Urinary Excretion: Does It Accurately Reflect Relative Differences in Bioavailability/Systemic Exposure When Renal Clearance Is Nonlinear?

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Purpose. The purpose of this study was to assess the influence of nonlinear renal clearance on the ability of urinary excretion data to accurately determine relative differences in systemic exposure and bioavailability.

Methods. Serum concentration and urinary excretion-time profiles were simulated assuming an open one-compartmental model with first-order absorption, linear nonrenal clearance, and either linear or nonlinear renal clearance (saturable secretion). Renal clearance comprised 5% or 95% of total clearance. Doses were varied over a 100-fold range (10-fold decrease/increase from the reference dose). Relative systemic exposures were based on the ratios of AUC and C_{max} and the corresponding ratios of cumulative amount excreted in urine (A_e) and the maximum urinary excretion rate. Relative bioavailability was based on the ratios of A_e and the test to reference dose (D_{ratio}).

Results. When renal clearance was linear and urinary excretion data were used to assess relative systemic exposure and relative bioavailability, no significant errors in accuracy were observed. However, when renal clearance was nonlinear, errors in the accuracy of estimation of relative bioavailability (Cl_r = 5% only) and relative systemic exposure ranged from –53% to +125%; minimal error in accuracy existed in the estimation of relative bioavailability when Clr = 95% (–3% to +6%).

Conclusions. Prior to the use of urinary excretion data to assess relative systemic exposure or bioavailability, the relationship between serum concentration and renal clearance should be established.

KEY WORDS: bioavailability; nonlinear renal clearance; systemic exposure; urinary excretion.

INTRODUCTION

In 1977, the United States Food and Drug Administration issued the initial regulation on the assessment of bioavailability and bioequivalence (1). As outlined in this regulation and in subsequent regulatory guidances issued throughout the world, the types of data that could be used to assess bioavailability/bioequivalence included serum concentration-time data, urinary excretion-time data, and pharmacodynamics. Although the use of serum concentration-time data was primarily recommended, the use of urinary excretion data was viewed as an alternative approach if the bioanalytical method lacked the appropriate sensitivity to adequately characterize the serum concentration-time profile. Since the issuance of the initial regulation, statistical methods to assess bioequivalence have evolved (ANOVA, 75/75 rule, 90% confidence intervals; population, average and individual bioequivalence) (2–9); however, the type of data used in these assessments do not appear to have been critically evaluated.

Since the initial regulation, C_{max} and AUC obtained from serum concentration-time profiles have been recommended as the primary parameter to assess rate and extent of absorption, respectively. During the ensuing years, many authors have criticized the use of C_{max} as a measure of rate because it is confounded with extent of absorption and some have proposed alternative parameters (10–13). More recently, a philosophical change in the interpretation of C_{max} has occurred with it being viewed more as a clinically important measure of peak systemic exposure instead of an indirect measure of rate of absorption (14). This change in "interpretation" is also reflected in more recent FDA guidances, which also focus on systemic exposure concepts (15–17).

Due to the recent focus on systemic exposure, this study assessed the influence of nonlinear renal clearance on the use of urinary excretion data to assess both relative changes in systemic exposure as well as bioavailability.

METHODS

Pharmacokinetic Model

An open one-compartmental model with first-order absorption, linear and/or nonlinear (saturable secretion) renal clearance, and linear non-renal clearance was assumed (Fig. 1). Two different relationships between serum concentration (Conc) and renal clearance were used: 1) renal clearance was independent of concentration (K_m >> Conc); and 2) renal clearance was concentration dependent (Conc ~ K_m) due to saturation of secretion. The equations describing this model are summarized below (18,19):

$$dA/dt = -A * K_a$$
$$dB/dt = A * K_a - B * (Cl_{nr} + CL_r)/V$$
$$dC/dt = B * (Cl_{nr} + CL_r)/V$$
$$Cl_r = CL_f + T_{max}/(K_m + Conc)$$
$$Conc = B/V$$

where A is the amount of drug at the "site" of absorption; K_a is the first-order absorption rate constant, B is the amount of drug in the body, CL_r is renal clearance, CL_{nr} is nonrenal clearance, CL_f is the filtration clearance via the kidney, C is the amount of drug in urine, V is the volume of distribution, T_{max} is the maximum renal transport (secretion), K_m is the concentration at one-half the maximum renal transport, and Conc is the drug serum concentration.

