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Fluconazole: Interspecies Scaling and Allometric Relationships of Pharmacokinetic Properties

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Abstract—Fluconazole is a novel azole antifungal agent with low lipophilicity and high metabolic stability which has been investigated pharmacokinetically in six animal species and in man. The pharmacokinetic parameters of this drug have been compared across species and allometric relationships for fluconazole have been established. The volume of distribution was an 'invariant' parameter. When expressed in units corrected for bodyweight, the volume of distribution was constant across species, in keeping with being distributed throughout body water. Allometric relationships were obtained for total and renal clearance parameters. The closeness of the allometric exponents was in keeping with renal elimination accounting for most of the clearance in all species investigated. It also follows from the invariant characteristics of the volume of distribution term that an allometric relationship for plasma elimination half-life ($t_{\frac{1}{2}}$) was also evident. Fluconazole thus possesses pharmacokinetic properties which are predictable for all terrestrial mammals. More detailed analysis of renal clearance (CL_R) with regard to its relationship with glomerular filtration rate (GFR) has also been carried out. The data suggest that CL_R is a direct function of GFR, involves only passive diffusion phenomena and that the extent of tubular re-absorption (approx. 80%) is constant across species. These observations are in keeping with the moderate lipophilicity and plasma protein binding of fluconazole and the incomplete re-absorption of the drug from the kidney tubules. It follows from these investigations that a knowledge of GFR in patients with altered renal function should allow a mechanistically based prediction of elimination characteristics of fluconazole.

Fluconazole is a recently marketed antifungal agent with broad spectrum antifungal activity (Troke et al 1990). It has been a subject of several pharmacokinetic evaluations in various species including man. Overall, fluconazole is characterized by virtually complete absorption from the gastrointestinal tract, distributed throughout body tissues and is not extensively metabolized, excretion being predominantly by renal elimination of unchanged drug (Humphrey et al 1985). This paper describes the pharmacokinetic properties of fluconazole across several species, focussing in particular on the allometric comparison of the more fundamental pharmacokinetic properties: volume of distribution, total clearance and renal clearance.

Materials and Methods

Pharmacokinetic data

Values for total clearance (CL), renal clearance (CL_R), volume of distribution (Vd) and elimination half-lives of fluconazole for mouse, rat, rabbit, dog and man were obtained from the literature. Additional pharmacokinetic data were obtained for rabbit, cat and guinea-pig by administering fluconazole either by the intravenous route or gavage at a dose level of 10 mg kg^{-1}, known to yield linear pharmacokinetics in all species investigated. Plasma samples were obtained over periods of 120 and 96 h by venepuncture (cat and rabbit, respectively) and for 48 h by terminal exsanguination (guinea-pig). Urine was collected over a period of 72 h in the guinea-pig study. Fluconazole was assayed by specific HPLC or bioassay methods as described by Rex et al (1991). The pharmacokinetic parameters were derived using standard methods: systemic clearances were calculated from $AUC_{0-\infty}$ values by the trapezoidal method, elimination half-lives ($t_{\frac{1}{2}}$) were calculated using the slope (λ) of the log transform of plasma concentration-time data. Volume of distribution values were derived from clearance and $t_{\frac{1}{2}}$ data.

Physiological properties such as body weight and body water content were as described in each respective report or obtained from literature references. The body weight for man used in the correlations was 70 kg. The mean data are summarized in Table 1.

Allometric parameters

Allometric equations describing the mathematical relationships between bodyweight and various pharmacokinetic properties were derived using regression analysis. The interspecies allometric relationships were investigated in accordance with established pharmacokinetic principles (Boxenbaum 1984). The variable parameter P is described as a function of body weight B as $P=\alpha \cdot B^{\beta}$, where α is the allometric coefficient and β the allometric exponent.

Regression analysis and statistical characterization of regression lines were carried out using algorithms available on the computer software RS/1 (BBN Software Products Corporation, Cambridge, MA, USA).

Physicochemical properties

The partition coefficient of fluconazole (log $P_{octanol}$) was determined by the method of Stopher & McClean (1990). The drug (total concentration 0·5 mg mL^{-1}) was distributed between equal volumes (1 mL) of octanol and buffer (0·1 M sodium hydrogen phosphate pH 7·4). The two phases were separated by centrifugation (2500 *g*) and analysed by the HPLC method of Rex et al (1991) but using a mobile phase of acetonitrile: 0·03 M ammonium phosphate pH 3·0 (36:64). The ionization constant (pK_a) was determined by solubility measurements in 0·1 M sodium chloride (Albert & Serjeant 1984).

