Comparison of Oral Absorption and Bioavailability of Drugs between Monkey and Human

Win L. Chiou[1,2] and Paul W. Buehler[1]

Received November 13, 2001; accepted February 13, 2002

Purpose. To compare the oral absorption and bioavailability of numerous drugs with a wide variety of physicochemical and pharmacological properties between humans and monkeys and to explore potential reasons for the findings.

Methods. Data for fraction of dose absorbed (F_a) and oral absolute bioavailability (F) were obtained by an extensive Medline database search. Inclusion and exclusion criteria were the same as those reported in our previous studies. A total of 43 and 35 drugs were selected for F_a and F comparison, respectively. The time to reach peak concentration (t_{max}), total clearance, and nonrenal clearance were evaluated for 15, 28, and 13 drugs, respectively.

Results. F_a values in monkeys were similar or identical to those in humans. Additionally, similar t_{max} values were seen in monkeys and humans at comparable doses, thus indicating comparable absorption kinetics between the two species. Conversely, F values in monkeys were generally lower with coumarin being a marked exception. Both total and nonrenal clearances were evaluated and found to be generally greater in monkeys, supporting a generally higher first-pass metabolism and lower F in this species. This was also supported by published data suggesting greater *in vitro* hepatic drug metabolism for monkeys as compared to humans.

Conclusions. Monkeys appear to be a good predictor of F_a in humans. However, a generally lower F makes monkeys a potentially poor predictor of human F. Higher reported metabolic clearances and hepatic enzyme activities in monkeys may account for this observation.

KEY WORDS: drug absorption; drug bioavailability; first-pass metabolism; monkey; pharmacokinetics; plasma clearance.

INTRODUCTION

Understanding of the relationship of oral absorption and oral bioavailability of potential drug candidates between animals and humans is important in drug discovery and development (1–4). It has recently been shown that rat may serve as a good model in predicting dose-independent and dose-dependent oral absorption properties in humans (5–7). On the other hand, for many relatively hydrophilic drugs, oral absorption may often be much more complete and faster in dogs relative to humans in spite of a much shorter small intestinal transit time (7).

Due to evolutionary proximity with humans, the monkey, a nonrodent species, is widely used in preclinical pharmacokinetic and toxicological studies in spite of a relatively high cost and ethical concerns (8,9). Qualitative or quantitative correlation of oral drug absorption between monkeys and humans appears largely unknown to date. In an earlier study (10), the correlation of absolute bioavailability (F) of drugs between these two species was found to be poor with an $r^2 = 0.2$. The inclusion of only seven drugs in the study may also suggest a paucity of published monkey data at the time of evaluation. Potential reason(s) for the lower F in monkeys reported in the study was not provided (10). However, the observation may be attributable to incomplete gastrointestinal absorption, greater first-pass metabolism, or a combination of the two factors (4).

The main purpose of this communication is to report results of our extensive literature study on fraction of oral dose absorbed (F_a) and absolute oral bioavailability (F) between humans and Old World monkeys with emphasis on rhesus and cynomolgus macaques, based on their wide use in pharmaceutical research. In addition, potential reasons for marked differences in bioavailability of many drugs between monkeys and humans are explored.

METHODS

Evaluation of Oral Absorption

In the preliminary search of references for F_a data in monkeys, all drugs from our two recent studies (5,7) were used and cross-referenced with the key words or phrases "oral absorption," "monkey," and "non-human primate" in a Medline database search. Additionally, all other drugs listed in a pharmacokinetic table of a textbook (11) were similarly cross-referenced. Since not all drugs evaluated in humans (5,7,11) were evaluated in monkeys, additional key words or phases including "oral drug absorption" and "pharmacokinetics" were cross-referenced with "monkey" and "non-human primate" in an effort to extend the F_a data. Corresponding data in humans were obtained from standard references (12) or Medline if necessary.

Methods for estimating F_a as well as inclusion and exclusion criteria of drugs reported in the current study were the same as those employed previously (5,7). A total of 43 drugs possessing widely different physicochemical and pharmacological properties were chosen. Among them 28 drugs are basic, 7 acidic, 3 zwitterionic, and 5 neutral with molecular weights ranging from 146 to 877 Da. The F_a values range from zero to approximately unity ($F_a \geq 0.9$).

Evaluation of Oral Absolute Bioavailability

Of the 43 drugs chosen in the evaluation of absorption, only 15 drugs provided useful data in the evaluation of absolute bioavailability. To obtain additional data, a Medline database search was performed using the key words or phrases "absolute bioavailability," "drug," "monkey," and "non-human primate." Human F data were then obtained using a standard reference (12). Additionally, F values for other drugs were estimated from references using AUC_{iv} and AUC_{oral} values obtained from the same individuals and according to standard methods (13). A total of 35 drugs were selected in the current study.