Parameter Estimation

Predicted serum concentration and urinary excretion-time profiles were estimated using deterministic simulations (20). Parameters values used in these simulations are summarized in Table I. The reference dose was chosen to ensure concentration-dependent renal clearance (Dose ~4*K_m). Relative bioavailability (amount of drug absorbed) was varied over a 100-fold range (i.e., 10-fold increase and decrease

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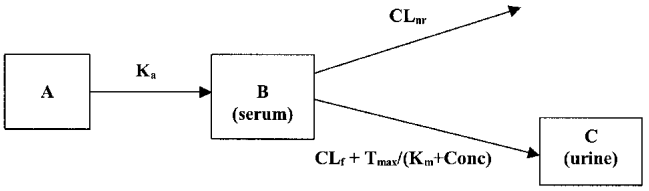

Fig. 1. Pharmacokinetic model used in the simulations.

from the reference dose). Renal clearance was assumed to comprise either 5% or 95% of total clearance. The following parameters were obtained for each simulation. Area under the serum concentration-time profile was obtained using the linear trapezoidal rule, and the peak serum concentration was obtained as by visual inspection. Corresponding urinary excretion parameters were obtained based on the amount excreted at infinite time (A_e) and the peak urinary excretion rate (dA_e/dt_{max}) based on the amount excreted within an interval divided by the interval collection time (i.e., 0.25 h step size for predicted serum and urinary excretion-time data). Simulations were conducted using Ithink (Version 5.0; High Performance Systems, Inc., Lebanon, NH, USA).

Comparison of estimates for relative bioavailability (RB), relative total systemic exposure (TE), and peak systemic exposures (PE) were obtained from the following equations:

$$RB_{dose} = Dose_{test}/Dose_{reference}$$
$$RB_{urine} = A_{e\ test}/A_{e\ ref}$$
$$TE_{serum} = AUC_{test}/AUC_{ref}$$
$$TE_{urine} = A_{e\ test}/A_{e\ ref}$$
$$PE_{serum} = C_{max\ test}/C_{max\ ref}$$
$$PE_{urine} = (dA_e/dt_{max,\ test})/(dA_e/dt_{max,\ ref})$$

Error Estimation

Parameters obtained from serum concentration-time data were used as the reference for systemic exposure comparisons, and the ratio of administered doses was used as the reference for bioavailability comparisons. Error in the accuracy of the estimation for systemic exposure and bioavailability were obtained from the following equations, respectively.

$$\text{Percent error}_{\text{systemic exposure}} = [\text{urine ratio} - \text{serum ratio})/\text{serum ratio}] * 100\%$$
$$\text{Percent error}_{\text{amount absorbed}} = [\text{urine ratio} - \text{dose ratio})/\text{dose ratio}] * 100\%$$

Results with a negative error indicate an underestimation and a positive error indicates an overestimation of the differences associated with the use of urinary excretion-time data.

Table I. Parameter Values Used in the Simulations

Parameter	CLr = 5%	CLr = 95%
Dose (mg)	100	100
K_a (1/h)	10,000	10,000
V (L)	1	1
CL_{nr} (L/h)	1	0.06
CL_f (L/h)	0.01	0.16
T_{max} (mg/h)	1.25	21
K_m (mg/L)	25	25

Where K_a is the first-order absorption rate constant, V is the volume of distribution, CL_{nr} is nonrenal clearance, CL_f is the filtration clearance via the kidney, T_{max} is the maximum transport (secretion) clearance, and K_m is the concentration at one-half the maximum transport.