Table 1. Summary of mean pharmacokinetic parameters of fluconazole in several species.

Species	Bodyweight (B) (kg)	Elimination half-life ($t_{\frac{1}{2}}$) (h)	Total clearance (CL) (mL min^{-1})	Renal clearance (CL_R) (mL min^{-1})	Volume of distribution (Vd) (L)	Volume of distribution (Vd) (L kg^{-1})
Mouse[a]	0·02 ± 0·002	4·8	0·08	0·06	0·02	1·1
Rat[a]	0·1 ± 0·01	4·0	0·22	0·18	0·08	0·80
Guinea-pig[b]	0·4 ± 0·08	5·2	0·64	0·29	0·3	0·75
Rabbit[c]	3·0 ± 0·7	10·4 ± 2·3	3·0 ± 0·4	ND	2·6 ± 0·1	0·88 ± 0·04
Cat[d]	2·4 ± 0·06	11·0 ± 1·5	1·5 ± 0·4	ND	1·2 ± 0·2	0·50 ± 0·08
Dog[e]	13·2	14·0	8·4	6	9·1	0·70
Man[f]	70·0	26·4 ± 4·1	21·9 ± 4·4	14·1 ± 3·1	49·4 ± 7·6	0·71 ± 0·11

Standard deviations are given for pharmacokinetic parameters in which serial samples were taken (rabbit, cat and man). Pharmacokinetic data from the smaller species were obtained from single-sample studies. ND = no data. [a] Pharmacokinetic parameters were derived from plasma data obtained using groups of 40 mice and rats, pooled samples were from five animals per time point, sampling was over 24 h (Humphrey et al 1985). Clearance and volume parameters are from intravenous data only, elimination $t_{\frac{1}{2}}$ is the mean from oral and intravenous data. [b] Study design was as for a above, using n = 17 animals, one animal per time point. Sampling was over 48 h. [c] Mean data from Walsh et al (1989) and values obtained as described in the Material and Methods section: n = 5 animals, sampling over 96 h. [d] Pharmacokinetic parameters were obtained from four cats using an oral/intravenous cross-over study design. Sampling was over 120 h. [e] Pharmacokinetic parameters were obtained from two dogs (both 13·2 kg) using an oral/intravenous cross-over study design. Sampling was over 48 h (Humprey et al 1985). [f] Mean data from published literature values (Humphrey et al 1985; Brammer & Tarbit 1987; Toon et al 1990; Brammer et al 1991; Ferrante et al 1992). Total number of subjects = 27. Body weight values were in the range 53–81 kg when quoted; a standard value of 70 kg was used in calculations.

Results and Discussion

Physicochemical properties and bioavailability

The lipophilicity of fluconazole is moderate, being characterized by a log $P_{octanol} = 0·5$ in contrast to most other azole antifungal drugs which are very lipophilic (e.g. ketoconazole log $P_{octanol} = 3·8$ and itraconazole log $P_{octanol} = 5·7$). Fluconazole is a weak base with a pK_a value of 1·76 and is thus essentially un-ionized at blood and urine pH values. These properties, in conjunction with good solubility in water (6 mg mL^{-1} at 37°C (Marriott & Richardson 1987)) account for its rapid and complete absorption. Due to the absence of metabolically labile structural components, fluconazole undergoes a very low degree of metabolism. This ensures an absence of pre-systemic metabolism and thus good bioavailability (> 80%) in all species investigated.

Volume of distribution

The allometric relationships between volume of distribution (Vd) and bodyweight (B) across the species is illustrated in Fig. 1, and characterized by $Vd = 0·76 \cdot B^{0·96}$.