RESULTS AND DISCUSSION

The F_a values, dosage forms used, and relevant physicochemical properties of the 43 drugs studied in humans and

[1] Department of Pharmaceutics and Pharmacodynamics (M/C 865), College of Pharmacy, The University of Illinois at Chicago, 833 South Wood Street, Chicago, Illinois 60612.

[2] To whom correspondence should be addressed. (e-mail: Chiou@uic.edu)

0724-8741/02/0600-0868/0 © 2002 Plenum Publishing Corporation

monkeys are summarized in Table I. The correlation of F_a values between human and monkey are depicted in Fig. 1.

Similar to the rat yet different from the dog, the F_a values of drugs evaluated in monkeys appear to correlate well with humans, showing a slope near unity. The similarities in F_a between monkeys and humans occur in spite of the wide diversity in physicochemical and pharmacological properties of these drugs. For drugs with high intestinal permeability or absorptive clearances (14,15) in humans, one may expect such drugs to demonstrate similar, high absorption in other mammals (1,2,5,7) because of comparable chemical properties of intestinal mucosal membranes across species. In this regard, a total of 27 drugs evaluated approached complete absorption ($F_a \geq 0.9$) in both species (Table I). The exact mechanisms leading to similar absorption for drugs with F_a ranging from zero to 0.9 in this study and earlier rat/human comparative studies (5,6) are not clear. This is interesting in view of marked differences in intestinal permeability or absorptive clearances (5) as well as intestinal length, radius, and secretion (16). Additionally, compared to humans, monkeys have a lower intestinal pH and higher bile flow per kilogram of body weight (16). From a modeling point of view, the linear corre-

Table I. Summary of Data[a] on the Percentage of Oral Dose Absorbed in Humans and Monkeys for 43 Drugs

Drug	Molecular weight[b]	Property[c]	Dosage form		Oral dose absorbed[d] (%)	
			Humans	Monkeys	Humans	Monkeys
Cyclobenzaprine	311	B	Tablet	Capsule	100	100
Fluvastatin	433	N	Solution	Capsule	98	100
Rolipram	275	B	Suspension	Suspension	100	100
Propranolol	259	B	Capsule	Tablet	100	100
Pindolol	248	B	Tablet	Tablet	95	100
Lormetazepam	335	B	Tablet	Capsule	100	100
Flunisolide	443	B	Solution	Solution	100	100
Naltrexone	364	B	Tablet	Solution	100	100
Carbamazepine	236	B	Tablet	Solution	100	100
Viloxazine	237	B	Capsule	Capsule	100	100
Caffeine	194	N	Solution	Solution	100	100
Valacyclovir	361	Z	Tablet	Solution	100	100
Moxestrol	326	N	Capsule	Capsule	100	100
Bisoprolol	268	B	Tablet	Solution	100	100
Rifapentine	877	A	Solution	Suspension	100	100
Ropinirole	297	Z	Tablet	Solution	100	100
BM-113	375	B	Solution	Solution	100	100
Latanoprost	433	B	Solution	Solution	100	100
Droloxifene	387	N	Solution	Solution	100	100
Lisuride	455	B	Solution	Solution	100	100
Zolpidem	392	B	Tablet	Suspension	100	100
Pirmenol	375	B	Tablet	Solution	100	98
Nisoldipine	388	A	Suspension	Suspension	97	97
Azipranone	495	B	Capsule	Solution	100	95
Zomepirac	350	A	Solution	Solution	96	94
Irbesartan	428	B	Tablet	Suspension	100	92
Metoprolol	342	B	Tablet	Solution	98	92
Recainam	263	B	Capsule	Solution	85	88
Guanabenz	291	B	Tablet	Solution	79	88
Coumarin	146	B	Solution	Solution	100	87
Bepridil	421	B	Tablet	Suspension	99	83
Moxifloxacin	438	B	Tablet	Tablet	95	82
Captopril	217	A	Tablet	Solution	68	79
Menogaril	542	B	Solution	Solution	59	63
Furosemide	331	Z	Tablet	Solution	55	60
Atenolol	266	B	Tablet	Solution	50	45
Bromocriptine	654	B	Tablet	Solution	30	35
Benazepril	425	B	Tablet	Capsule	30	32
Lovastatin	405	N	Tablet	Solution	30	31
Nadolol	309	B	Tablet	Solution	20	23
Tiludronate	381	A	Tablet	Solution	12	15
Etidronate	249	A	Tablet	Solution	10	6
Ceftriaxone	599	A	Solution	Solution	0	0

[a] The references providing data on percentage of oral dose absorbed are available on request.

[b] Molecular weights obtained from the following references: *Martindale's Extra Pharmacopeia* (1996 edition), *European Pharmacopeia* (2000 edition), and the *U.S. Pharmacopeia/National Formulary* (2000 edition).