RESULTS

Simulation results for estimation of systemic exposure and bioavailability when renal clearance is linear or nonlinear are illustrated in Figs. 2 through 4. As expected, these results indicate that when renal clearance is linear, excellent agreement exists in the estimates of relative bioavailability and systemic exposure obtained between serum concentration-time and urinary excretion-time data (error < 0.4%; related to precision of the estimates/step sizes), irrespective of the percent contribution of renal clearance to total clearance.

Whereas renal clearance comprises 5% of total clearance under linear conditions, it accounts for 1.5–5% of total clearance depending on the degree of nonlinearity assumed. Under these nonlinear conditions, significant errors exist between the estimated differences obtained using urinary excretion data vs. serum concentration-time data. When the bioavailability of the test formulation is less than the reference formulation, differences in systemic exposure, peak exposure, and bioavailability are overestimated by up to 120%. On the other hand, differences for these parameters are underestimated by up to 50% when the test formulation relative bioavailability is greater than the reference formulation.

When total clearance is predominately determined by renal clearance (95% under linear conditions vs. 79–95% under nonlinear conditions), significant errors also exist in the estimation of relative systemic exposure obtained using urinary excretion data. When the bioavailability of the test formulation is less than the reference formulation, the use of urinary excretion data overestimates formulation differences by as much as 125%. When the bioavailability of the test formulation is greater than the reference formulation, differences between the two formulations are underestimated by up to approximately 50%. However, in contrast to the error associated with the estimation of relative bioavailability, minimal error (~6% or less) exists in the estimation of the amount absorbed using urinary excretion data when renal clearance is the predominate determinate of total clearance.

DISCUSSION

Since the inception of the bioavailability/bioequivalence regulation, the use of urinary excretion data has been viewed

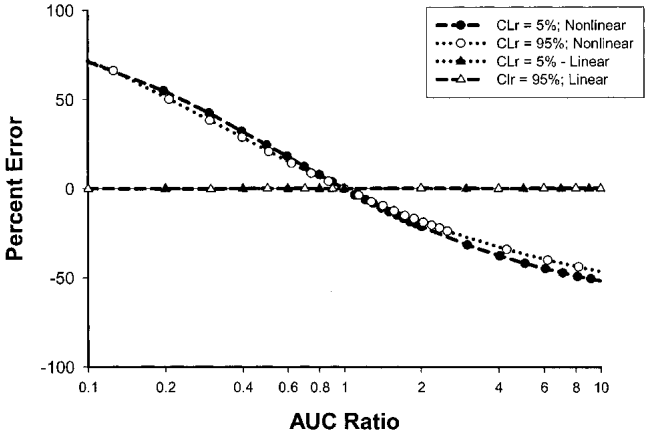

Fig. 2. Percent error associated with the use of urinary recovery to assess differences in relative systemic exposure.

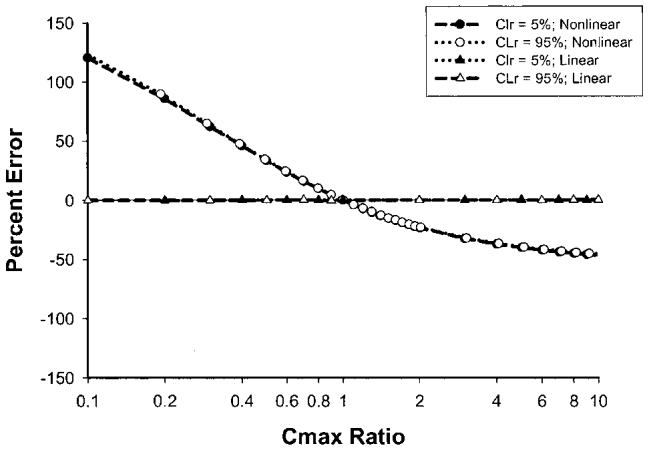

Fig. 3. Percent error associated with the use of urinary recovery to assess differences in relative systemic peak exposure.

as an acceptable approach to assess bioavailability/bioequivalence and more recently has been viewed as a means to assess relative systemic exposure (16). However, limited evaluations on the appropriateness of this approach to assess relative bioavailability and systemic exposure have been conducted. In the current study, the error associated with the use of urinary excretion data in these assessments has been investigated under linear and nonlinear conditions.