Table 2 provides a summary of the allometric parameter estimates and statistical characterization of the regression analysis. The value of 0·96 for the allometric exponent is so close to unity as to make Vd directly proportional to B, i.e. an invariant parameter. Vd corrected for body weight is therefore relatively constant across the species with a mean value of 0·78 ± 0·18 L kg^{-1}. The calculated mean value of 0·78 L kg^{-1} for fluconazole is compatible with this drug being distributed throughout body water; percentage body water is essentially constant at about 80% for mammals (Altman & Dittmer 1974). This concept is supported by the excellent efficacy of the drug for both systemic and deep-seated candidal or cryptoccocal infections (Brammer et al 1991). Antipyrine is a drug with very similar physicochemical properties ($pK_a = 2·2$ and log $P_{octanol} = 0·3$) to fluconazole and for which allometric equations have been derived (Ritschel & Banerjee 1986). Antipyrine has an identical allometric exponent value (0·96) and identical allometric coefficient (0·76) to fluconazole. Both these compounds are neutral, water-soluble and moderately lipophilic. These properties ensure that the drugs will have no specific tissue affinity but pass readily through membranes to occupy total body water.

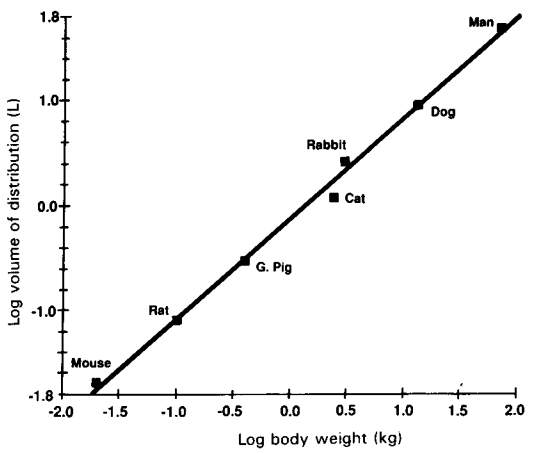

FIG. 1. Allometric relationship between bodyweight and volume of distribution.

Clearance

The total clearance (CL) can be related to bodyweight (B) as shown in Fig. 2. The relationship is characterized by $CL = 1·15 \cdot B^{0·71}$. Renal clearance (CL_R) was also investigated (Fig. 3) and the equation $CL_R = 0·82 \cdot B^{0·67}$ was obtained.

Total clearance correlates very well with bodyweight (Fig. 2, Table 2). The allometric relationship for renal clearance in five species (no urinary data were available for rabbit or cat)

Table 2. Summary of allometric coefficients, exponents and statistical characterization of regression lines.

Parameter	Coefficient α	Exponent β	Analysis of variance P	Analysis of variance r^2
Vd	0·76	0·96	$0·5 \times 10^{-7}$	0·995
CL	1·15	0·71	2×10^{-6}	0·992
CL_R	0·82	0·67	0·0007	0·986
*$CL_{creatinine}$	4·2	0·69	—	—
$t_{\frac{1}{2}}$	8·7	0·24	0·0017	0·882

* Adolph (1949).

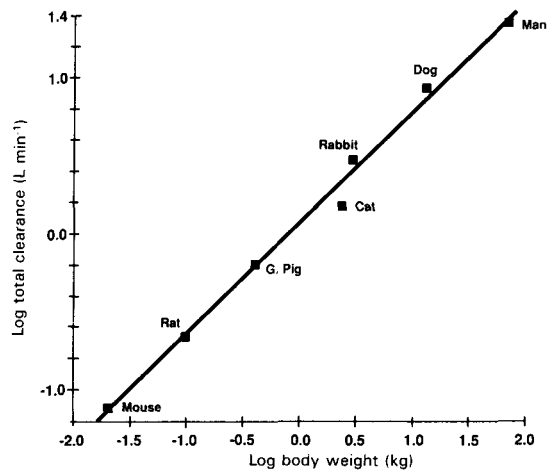

FIG. 2. Allometric relationship between bodyweight and total plasma clearance.