[c] N: neutral compound; A: weak acid; B: weak base; Z: zwitterionic compound.

[d] Represents mean values for % absorption obtained from individual drug references or the *Physician's Desk Reference* (2001 edition).

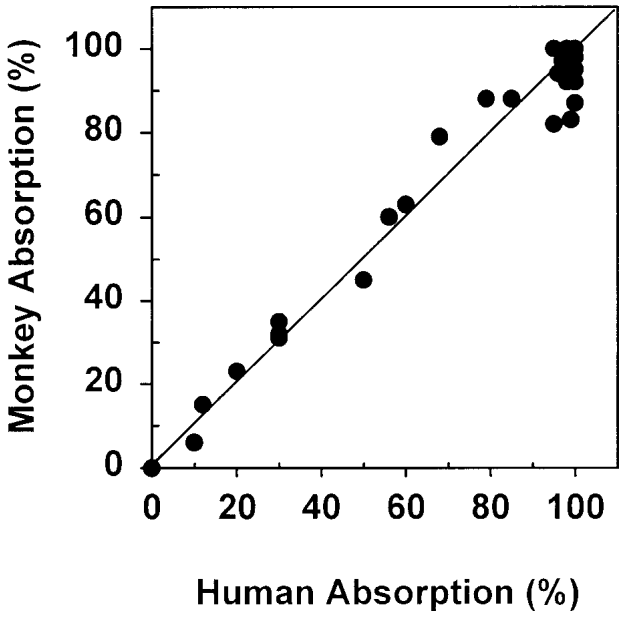

Fig. 1. Correlation of percentage oral dose absorbed between humans and monkeys for 43 drugs with a regression equation of F_a (M) = $0.958F_a$ (H) + 2.8; r^2 = 0.974. Complete absorption demonstrated by 27 drugs in both species. The depicted line has a slope of unity.

lation of F_a between rat and human can be attributed to similar first-order absorption rate constants of drugs (6,17) and similar small intestinal transit times between the two species (6). Whether or not such a rationale may be extended to the current observations between monkey and human remains to be investigated. To date, it appears that no study on intestinal transit times in nonhuman primates has ever been reported.

The time to reach maximum plasma concentration after oral administration (t_{max}) in fasting humans and monkeys was also evaluated from the references used in the F_a and F studies. Fifteen drugs were judged to be adequate for comparison (Table II). Unlike the dog (7), t_{max} values were generally similar in humans and monkeys especially when comparable doses were used. When drugs were administered to monkeys at doses far exceeding that of humans, most notably ifetroban, rolipram, tiludronate, and venlafaxine, t_{max} values tended to be prolonged. This may be attributed to dose-dependent pharmacological effects and/or dissolution/precipitation problems. For metoprolol, the shorter t_{max} observed in monkeys in spite of the large dose employed might be the result of the solution dosage form used in contrast to the tablets used in humans.

The dosage form (solution, fast-release suspension, tablet, or capsule) employed in monkey studies was often different from that used in human studies (Tables I and II). However, despite the differences in dosing formulations, this generally did not seem to have a significant influence on the rate and extent of oral absorption of most drugs evaluated in this study. A similar pattern was also observed between rats and humans (5,6).

Results of the F comparison of 35 drugs are shown in Table III and depicted in Fig. 2. Approximately half of the drugs evaluated demonstrate comparable F values between humans and monkeys. This is consistent with the prediction of similar hepatic first-pass metabolism across the species (18). However, several drugs evaluated reveal a considerably lower F in monkeys (Table III and Fig. 2). For disopyramide (12,19), venlafaxine (12,20,21), and methotrexate (12,22), the differences were approximately 10-fold whereas zolpidem (12,23) and rolipram (24–26) exhibited differences of 34- and 730-fold, respectively. Since the F_a between humans and monkeys is generally similar for the 43 drugs evaluated, the considerably lower F found in monkeys may be attributed to a greater first-pass metabolism taking place in the gut wall, liver, or both.

Data on total and nonrenal clearances (assumed to be equal to total clearance minus renal clearance) of drugs in humans and monkeys were evaluated and compared in an effort to understand the apparent interspecies differences in first-pass metabolism. Total clearance data were obtained for

Table II. Summary of Data[a] on Time to Peak Concentration following Oral Administration (t_{max}) in Humans and Monkeys for 15 Drugs

