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PHYSIOLOGICAL PHARMACOKINETICS

Robert L. Dedrick

Biomedical Engineering and Instrumentation Program

National Center for Research Resources

National Institutes of Health

Bethesda, MD 20892

The distribution and disposition of a foreign chemical in the body are a result of a complex interacting set of physiological processes and biochemical interactions. Physiological pharmacokinetics is based on the thesis that it is possible to describe the essential processes and interactions in mathematical terms and use the mathematics to simulate chemical (and metabolite) concentrations at relevant sites in the body. Some of these concepts are illustrated by the diagram.

Diagram of a compartment for pharmacokinetic analysis (Dedrick et al, 1973). Q is the blood (or plasma) flow rate to the compartment; C_p is the free concentration in the plasma; q is the total (free plus bound) concentration; $(JA)_{12}$ is the rate of transport across capillary membranes; $(JA)_{23}$ is the rate of transport across cell membranes.

A chemical enters the compartment with the flowing blood. The chemical may cross the capillaries and cell membranes to enter the interstitial fluid. There it may bind reversibly or irreversibly to intracellular constituents, undergo a variety of chemical reactions or be excreted. Chemicals not eliminated or irreversibly bound in the intracellular space can reenter the blood and leave the compartment with the venous drainage. The interstitial compartment is drained by lymphatics in most compartments. While the contribution of the lymphatic route to

small molecule transport is generally negligible, lymphatics may dominate the efflux of many macromolecules.

In the above discussion, the extracellular, interstitial and intracellular spaces are individually lumped; i. e., the concentration in each is assumed to be spatially uniform. Spatially distributed models are a subject of much current interest, but they will not be discussed here. The single compartment shown in the diagram may be studied in connection with measured systemic plasma concentrations *in vivo* or perfusate concentration *in vitro* to obtain information about that compartment. If a whole-body pharmacokinetic model is desired, then compartments appropriate to the properties of the chemical and route of exposure are connected in an anatomically correct organization. A set of ordinary differential equations expressing mass balances on the compartments may be solved to yield predicted concentrations of chemical (and metabolite) in each compartment as a function of time (Lutz et al, 1980; Gerlowski and Jain, 1983).

A considerable simplification occurs if the intracompartment transport processes are rapid compared with the blood flow rate. Then it may be assumed that the chemical in the venous blood is in equilibrium throughout the compartment ($C_1 = C_2 = C_3$), and precise information concerning the rates of transport is not required. Models derived with this simplification are called "flow limited." Physiological pharmacokinetic models are sometimes referred to as "flow models" because intercompartment transport by processes other than convection has been neglected. This concept should not be confused with flow limitation defined above.

Physiological pharmacokinetic models provide a powerful tool in drug development, toxicology and clinical applications. Because they are based on known or plausible physiology, considerable insight may be gained from studies not involving the chemical being described. For example, we know much about organ sizes, blood flow rates and lymph flow rates which do not depend on the particular chemical being modeled. There is an extensive literature on capillary permeability and organ function which may be employed in the development and validation of a model. Physiological models are a rational construct for the incorporation of binding and metabolic reactions at the conditions thought to exist within tissues. They are a particularly useful construct for the quantitative application of *in vitro* data (Sugiyama et al, 1989). The models are not species specific. Because of the remarkable similitude among mammals a model developed for a mouse may be applied to predict pharmacokinetics in humans or other species with the appropriate choice of parameters. Parameters such as tissue perfusion, capillary permeability and tissue-to-blood partition coefficients may often be quite similar among species. The variation of others such as organ sizes, blood flow and glomerular filtration follows simple allometric concepts.

Physiologically based pharmacokinetic models have played an increasingly important role in our thinking about risk assesment (Pharmacokinetics in Risk Assessment, 1987). They form a sound basis for three related extrapolation issues: differing routes of exposure; high dose to low dose; and experimental animals to human subjects. Such models have also provided insight into the pharmacokinetic advantage that can be achieved by regional drug administration and the interspecies scaling of this advantage (Dedrick, 1986).

REFERENCES

- Dedrick RL. Interspecies scaling of regional drug delivery. J Pharm Sci 75, 1047-1052, 1986.
- Dedrick RL, Zaharko DS, Lutz RJ. Transport and binding of methotrexate *in vivo* . J Pharm Sci 62:882-890, 1973.
- Gerlowski LE, Jain RK. Physiologically based pharmacokinetic modeling: Principles and applications. J Pharm Sci 72:1103-1127, 1983.
- Lutz RJ, Dedrick RL, Zaharko DS. Physiological pharmacokinetics: an *in vivo* approach to membrane transport. Pharmac Ther 11:559-592, 1980.
- Pharmacokinetics in Risk Assessment. Drinking Water and Health, Vol 8, National Academy Press, Washington DC, 1987.
- Sugiyama Y, Sawada Y, Iga T, Hanano M. Reconstruction of *in vivo* metabolism from *in vitro* data. Proc 2nd Int ISSX Meeting on Xenobiotic metabolism and disposition. Kato R, Estabrook RW, Cayen MN (eds), Taylor and Francis, 1989, pp 225-235.