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Pharmacokinetics in Drug Screening

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The bioavailability of a drug describes the proportion of an administered drug delivered intact to the systemic circulation, and the rate at which this occurs. In the case of an orally administered drug, the quantity of a drug delivered intact to the systemic circulation is generally smaller than the quantity administered, because absorption of a drug from the gastrointestinal tract is usually incomplete.

The subject of bioavailability deals only with the transfer of a drug from the site of administration into the systemic circulation. Once there, however, the drug must be distributed in the body, and is simultaneously metabolized and excreted. The subject of pharmacokinetics deals with the entire "history" of the drug in the body, from administration to elimination, and includes absorption, distribution, metabolism and excretion ([10]). Pharmacokinetics may be thought of as the science of what the body does to a drug, whereas pharmacology is the science of what a drug does to the body.

The pharmacokinetics of a drug in an experimental animal are almost always different from those of the drug in man. For a given drug, its properties of absorption, distribution, metabolism and excretion may all be different in man from those in the experimental animal. Therefore, extrapolation of the activity of a drug in an experimental animal to its activity in man must be made carefully, considering the pharmacokinetic differences of the drug in man and in the experimental species.

In general, active dosages of a drug in the laboratory animal are larger than those in man. Therefore, drug dosages active in man are often too small to be active in the animal. In fact, although there are exceptions to the rule, it appears that the smaller the animal species, the larger the dosage required for activity. Even in man, equipotent dosages for young children are generally larger than those for adults. One possible reason for this is that metabolic activity appears to correlate better with surface area than with body weight ([10]); and, as shown in Table 1, the ratio body surface area : body weight decreases sharply with increasing body weight.

In Table 2 are shown for different species the dosages of a drug in mg per kg body weight that provide an equally potent dosage in mg per cm^2 of body surface area. As may be noted, for most drugs, the equipotent dosage is 12 times larger in the mouse than in man. An application of these relationships is shown in Table 3, which presents the once-daily dosages in mg per kg body weight administered to different experimental animals that are equipotent with a variety of daily doses in man.

Before attempting to measure the activity of a drug against *Mycobacterium leprae* in the mouse, it would be helpful to know the minimal inhibitory concentration (MIC) of the drug against mycobacteria other than *M. leprae.* One should also assemble all of the data available on the pharmacokinetics of the drug in man and in experimental animal species, and examine these data in light of the relationships presented in Tables 1–3. Then, one begins by administering the drug in a dosage approximately 12 times that expected to be effective in man. After a single dose administered in a volume smaller than 0.5 ml by esophageal cannula (gavage), blood should be collected at intervals by retroorbital puncture from 3–5 mice, in order to determine the maximal concentration (C_{max}) of the drug in plasma or serum, the time after administration when the C_{max} is obtained (T_{max}), the half-time of disappearance of the drug from the blood ($T_{½}$), and the area, in units of concentration × time, under a curve (AUC) representing the concentration of the drug in the plasma or serum at different intervals after administration. At the least, rough estimates of these parameters will assist one to choose the drug dosages to be tested, in order to obtain a valid assessment of the antimicrobial activ-

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TABLE 1. *Comparison of body weight and body surface area for several species.*

Species	Body weight (g)	Range of body surface area (cm^2)	Surface area (cm^2)
	Mean (range)		Weight (g)
Mouse	22 (18–25)	65–70	2.9–3.1
Rat	250 (200–350)	350–400	1.4–1.6
Rabbit	2500 (1800–2600)	1600–1900	0.6–0.7
Dog	12,000 (10,000–15,000)	5600–6500	0.4–0.5
Man	66,000 (64,000–75,000)	16,000–18,000	0.2–0.3

ity of the drug against *M. leprae* in the mouse. The data obtained from studies of dapsone (DDS), rifampin (RMP), and ofloxacin (OFLO) serve to explain the rationale of these recommendations.

Pharmacokinetics of DDS in man and the mouse. DDS, the primary drug for treatment of leprosy for more than 20 years, and still an obligatory component of the multidrug regimens employed currently in leprosy treatment and control, exhibits different pharmacokinetics in man and in the mouse. In man, a single oral dose of 1.6 mg per kg body weight, corresponding to the ingestion of a 100-mg tablet by a man weighing 60 kg, yields a C_{max} of 1.2 μg per ml, and a mean $T_{½}$ of 20.6 hr ([3]). Because of the long $T_{½}$, DDS is not completely eliminated from the body within 24 hr; therefore, daily administration of 100 mg of the drug leads to a steady state, characterized by a C_{max} of 2.2 μg per ml, and a trough level of 1 μg per ml ([1]). In the mouse, a single intraperitoneal (IP) dose of 10 mg per kg yields a C_{max} of 5.6 μg per ml, and a $T_{½}$ of 2.7 hr ([1]), whereas a single IP dose of 1 mg per kg yields a C_{max} of 0.28 μg per ml, and a $T_{½}$ of 2.6 hr ([7]). To compensate for the relatively short $T_{½}$ of DDS in the mouse, and to obtain stable concentrations of the drug in the body, such as occur in man, DDS is usually administered incorporated into the mouse diet in concentrations of 0.01, 0.001 and 0.0001 g per 100 g diet; assuming that a mouse weighing 25 g consumes 5 g diet per day, these concentrations correspond roughly to 20, 2, and 0.2 mg DDS per kg per day, respectively. As shown in Table 4, the plasma levels of DDS measured in the plasma of mice administered DDS in concentrations in the diet of 0.01, 0.001 and 0.0001 g per 100 g diet correlate well with the plasma concentrations achieved in man administered, respectively, 100, 10 and 1 mg DDS per day. Thus, to obtain in mice plasma levels of DDS equal to those obtained in man, one administers a dosage to mice approximately 12-fold that administered to man.