	Dose		Dosage form		t_{max} in hours[b]	
Drug	Humans	Monkeys	Humans	Monkeys	Humans	Monkeys
Coumarin	0.857 mg/kg	1 mg/kg	Solution	Solution	0.2	0.21 ± 0.03
Ifetroban	50 mg	1 mg/kg	Solution	Solution	0.33	0.33
Flunisolide	2 mg	1 mg	Solution	Solution	0.5	0.5
Methotrexate	30 mg/m^2	0.5 mg/kg	Tablet	Solution	1.5	1.5 ± 0.3
Tiludronate	200 mg	60 mg/kg	Tablet	Solution	1.5 ± 0.9	4.5 ± 2
Venlafaxine	50 mg	10 mg/kg	Tablet	Solution	2.0 ± 0.5	4.3 ± 1.5
Moxifloxacin	1.4 mg/kg	9.2 mg/kg	Tablet	Tablet	2 ± 1.9	4 ± 2
Irbesartan	50 mg	10 mg/kg	Tablet	Suspension	0.33 ± 0.17	2.5
Trovafloxacin	200 mg	20 mg/kg	Tablet	Suspension	1.8 ± 0.9	2.3 ± 1.5
Nicardipine	30 mg	5 mg/kg	Tablet	Solution	1.0	2
Zomepirac	25 mg	5 mg/kg	Solution	Solution	0.6 ± 0.3	1.2 ± 0.8
Fluvastatin	40 mg	0.57 mg/kg	Solution	Capsule	1.2 ± 0.9	1.8 ± 1.0
Rolipram	1 mg	20 mg/kg	Suspension	Suspension	0.38 ± 0.22	1.7 ± 0.9
Indinavir	200–1000 mg	10 mg/kg	Tablet	Solution	0.8 ± 0.03	1.08
Metoprolol	100 mg	9 mg/kg	Tablet	Solution	1.4 ± 0.3	0.4

[a] The references providing data on time to peak concentration are available on request.

[b] Represents mean values for t_{max} ± SD obtained from individual drug references or the 2001 edition of the *Physician's Desk Reference* (2001 edition).

Table III. Summary of Data[a] on Percentage Absolute Bioavailability in Humans and Monkeys for 35 Drugs

Drug	Molecular weight[b]	Property[c]	Dosage form		Bioavailability[d] (%)	
			Humans	Monkeys	Humans	Monkeys
Zomepirac	350	A	Solution	Solution	100	100
Clofibrate	243	A	Suspension	Capsule	100	100
Piroxicam	331	A	Capsule	Suspension	100	89
Nufenoxole	361	B	Capsule	Solution	100	85
Ethosuximide	141	B	Capsule	Solution	100	96
Pirmenol	375	B	Tablet	Solution	87	89
Recainam	263	B	Capsule	Solution	84	87
Trovafloxacin	416	B	Tablet	Suspension	88	85
Irbesartan	428	B	Tablet	Suspension	82	78
Stavudine	224	B	Capsule	Solution	86	77
Carbamazepine	236	B	Tablet	Solution	100	71
Moxifloxacin	438	B	Tablet	Tablet	90	52
Bisoprolol	268	B	Tablet	Solution	80	45
Progabide	335	B	Solution	Solution	60	45
Coumarin	146	B	Solution	Solution	3	45
Captopril	217	A	Tablet	Solution	38	35
Menogaril	542	B	Solution	Solution	35	33
Δ^9-THC	315	A	Capsule	Capsule	20	26
Metoprolol	342	B	Tablet	Solution	38	25
Ifetroban	439	A	Solution	Solution	48	23
Methylphenidate	270	B	Tablet	Solution	30	22
Indinavir	712	B	Tablet	Solution	60	19
Fluvastatin	433	N	Solution	Capsule	24	15
Tiludronate	381	A	Tablet	Solution	6	13
Droloxifene	387	N	Solution	Solution	80	11
Nicardipine	516	B	Tablet	Solution	7	10
Disopyramide	340	B	Capsule	Solution	83	8
Venlafaxine	314	B	Tablet	Solution	60	7
Flunisolide	433	B	Solution	Solution	20	5
Methotrexate	498	A	Tablet	Solution	60	5
Naltrexone	364	B	Tablet	Solution	5	4
Mercaptopurine	152	B	Tablet	Tablet	12	4
Zolpidem	392	B	Tablet	Suspension	67	2
Remikiren	631	B	Suspension	Suspension	2	0.3
Rolipram	275	B	Suspension	Suspension	73	0.1

[a] The references providing data on percentage absolute bioavailability are available on request.
[b] Molecular weights obtained from the following references: *Martindale's Extra Pharmacopeia* (1996 edition), *European Pharmacopeia* (2000 edition), and the *U.S. Pharmacopeia/National Formulary* (2000 edition).
[c] N: neutral compound; A: weak acid; B: weak base; Z: zwitterionic compound.
[d] Represents mean values for percentage absolute bioavailability (%F) from individual drug references or the *Physician's Desk Reference* (2001 edition).