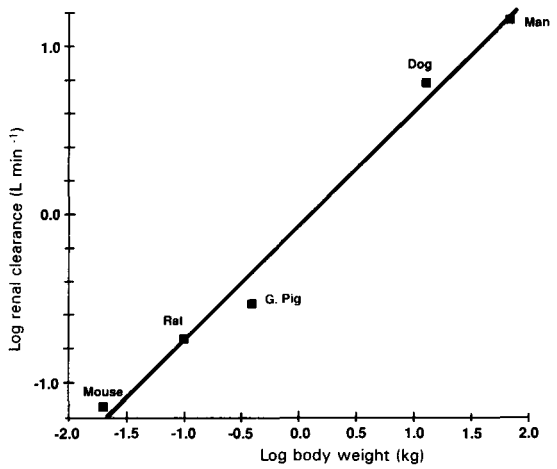

FIG. 3. Allometric relationship between bodyweight and renal clearance.

is also good, with a very similar slope to that observed for CL (allometric exponent values of 0·71 and 0·67 for CL and CL_R, respectively). This is in keeping with the observation that the major route of elimination is renal clearance for mouse, rat, guinea-pig, dog, man and probably all species (Humphrey et al 1985). Non-renal clearance has been shown to be a small but significant elimination pathway in man (Brammer et al 1991) and appears to be even more significant in the guinea-pig, as shown in Table 1.

The allometric relationship is very similar to that reported by Adolph (1949) to describe the allometric analysis of creatinine clearance (a common measure of glomerular filtration rate, GFR): $CL_{creatinine} = 4{\cdot}2 \cdot B^{0{\cdot}69}$.

In the case of fluconazole, the relationship between CL_R and GFR is characterized by the ratio between their allometric coefficients; CL_R is a relatively constant fraction of GFR (19·5%) and confirms the finding of Toon et al (1990). This would be consistent with a constant extent of tubular reabsorption across the species. The value itself is possibly an indication that most of the tubular absorption of

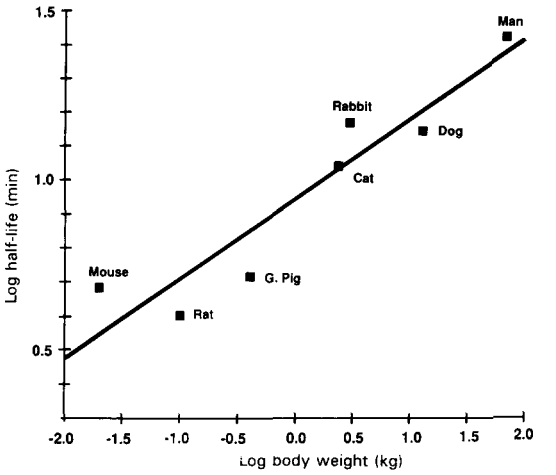

FIG. 4. Allometric relationship between bodyweight and plasma elimination half-life.

fluconazole takes place in the proximal tubule where some 80% of water is re-absorbed (Rowland & Tozer 1980). The dependency of renal clearance on GFR is in keeping with the work of Toon et al (1990) who have shown that, in patients with various degrees of renal function, fluconazole CL_R was positively correlated with GFR. The moderate lipophilicity of fluconazole, its low plasma protein binding (12%) across species (Humphrey et al 1985) and the low degree of ionization at physiological pH are also compatible with high filtration at the glomerulus, followed by extensive but incomplete reabsorption (80%) by passive diffusion processes.

Elimination half-life

The overall invariancy of the Vd term and the allometric relationship observed for CL would allow a prediction that an allometric relationship should also be observed for the elimination half-life ($t_{\frac{1}{2}}$). The $t_{\frac{1}{2}}$ data is illustrated in Fig. 4 and gives the relation $t_{\frac{1}{2}} = 8{\cdot}7 \cdot B^{0{\cdot}24}$.

Examination of Fig. 4 shows that the mouse $t_{\frac{1}{2}}$ parameter biases the regression; the mouse has the highest value for bodyweight-corrected Vd (1·1 L kg^{-1}). In addition, if the method of Rowland (1985) is used to obtain an allometric equation for $t_{\frac{1}{2}}$ using the allometric parameters for Vd and CL, the relationship is notably different and becomes $t_{\frac{1}{2}} = 0{\cdot}44 \cdot B^{0{\cdot}25}$. Applying this equation to the mouse, a theoretical value of 2·8 h is obtained, which is in contrast to that of 4·8 h observed by Humphrey et al (1985). This discrepancy probably arises from the inherent difficulties involved in measuring pharmacokinetic parameters in very small species such as the mouse.

Overall, allometric analysis for fluconazole shows that the pharmacokinetic properties of this drug are predictable. The correlations obtained allow the calculation of elimination $t_{\frac{1}{2}}$ values not only for healthy mammals on the basis of bodyweight, but also for subjects with impaired renal function on the basis of residual GFR.

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