ABSTRACT SUMMARY

Interspecies extrapolation of dosing concepts can be challenging. The anatomic and physiologic differences among animals and between animals and people can be significant. Although there are examples in which animals have predicted human drug dosing, and vice versa, there are many more examples where the dosing concepts cannot be extrapolated across species.

INTRODUCTION

Interspecies extrapolation of drug dosing would indeed be beneficial for human drug development. It would also help to extrapolate doses of medications from human medicine for application to animals treated by veterinarians. If interspecies dosing prediction methods could be better established, it would enhance treatment and minimize the risk of adverse effects. These concepts also could predict clearance in livestock and reduce unwanted drug residues in food animals. Extrapolations also would facilitate drug development by using other species for screening potential new drugs.

EXPERIMENTAL METHODS

An examination of the available literature was conducted to determine the extent to which interspecies extrapolation was possible. The authors also examined the possibility of using the Biopharmaceutical Classification System, (BCS) to predict oral absorption in dogs. Reviews of published studies in humans and veterinary species were examined for the ability to use allometric scaling (allometry) to extrapolate pharmacokinetic properties across species.

RESULTS AND DISCUSSION

Although there are examples in which interspecies extrapolation of dosing in animals is possible, there are many other examples for which accurate predictions are unlikely and could potentially result in errors. The errors can be caused by drugs with extreme clearance or disposition differences among species, or because we have used inappropriate models in our attempt to extrapolate across species.

Properties of drugs that impair our ability to extrapolate across species are lipophilicity, solubility, and protein binding. Drugs with high lipophilicity (high LogP) are subject to metabolic differences among animal species. They also tend to be more highly protein bound, which can greatly affect distribution and clearance.

Differences among animals affect many pharmacokinetic properties. Because of the differences among species with respect to cytochrome P450 enzyme (CYP) expression and drug substrate specificity, interspecies extrapolation can often result in error. Drug transporters (membrane efflux and uptake pumps) also show interspecies variability and can account for differences in drug absorption, distribution, and clearance.

In the evaluation of over 45 drugs for which there was BCS classification data as well as pharmacokinetic data from studies in dogs, there was little correlation between humans and dogs. For example, BCS Class I drugs in people had extremely high oral absorption variability in dogs. Oral absorption in dogs could not be predicted by using the BCS criteria of solubility and permeability (Log P used as a surrogate for permeability) that have been used in people.

The explanation for these interspecies differences is varied, depending on the animal
species studied and physical properties of the drug. Cytochrome P450 activity, enzyme specificity, and drug transporter activity can be extremely different among species. Many variations can also be accounted for simply by anatomical differences among species. These were discussed thoroughly in other reviews \(^3\), \(^4\). Anatomic differences account for variation in gastrointestinal transit time among species and physiologic differences account for changes in drug absorption. Dogs are sometimes used as models for human oral drug absorption, but differences in stomach emptying and gastrointestinal (GI) physiology between dogs and people were also reviewed.\(^4\),\(^5\)

Despite the many differences observed among species that preclude interspecies dose extrapolation, there are some instances where extrapolation is possible. For example, interspecies pharmacokinetic predictions can be accomplished using allometric scaling \(^6\),\(^7\). However, this is possible for some, but certainly not all drugs. The problem that investigators have encountered with this approach is that it is possible to examine the correlations for known drugs using retrospective analysis. However, success shown in the retrospective analysis does not necessarily predict success in prospective applications \(^8\).

**CONCLUSION**

Interspecies scaling of dosing concepts can be a useful tool if the investigator understands the limitations. Some extrapolation is possible from human drugs to animals if absorption is high and predictable, and if protein binding, metabolism, and clearance are similar across species. Unfortunately, this is not always the case. Oral absorption is one of the most difficult aspects of pharmacokinetics to accurately predict among species because of tremendous variation in gastrointestinal anatomy and physiology. Allometric scaling of some drugs is possible, but it is difficult prospectively to predict which drugs will not scale.

**REFERENCES**