28 drugs whereas nonrenal clearances were only available for 13 drugs (Table IV and Fig. 3). Based on unit body weight, it seems clear that both total and nonrenal clearances in monkeys are generally much higher than those in humans, an observation consistent with the hypothesis of generally higher first-pass metabolism and lower F in monkeys. It is of interest to note that for disopyramide, there was nearly a 10-fold difference in F between monkeys and humans (0.08 vs. 0.83, respectively) (12,19). The total and nonrenal clearances of this drug are 12.3 and 20 times higher, respectively, in monkeys compared to humans. The much higher nonrenal clearance for disopyramide in monkeys may account for its dramatically lower F in this species.

Further examination of Fig. 3 also reveals that the relative magnitude of difference of total or nonrenal clearances between humans and monkeys appears generally greater for drugs with clearances below 15 ml/min per kg in monkeys. However, the differences are only approximately twofold for drugs with clearances greater than 15 ml/min per kg. This observation may be useful in predicting human clearances from monkey clearances. An additional observation in the current study is that the extent of first-pass metabolism ($F_a\% - F\%$) in both monkeys and humans appears to generally correlate well with their total or nonrenal clearances as shown in Fig. 4.

The generally greater first-pass metabolism of drugs in monkeys is also supported by published *in vitro* studies showing greater hepatic cytochrome P450 activity in monkeys compared to humans (8,9,27). For example, the oxidative activity of microsomal protein using nifedipine as a substrate for CYP3A4, a major enzyme for metabolism of drugs in the liver, was found to be approximately 6 times higher in monkeys than in humans (27). This may account for much greater first-pass metabolism associated with zolpidem (*F:* 0.67 in hu-

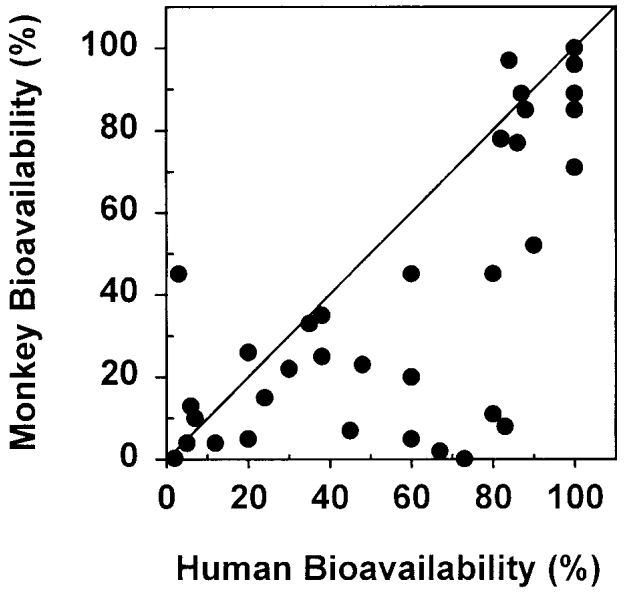

Fig. 2. Correlation of percentage absolute bioavalability between humans and monkeys for 35 drugs with a regression equation of F (M) = 0.723F (H) + 0.06; r^2 = 0.502. The depicted line has a slope of unity.

Table IV. Summary of Data[a] on Total and Nonrenal Clearance (ml/min per kg) in Humans and Monkeys for 28 Drugs

	Total clearance[b]		Nonrenal clearance[c]	
Drug	Humans	Monkeys	Humans	Monkeys
Ethosuximide	0.2	0.3	0.2	0.3
Pirmenol	2.4	4.5	1.7	4.0
Trovafloxacin	2.2	7.2	1.1	7.1
Irbesartan	2.2	3.3	2.2	3.2
Carbamazepine	1.3	8.5	1.1	8.24
Moxifloxacin	2.2	11.5	1.8	10.8
Disopyramide	1.3	16	0.7	14.3
Nicardipine	8.3	27	8.0	27
Indinavir	18	35.7	13.2	28.8
Fluvastatin	23	35	22	33
Tiludronate	3.5	0.8	3.5	0.8
Venlafaxine	22	41	21	41
Flunisolide	12	25	12	22
Naltrexone	48	65		
Zolpidem	4.3	15.8		
Coumarin	24	19		
Menogaril	11	23.2		
Recainam	7.2	22		
Stavudine	8.3	14.5		
Droloxifene	13	23		
Remikiren	11	19.2		
Ifetroban	6.3	19.2		
Zomepirac	4.6	4.3		
Clofibrate	0.1	2.2		
Piroxicam	0.04	0.1		
Methotrexate	1.8	13.5		
Metoprolol	15	29		
Rolipram	7.2	15		

[a] The references providing data on clearance (total and nonrenal) are available on request.

[b] Represents mean values for total clearance from individual drug references or the *Physician's Desk Reference* (2001 edition).

[c] Represents mean values for nonrenal clearance from individual drug references or the *Physician's Desk Reference* (2001 edition).

