Thus, human intestinal exposure to this drug would be underestimated on the basis of rat data but overestimated on the basis of dog data.

The extent of biliary excretion, if followed by enterohepatic circulation, can be an important factor contributing to the risk of drug toxicity. This point is clearly demonstrated with indomethacin where there is a distinct relationship between enterohepatic recycling, intestinal drug exposure, and toxic dose. When administered indomethacin, marked interspecies differences in cumulative intestinal exposure were observed, where dog > rat > rhesus monkey > guinea pig > rabbit > man. The corresponding toxic dose in these species was related to the magnitude of their intestinal indomethacin exposure. Therefore, while the toxic dose was only 0.5 mg/kg/day in dogs, it was as high as 20 mg/kg/day in rabbits (137). Similarly, unusually high bile/plasma concentration ratios of the sulfasalazine analogue, susalimod, were observed in dogs (ratio = 3400) as compared to monkey (ratio = 300) and rat (ratio = 50). This difference in bile concentrations correlated with the long-term use hepatobiliary toxicity observed in dogs but not in the other two species (138).

Since presence or absence of a gall bladder also impacts the characteristics of bile release into the intestine, we anticipate that the presence of a gall bladder and the pattern of bile release in the intestine will influence the rate and extent of biliary drug recycling. In species with gall bladders, the discharge of bile into the duodenum occurs during Phase II of the migrating motor complex (139). The latter is a myoelectric cycle, originating in the stomach and propagating throughout the intestine (140). Since rats lack a gall bladder, these fluctuations are not observed. Rather, bile flow appears to follow a circadian pattern, with secondary (superimposed) variation occurring as a result of food intake (141).

Efficient biliary excretion of a compound is both a function of the molecular weight, chemical nature, and target animal species. The molecular weight threshold for the biliary excretion of acidic compounds is approximately 300–350 in dogs and rats but greater than 500 in humans. Similar molecular weight considerations apply to most neutral compounds (102).

6. ALLOMETRY

Allometry serves as a black-box approach for interspecies scaling of drug concentrations within some biological matrix (generally blood). While there are numerous examples of its successful application (142,143), there are also examples of where allometry fails to accurately predict drug pharmacokinetics across species.

The variable generally considered to be the most highly predictive factor for interspecies scaling is total body surface area. This is because pharmacokinetic elimination processes are affected by the size and function of the eliminating organ, which in turn, reflects the organisms' metabolic