Pharmacokinetics of RMP in man and the mouse. Although, in general, the active dosages of drugs are about 12 times larger in the mouse than in man, there are exceptions to this rule. RMP represents one of these exceptions ([4]). As shown in Figure 1, the $T_{½}$ of RMP administered in a daily oral dose

TABLE 2. *Equivalent dosages in mg per kg body weight for equipotent doses for several species.*

Species	Dosage (mg per kg)					Species ratio*
Mouse	100	200	400	800	1600	12
Rat	50	100	200	400	800	6
Rabbit	25	50	100	200	400	3
Dog	15	30	60	120	240	1.8
Man	8–8.5	17 (15–20)	34 (30–35)	67 (65–70)	133 (130–135)	1.0

* Ratio of dosages in experimental species equipotent with the dose for man.

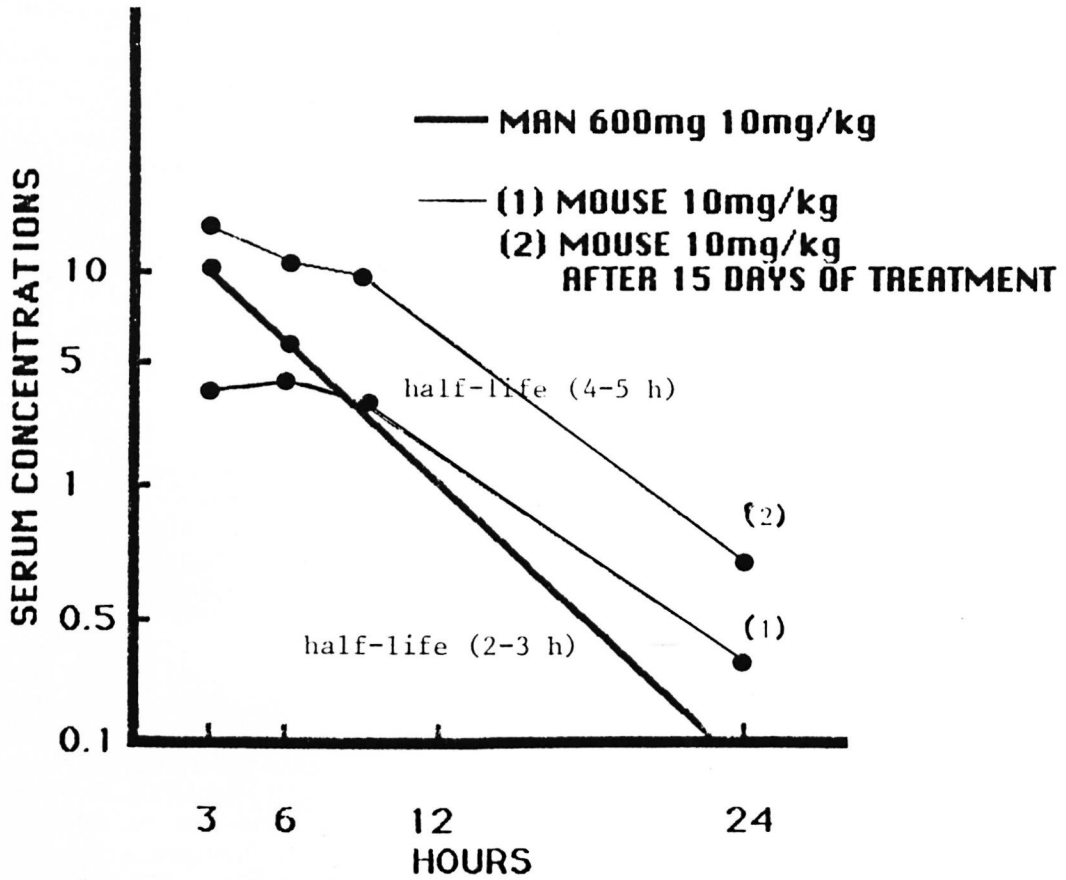

FIG. 1. Comparative plasma concentrations of RMP in man and in the mouse after single oral doses of 10 mg per kg body weight (adapted from reference no. 4).