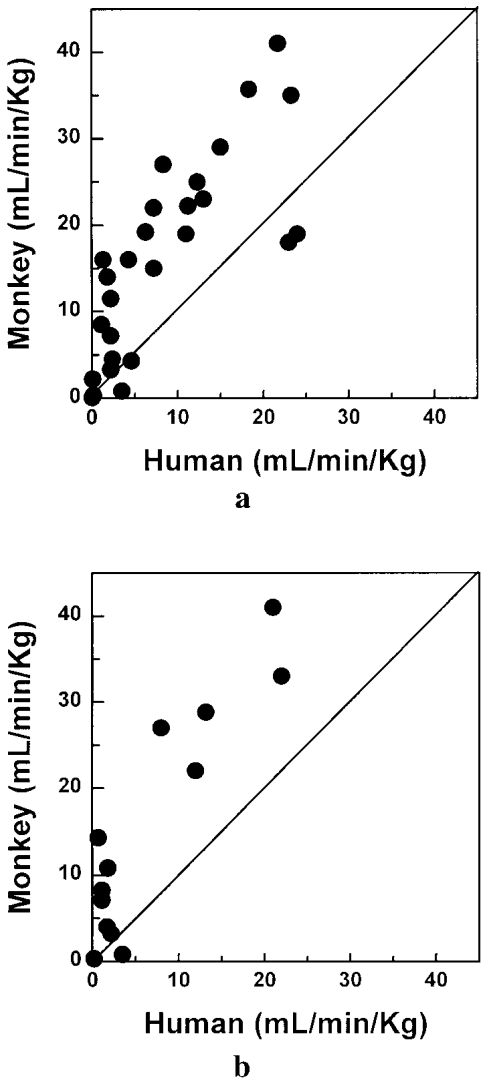

Fig. 3. (a): Correlation of total clearance (Cl_t) between human and monkey for 28 drugs with a regression equation of Cl_t (M) = 1.26Cl_t (H) + 6.12; r^2 = 0.817. (b): Correlation of nonrenal clearance (Cl_{nr}) between human and monkey for 13 drugs with a regression equation of Cl_{nr} (M) = 1.57Cl_{nr} (H) + 4.71; r^2 = 0.820. The depicted line has a slope of unity.

man and 0.02 in monkey) (23) and indinavir (*F:* 0.60 in human and 0.19 in monkey) (28) in monkeys. Both zolpidem and indinavir are known to predominantly undergo phase-I oxidative transformation by CYP3A4 in humans (29,30). Currently, no data seem available on gut wall CYP3A4 activity in monkeys as compared to humans. Based on the importance of gut wall metabolism by CYP3A4 for certain drugs such data may further explain potential differences in first-pass effect between monkeys and humans.

Relative to the interspecies differences in *F,* the most remarkable exception found in the current study is coumarin. The mean F is 3% in humans (31) and 45% in monkeys (32). This may be rationalized by higher (fourfold) hepatic coumarin-7-hydroxylase activity in humans compared to monkeys (8); coumarin-7-hydroxylation being the predominant phase-I metabolic pathway (32). Additionally, the extensive first-pass metabolism of coumarin in humans may be predicted by its high total plasma clearance (24 ml/min per kg),

