized by sulfate conjugation, and the organ availabilities affecting oral bioavailability were differentiated. Sequential analysis gave the following results. The intestinal availability (Fg) of salbutamol was 0.700, whereas hepatic availability (Fh) and bioavailability (F) were 0.893 and 0.493, respectively. Fg of (+)-terbutaline, (−)-terbutaline, and (±)-terbutaline was 0.128, 0.254, and 0.250, respectively. In contrast, Fh of (+)-terbutaline, (−)-terbutaline, and (±)-terbutaline was 0.979, 0.971, and 0.946, respectively. Fg and Fh of ethynylestradiol were 0.536 and 0.780, respectively. Simultaneous analysis also gave similar results, although the sequential analysis overestimated the intestinal availability. These results indicate that intestinal sulfation metabolism has more impact on intestinal availability than on hepatic availability, resulting in low bioavailability in humans. J Pharm Sci 94:571–575, 2005

Keywords: intestinal metabolism; phase II enzymes; conjugation; bioavailability; pharmacokinetics

INTRODUCTION

Orally administered drugs must pass through three key processes to enter the systemic circulation.[1] These processes are: the fraction entering the tissue (Ff), which is the fraction neither lost in the feces nor decomposed in the lumen; the fraction escaping destruction (metabolism) within the walls of the gastrointestinal tract (Fg); and the fraction escaping liver extraction (Fh). Although Ff and Fh have been recognized as primary factors in bioavailability (F), Fg has not. Now, however, intestinal phase I oxidative metabolism by CYPs has been recognized as being as important as hepatic oxidative metabolism in humans.[2,3]

In contrast, the impact of gastrointestinal phase II conjugative metabolism on bioavailability in humans is not clear. Although evidence of the impact of conjugative metabolism on intestinal availability (or extraction) has been reported in animals,[4–7] this evidence is not applicable to pharmacokinetics in humans because there is a large species difference in drug metabolism. We therefore surveyed human studies for kinetic analysis of the data, and to clarify the real impact of gastrointestinal phase II conjugative metabolism on intestinal availability. The kinetic analysis involved two methods, the conventional method

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(sequential analysis) and a new method (simultaneous analysis). Sulfation metabolism was selected as the conjugative (phase II) metabolism in the first study. Because salbutamol,[8] terbutaline,[9] and ethynylestradiol[10] are metabolized to sulfate conjugates as primary metabolites, these drugs were studied.

METHODS

Sequential Analysis

Hepatic clearance (CLh) is obtained by eqs. 1 and 2[2,3].

$$\mathrm{CLh} = \mathrm{CLm} \tag{1}$$

$$= \mathrm{CLt} - \mathrm{CLr} \tag{2}$$

where CLm, CLt, and CLr are metabolic clearance in the body, total body clearance, and renal clearance, respectively.

$$\mathrm{CLt} = \mathrm{Div}/\mathrm{AUCiv} \tag{3}$$

$$\mathrm{Fh} = 1 - \mathrm{CLh}/\mathrm{Qh} \tag{4}$$

$$\mathrm{F} = (\mathrm{AUCpo}/\mathrm{Dpo})/(\mathrm{AUCiv}/\mathrm{Div}) \tag{5}$$

$$\mathrm{Fg} = \mathrm{F}/(\mathrm{Ff} \times \mathrm{Fh}) \tag{6}$$

where Fh and Fg are hepatic availability and intestinal availability, respectively, obtained by sequential analysis. Div and Dpo are intravenous and oral dose, respectively. AUCiv and AUCpo are under the concentration curve of the drug after intravenous and oral administration, respectively.

Simultaneous Analysis

It should be noted that hepatic clearance does not equal metabolic clearance in the body. Therefore, the following equation should be used in simultaneous analysis:

$$\mathrm{CLh} = \mathrm{CLm} - \mathrm{CLg} \tag{7}$$

where CLh is defined as the hepatic clearance obtained from eq. 7 of the simultaneous analysis. CLg is the intestinal clearance. Therefore

$$\mathrm{CLh} = \mathrm{CLt} - \mathrm{CLr} - \mathrm{CLg} \tag{8}$$

$$\mathrm{Fh} = 1 - \mathrm{CLh}/\mathrm{Qh} \tag{9}$$

$$\mathrm{Fg} = 1 - \mathrm{CLg}/\mathrm{Qg} \tag{10}$$

$$\mathrm{CLt} = \mathrm{Div}/\mathrm{AUCiv} \tag{11}$$

$$\mathrm{F} = (\mathrm{AUCpo}/\mathrm{Dpo})/(\mathrm{AUCiv}/\mathrm{Div}) \tag{12}$$

$$\mathrm{Fg} = \mathrm{F}/(\mathrm{Ff} \times \mathrm{Fh}) \tag{13}$$

where Fh and Fg are hepatic availability and intestinal availability, respectively, obtained by simultaneous analysis. Qg is the intestinal blood flow rate and 250 mL/min/70 kg body weight[11] (approximate value of 248 mL/min/body[12]). From these equations, Fg and Fh are derived as follows:

$$\mathrm{Fg} = \frac{1}{2}\left(1 + \frac{\mathrm{CLr}}{\mathrm{Qg}} - \frac{\mathrm{CLt}}{\mathrm{Qg}} + \frac{\mathrm{Qh}}{\mathrm{Qg}} - \frac{\sqrt{\mathrm{Ff}^2(-\mathrm{CLr} + \mathrm{CLt} - \mathrm{Qg} - \mathrm{Qh})^2 - 4\mathrm{F}\,\mathrm{Ff}\,\mathrm{Qg}\,\mathrm{Qh}}}{\mathrm{Ff}\,\mathrm{Qg}}\right) \tag{14}$$

$$\mathrm{Fh} = \frac{1}{2\mathrm{Ff}\,\mathrm{Qh}}\left(-\mathrm{Ff}(\mathrm{CLr} + \mathrm{CLt} - \mathrm{Qg} - \mathrm{Qh}) + \sqrt{\mathrm{Ff}^2(-\mathrm{CLr} + \mathrm{CLt} - \mathrm{Qg} - \mathrm{Qh})^2 - 4\mathrm{F}\,\mathrm{Ff}\,\mathrm{Qg}\,\mathrm{Qh}}\right) \tag{15}$$

In both analyses, the hepatic blood flow rate was 1,500 mL/min/70kg body weight. The blood to plasma concentration ratio was assumed equal. A body weight of 70 kg was assumed, except where noted.

RESULTS AND DISCUSSION

Salbutamol

Fg and Fh, which were obtained by sequential and simultaneous analyses, are shown in Table 1, together with related parameters. The total body clearance (CLt), renal clearance (CLr), and bioavailability (F) of salbutamol in volunteers were from the report of Morgan et al.[8] Ff was calculated by dividing the amount of urinary salbutamol and sulfate conjugate by the oral dose. Sequential analysis gave Fg of 0.700 and Fh of 0.893. Fg was lower than Fh, indicating that intestinal sulfation metabolism affects intestinal availability and contributes to low bioavailability