As expected, minimal error in the estimation of relative bioavailability (F) and relative systemic exposure (C_{max} and AUC) using urinary excretion-time data occurs when renal clearance is independent of serum concentrations. However, when renal clearance is concentration dependent (i.e., nonlinear), the error associated with the prediction of systemic exposure and bioavailability using urinary excretion significantly increases. Within these simulations, errors ranged up to ~120% for estimates of relative bioavailability (Cl_r = 5% only) and for relative systemic exposure regardless of the extent of renal involvement. The only notable exception is in the estimation of relative bioavailability when the drug is predominately renally cleared. Under this condition where the error in estimation of differences in relative bioavailability is <6%, most of the drug is ultimately recovered in urine so that the estimated amount absorbed is minimally influenced by

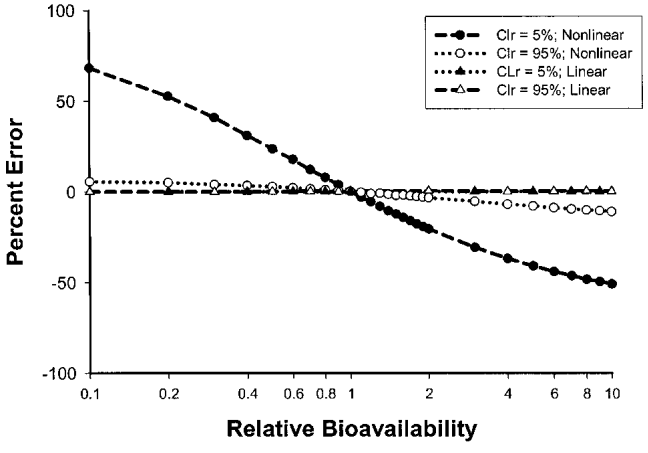

Fig. 4. Percent error associated with the use of urinary recovery to assess differences in relative bioavailability.

the nonlinearity in renal and total clearance and as such, the primary question is related more to the duration of time necessary to ensure "complete" recovery. However, as recently pointed out (14), clinically relevant comparisons should focus more on relative systemic exposure comparisons rather than on relative bioavailability where large errors still exist, regardless of the degree of renal involvement. These results also indicate that when the bioavailability of the test formulation is less than the reference formulation, differences observed in serum concentration-time data are overestimated when urinary excretion data are used, whereas differences are underestimated when the bioavailability of the test formulation is greater than the reference formulation. As such, test formulations with slightly higher bioavailability than the reference formulation may be more likely to appear as bioequivalent based on urinary excretion data as compared to an analysis based on serum concentration-time profiles.

With the advent of more sensitive bioanalytical methods, the need to use urinary excretion-time data in lieu of serum concentration-time to assess bioavailability appears to be less of a necessity. However, for some compounds within the class of bisphosphonates (compounds used in the treatment of osteoporosis), urinary excretion data appears to be the primary approach used to assess relative bioavailability and systemic exposure (21,22). For other compounds within this class, others have been able to develop bioanalytical methods of adequate sensitivity and have been able to assess the relationship between renal clearance and serum/plasma concentration (23–25). For those who have solely relied on the use of urinary excretion data, the error in the interpretation of their results appears to be unknown.

In the current study, nonlinear renal clearance was assumed to be related to saturation of renal excretion. Although saturation of secretion is the most common mechanism resulting in nonlinear renal clearance, nonlinearity may also be associated with transport-mediated reabsorption (19,26–29). Although not studied within the current investigation, results similar to those obtained in the current study would be anticipated; however, the sign of the error would be reversed (i.e., underestimation when the test formulation is less than the reference formulation and vice versa). In the current study, simulations were also conducted under conditions of "instantaneous" input. Under conditions more common to most extravascularly administered drugs (i.e., slower input), the magnitude of errors associated with the use of urinary excretion data may further increase if the time that serum concentrations remain above K_m increases.

In conclusion, these results indicate that prior to the use of urinary excretion data to assess relative systemic exposure or bioavailability, the relationship between serum concentration and renal clearance should be established.

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