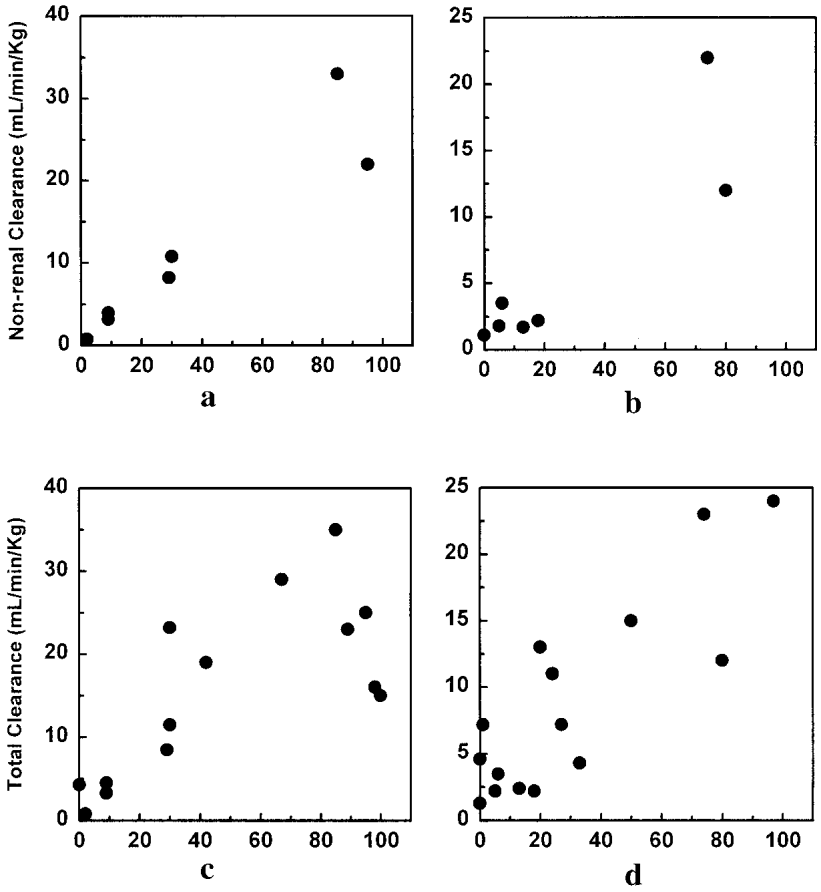

Fig. 4. First-pass metabolism in monkeys (a) and humans (b) vs. nonrenal clearance with $r^2 = 0.538$ and 0.720, respectively. First-pass metabolism in monkeys (c) and humans (d) vs. total clearance with $r^2 = 0.877$ and 0.802, respectively.

which approaches hepatic blood flow (33). The total plasma clearance of coumarin (19 ml/min per kg) may also be consistent with the moderate *F* in monkeys (33).

In conclusion, monkeys and humans appear to be generally similar with regard to the rate and extent of drug absorption. This is similar to that seen between rats and humans (5–7). However, despite the similarities in monkey and human absorption kinetics, marked differences are found in oral bioavailability (lower in monkey) as well as in total and nonrenal plasma clearances (both higher in monkey). Because bioavailability values may dictate the therapeutic potential of a drug, it appears that caution should be exercised in extrapolating data obtained in monkeys as it may not predict that in humans.

REFERENCES

1. B. Clark and D. A. Smith. Pharmacokinetics and toxicity testing. *Crit. Rev. Toxicol.* **12**:343–385 (1984).
2. J. H. Lin. Species similarities and differences in pharmacokinetics. *Drug Metab. Dispos.* **23**:1008–1020 (1995).
3. R. M. Feng, X. Lou, R. R. Brown, and A. Hutchaleelaha. Allometric pharmacokinetic scaling: Towards the prediction of human oral pharmacokinetics. *Pharm. Res.* **17**:410–418 (2000).
4. W. L. Chiou. Commentary: The rate and extent of oral bioavailability vs. the rate and extent of oral absorption: Classification and recommendation of terminology. *J. Pharmacokinet. Pharmacodyn.* **28**:3–6 (2001).
5. W. L. Chiou and A. Barve. Linear correlation of the fraction of oral dose absorbed of 64 drugs between humans and rats. *Pharm. Res.* **15**:1792–1795 (1998).
6. W. L. Chiou, C. Ma, S. M. Chung, Y. H. Jeong, and T. C. Wu. Similarity in the linear and non-linear oral absorption of drugs between human and rat. *Int. J. Clin. Pharmacol. Ther.* **38**:532–539 (2000).
7. W. L. Chiou, Y. H. Jeong, S. M. Chung, and T. C. Wu. Evaluation of dog as an animal model to study the fraction of oral dose absorbed for 43 drugs in humans. *Pharm. Res.* **17**:135–140 (2000).
8. J. C. Stevens, L. A. Shipley, J. R. Cashman, M. Vandenbranden, and S. A. Wrighton. Comparison of human and rhesus monkey *in vitro* phase I and phase II hepatic drug metabolism activities. *Drug Metab. Dispos.* **5**:753–760 (1993).
9. J. E. Sharer, L. A. Shipley, M. R. Vandenbraden, S. N. Binkley, and S. A. Wrighton. Comparison of phase I and phase II *in vitro* hepatic enzyme activities of human, dog, rhesus monkey, and cynomolgus monkey. *Drug Metab. Dispos.* **23**:1231–1241 (1995).
10. W. K. Sietsema. The absolute oral bioavailability of selected drugs. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **27**:179–211 (1989).
11. L. Z. Benet. S. Øie and J. B. Schwartz. Design and optimization of dosage regimines: Pharmacokinetic data. In A. Goodman-Gilman, J. G. Hardman, L. E. Limbard, P. B. Molinoff, and R. W. Ruddon (eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th edition, McGraw-Hill, New York, 1996, pp. 1707–1792.
12. *Physician's Desk Reference*, Medical Economics Company, Monvale, New Jersey, 2001.
13. M. Gibaldi and D. Perrier. *Pharmacokinetics*, Marcel Dekker, New York, 1982.
14. W. L. Chiou. Commentary: We may not measure the correct wall permeability coefficient of drugs: Alternative absorptive clearance concept. *J. Pharmacokinet. Biopharm.* **23**:323–343 (1996).