of 10 mg per kg is 2–3 hr in man and 4–5 hr in the mouse ([4]). Because of the relatively long $T_{1/2}$ in mice, the drug is not entirely eliminated within 24 hr, and accumulates, whereas this does not occur in man. Thus, after a dose of 10 mg per kg, the C_{max} of RMP is higher in the mouse than in man. Therefore, when one assesses the antimicrobial activity of RMP in the mouse, and wishes to extrapolate the results to man, one should employ a dosage no larger than that to be employed in man. That RMP displays more favorable pharmacokinetics in the mouse than in man appears to result from the more limited metabolism and excretion of the drug in the mouse.

TABLE 3. *Once-daily dosages in several animal species corresponding to daily doses in man.*

Daily dose in man (mg)	Equivalent once-daily dosage (mg per kg body weight)			
	Mouse	Rat	Rabbit	Dog
500	100	50	25	15
600	100	50	25	15
750	150	70	35	20
800	150	70	35	20
900	160	80	40	25
1000	180	90	45	25
1200	225	110	55	30–35
1500	275	140	70	40
2000	360	180	100	50
2500	450	225	150	70–75

Pharmacokinetics of OFLO in man and the mouse. OFLO is a new fluoroquinolone with low MICs against numerous mycobacterial species ([11]), and with activity *in vivo* against *M. tuberculosis* ([12]) and *M. leprae* ([9]; unpublished data). In man, OFLO administered orally is readily absorbed in the gastrointestinal tract, with the C_{max} obtained in less than one hr. As shown in Table 5, there

TABLE 4. *Plasma concentrations of DDS in man and the mouse.*

Man			Mouse		
Daily dose (mg)	Equivalence (mg/kg)	C_{max} (μg/ml)	DDS in diet (g/100 g)	Equivalence (mg/kg)	Plasma conc. (μg/ml)
100*	1.6	2.3	0.01†	20	0.74
10°	0.16	0.19	0.001°	2	0.093
1†	0.016	0.018	0.0001°	0.2	0.011

* Taken from reference no. 3.
† Taken from reference no. 1.
° Taken from reference no. 8.

TABLE 5. *Important pharmacokinetic parameters of OFLO in man.**

Single oral dose (mg)	100	200	400
Equivalence (mg/kg)	1.6	3.3	6.6
$T_{1/2}$ (hr)	6.74 ± 0.26	6.96 ± 0.39	7.40 ± 0.25
C_{max} (μg/ml)	1.33 ± 0.11	2.64 ± 0.22	5.64 ± 0.44
T_{max} (hr)	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
AUC (μg × hr/ml)	7.75 ± 0.39	15.6 ± 0.79	35.4 ± 1.88
Clearance (ml/min)	201 ± 9.8	201 ± 11.3	177 ± 9.9

* Adapted from reference no. 5.

is proportionality between the quantity of OFLO ingested and the C_{max}, at least for dosages between 100 and 400 mg daily ([2, 5]). The $T_{1/2}$ is 6–7 hr, so that the drug accumulates; during daily administration of 400 mg, the usual dosage in man, the C_{max} can reach 5–6 μg per ml, with trough concentrations of 1 μg per ml. In mice, OFLO administered by gavage is readily absorbed in the gastrointestinal tract, and the C_{max} is achieved after about 30 min ([6]). As shown in Table 6, the values of the C_{max} achieved after dosages of 50–150 mg per kg are much higher than those achieved in man after dosages of 1.6–6.6 mg per kg (Table 5). However, the $T_{1/2}$ of OFLO in the mouse, 0.65–1.12 hr, depending upon the dosage, is much shorter than that in man; as a result, the AUC, the integral of the plasma concentration of the drug over time following a single dose of the drug, is smaller in mice administered OFLO in a dosage of 50–100 mg per kg than in man administered the drug in a dosage of 6.6 mg per kg. If one assumes that dosages providing equivalent AUCs exhibit equivalent activity, then the equivalent dosage in mice is 15–22 times greater than that in man.

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TABLE 6. *Important pharmacokinetic parameters of OFLO in the mouse.**

Single oral dose (mg/kg)	50	100	150
$T_{1/2}$ (hr)	0.65 ± 0.12	0.83 ± 0.03	1.12 ± 0.48
C_{max} (μg/ml)	11 ± 5	22 ± 2	25 ± 9
T_{max} (hr)	0.5	0.38 ± 0.22	0.5
AUC (μg × hr/ml)	12.65 ± 3.85	29.7 ± 6.25	48.0 ± 7.98
Clearance (ml/min)	69 ± 21	56 ± 11	52 ± 9

* Previously unpublished data from this laboratory.

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