15. W. L. Chiou. Commentary: New perspectives on the theory of of permeability and resistance in the study of drug absorption and transport. *J. Pharmacokinet. Biopharm.* **24**:433–442 (1997).
16. T. T. Kararli. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. *Biopharm. Drug Dispos.* **16**:351–380 (1995).
17. E. Chen, Z. Chen, and J. Bielawski. Prediction of oral absorption rate constant in human from *in vivo* rat data—applications to interspecies scaling and first-dose in man study optimization. *J. Pharm. Sci.* (Suppl. 1)**1**:S-599 (1998).
18. S. Tannenbaum, H. Boxenbaum, and M. Mayersohn. Allometric analysis of organ extraction ratios. *J. Pharm. Sci.* **86**:1319–1320 (1997).
19. N. J. Haskins, K. A. Waddell, G. C. Ford, P. N. Spalton, C. M. Walls, T. J. Forrest, and R. F. Palmer. The absorption of disopyramide in animals determined using a stable isotope coadministration technique. *Biomed. Mass Spectrom.* **7**:80–83 (1980).
20. S. R. Howell, G. E. Husbands, J. A. Scatina, and S. F. Sisenwine. Metabolic disposition of 14C-venlafaxine in mouse, rat, dog, rhesus monkey and man. *Xenobiotica* **23**:349–359 (1993).
21. S. R. Howell, D. R. Hicks, J. A. Scatina, and S. F. Sisenwine. Pharmacokinetics of venlafaxine and O-desmethylvenlafaxine in laboratory animals. *Xenobiotica* **24**:315–327 (1994).
22. T. Kuroda, K. Namba, T. Torimaru, K. Kawashima, and M. Hayashi. Species differences in oral bioavailability of methotrexate between rats and monkeys. *Biol. Pharm. Bull.* **23**:334–338 (2000).
23. A. Durand. J. P. Thénot, G. Bianchetti, and P. L. Morselli. Comparative pharmacokinetic profile of two imidazopyridine drugs: zolpidem and alpidem. *Drug Metab. Rev.* **24**:239–266 (1992).
24. W. Krause and G. Kühne. Pharmacokinetics of rolipram in the rhesus and cynomolgus monkeys, the rat and the rabbit. Studies on species differences. *Xenobiotica* **18**:561–571 (1988).
25. W. Krause, G. Kühne, U. Jakobs, and G. A. Hoyer. Biotransformation of the antidepressant D,L-rolipram. I. Isolation and identification of metabolites from rat, monkey, and human urine. *Drug Metab. Dispos.* **21**:682–689 (1993).
26. W. Krause and G. Kühne. Biotransformation of the antidepressant D,L-rolipram. II. Metabolite patterns in man, rat, rabbit, rhesus and cynomolgus monkey. *Xenobiotica* **23**:1277–1288 (1993).
27. T. Shimada, M. Mimura, K. Inoue, S. Nakamura, H. Oda, S. Ohmori, and H. Yamazaki. Cytochrome P450-dependent drug oxidation activities in liver microsomes of various animal species including rats, guinea pigs, dogs, monkeys and humans. *Arch. Toxicol.* **71**:401–408 (1997).
28. J. H. Lin, M. Chiba, S. K. BalaniI, W. Chen, G. Y. Kwei, K. J. Vastag, and J. A. Nishime. Species differences in the pharmacokinetics and metabolism of indinavir, a potent human immunodeficiency virus protease inhibitor. *Drug Metab. Dispos.* **24**:1111–1120 (1996).
29. L. Prichard, G. Gillet, C. Bonfils, J. Domergue, J. P. Thénot, and P. Maurel. Oxidative metabolism of zolpidem by human liver cytochrome P450s. *Drug Metab. Dispos.* **23**:1253–1262 (1995).
30. M. Chiba, J. A. Nishime, W. Neway, Y. Lin and J. H. Lin. Comparative in vitro metabolism of indinavir in primates—a unique stereoselective hydroxylation in monkey. *Xenobiotica* **30**:117–129 (2000).
31. W. A. Ritschel, K. A. Hoffmann, H. S. Tan, and P. R. Sanders. Pharmacokinetics of coumarin upon i.v. administration in man. *Arzneimittelforschung* **26**:1382–1387 (1976).
32. W. A. Ritschel, D. D. Denson, and K. W. Grummich. Pharmacokinetics of coumarin and 7-hydroxycoumarin in the rhesus monkey after intravenous and peroral administration. *Arzneimittelforschung* **38**:1619–1623 (1988).
33. W. A. Ritschel, N. N. Vachharajani, R. D. Johnson, and A. S. Hussain. Interspecies scaling of the pharmacokinetic parameters of coumarin among six different mammalian species. *Methods Find. Exp. Clin. Pharmacol.* **13**:697–702 (1991).