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Some of My Own Contributions and Guidance for Future Graduate Students

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I always enjoyed doing research when I was at the College of Pharmacy, The Ohio State University, 1951-53, The Upjohn Company, 1953-68, and at The University of Michigan, 1968-71.

The article entitled: "Seventy Years in Retrospect" is a short autobiography and some of the material for this lecture came from it. It also discusses how I got into the fields of biopharmaceutics and pharmacokinetics.

I have studied 63 drugs during my 40-year career in academia and industry. I have been published in 71 scientific journals. Thirty eight articles were published in Drug Intelligence, which later became Drug Intelligence and Clinical Pharmacy, and still later DICP, The Annals of Pharmacotherapy. There were thirty five articles in the Journal of Pharmacokinetics and Biopharmaceutics. I tried to publish in the journal where readership would be the greatest for the specific material, or, in the journal where I thought the subscribers should read the material.

In 1961 I wrote a review article entitled: "Biopharmaceutics: Absorption Aspects" which caught the imagination of many scientists. It discussed the effects that the dosage form of a drug and the route of administration have on the biological effects of the drug. In the 1950's and before, pharmacy was considered only an art and most of the pharmacists believed that the drug had only intrinsic activity and that the dosage form, or drug delivery system, had little or no effect on the drug's action or the intensity of the drug's effect. This article was widely accepted and was used as teaching material in many schools and colleges of pharmacy.

In order to study the effects of the dosage form of a drug on its biological effects one had to have a method to estimate absorption rate of the drug. In 1963, Dr. Eino Nelson and I published an article entitled: "Per Cent Absorbed Time Plots Derived from Blood Level and/or Urinary Excretion Data."

$$\frac{A_T}{V_p} = C_T + K\int_0^T C\,dt$$

$$\frac{A_\infty}{V_p} = K\int_0^\infty C\,dt$$

$$FA = \frac{A_T}{A_\infty} = \frac{A_T/V_p}{A_\infty/V_p}$$

A_T is the amount absorbed to time T, V_p is the volume of the central compartment, C_T is the plasma or whoe blood drug concentration at time T, the integral is the area under the concentration versus time plot to time T after a single dose of drug and K is the first order elimination rate constant of the drug. At the bottom is FA, the fraction absorbed or bioavailable. The method became known as the T, V_P is the volume of the central compartment, C_T is the plasma or whole blood drug concentration at time T, the integral is the area under the concentration versus time plot to time Wagner-Nelson method and has been widely used.

The article "Blood Levels of Drug at the Equilibrium State after Multiple Dosing" was published in Nature in 1968 and gave the so-called "see bar" equation:

$$\overline{C_{ss}} = \frac{FD}{VK\tau}$$

Where C_{ss} is the average steady-state plasma or whole blood drug concentration, F is the fraction of the dose, D, which is absorbed or bioavailable, VK is the clearance of the drug and τ is the uniform dosage interval. This is a very useful equation allowing prediction of steady-state average concentrations from single dose data.

In the 1968 article: "Kinetics of Pharmacologic Response" published in the Journal of Theoretical Biology, I proposed that the intensity of a pharmacologic response, R, such as blood pressure, may often be related to the concentration, C, of drug in the body fluids of the intact animal or man by the equation:

$$R = \frac{R_M C^s}{1/Q + C^s}$$

Later, this equation was usually written as:

$$E = \frac{E_{max} C^s}{EC_{50}{}^s + C^s}$$

where E is the intensity of the pharmacodynamic effect, E_{max} is the maximum effect, EC_{50} is the effective concentration 50% and s is a power which is usually 1 to 3.

This equation has become very important in pharmacokinetic-pharmacodynamic modeling.

In 1974 in the journal Clinical Pharmacology and Therapeutics, I published the article "A Safe Method for Rapidly Achieving Plasma Concentration Plateaus." I had heard via the grapevine that several children had died as a result of being administered bolus intravenous doses of theophylline. Such a bolus dose leads to very high initial blood concentrations of the drug.

I suggested using two consecutive infusion rates - the first being more rapid than the second one. In this case the switch-over from one rate to the other occurred at one hour and resulted in much lower peak concentrations. I showed that ratio of the two infusion rates had to be dependent upon the elimination rate constant of the drug. The new method has

has been applied to several drugs.

In 1983, I published an article "Pharmacokinetic Absorption Plots from Oral Data Alone or Oral/Intravenous Data and An Exact Loo-Riegelman Equation" in the Journal of Pharmaceutical Sciences which provided new methods of preparing absorption or bioavailability plots based on multicompartment models.

$$\frac{A_T}{V_p} = C_T + k_{el}\int_0^T C dt + k_{12} e^{-k21T}\int_0^T C_e k21 t_{dt}$$

The Wagner-Nelson method is based on the one compartment open pharmacokinetic model. The new methods are based on two and three compartment disposition models.

In 1985 my article "Propranol: Pooled Michaelis-Menten parameters and the effect of input rate on bioavailability" in Clinical Pharmacology and Therapeutics showed that if a drug obeyed Michaelis-Menten elimination kinetics then often the bioavailability of the drug is dependent upon input rate.

$$\frac{(AUC\ \ 0\text{-}\tau)zero}{(AUC\ \ 0\text{-}\tau)bolus} = \left[\frac{1}{1-r}\right]\left[\frac{1}{1+\frac{D_m}{VK_m}\left(\frac{1}{2}+\frac{1}{eQ-1}\right)}\right]$$

$$where\ Q = \frac{Vm\tau - D_m}{VK_m} \ \wedge\ r = \frac{R_o}{V_m}$$

The equation gives the ratio of areas within a dosage interval at steady-state for zero order input over bolus input. It shows that this ratio is dependent upon the zero order input rate, R_o, the maintenance dose, D_m, the bolus dosage interval, τ, the volume of distribution, V, and the V_{max}, V_m, and Michaelis constant, K_m.

An article published in Selective Cancer Therapeutics, in 1989, relates the steady-state hepatic venous drug concentration, $C_{V^{ss}}$, and the steady-state hepatic arterial concentration, $C_{A^{ss}}$. In this case, V_m is the maximal velocity of metabolism, Q is the liver blood flow rate, and K_m is the Michaelis constant. V_m/Q is the maximal arterial-venous concentration difference.

$$C_{V^{ss}} = 0.5[C_{A^{ss}} - \frac{V_m}{Q} - K_m + \sqrt{(C_{A^{ss}} - V_m/Q - K_m)^2 + 4K_m C_{A^{ss}}}]$$

My last major contribution was the article "Stepwise Determination of Multicompartment Disposition and Absorption Parameters from Extravascular Concentration - Time Data. Application to Mesoridazine, Flurbiprofen, Flunarizine, Labetalol, and Diazepam" published in 1991 in the Journal of Pharmacokinetics and Biopharmaceutics. Classically, disposition parameters were only obtainable following intravenous administration of the drug. This article gives several methods to obtain disposition parameters from downslope extravascular concentration-time data.

$$C = \frac{AUC}{\lambda_2 - \lambda_1}[\lambda_1(\lambda_2 - k_{10})e^{-\lambda_1(t-t_s)} + \lambda_2(k_{10} - \lambda_1)e^{-\lambda_2(t-t_s)}]$$

The above equation is for Method IIIA, based on the two compartment disposition model.

Indoxole was an experimental non-steroidal anti-inflammatory drug studied by The Upjohn Company many years ago. The drug was about as soluble as sand and presented great pharmaceutical problems. My group prepared several different dosage forms of the drug. A bioavailability trial in 10 subjects was then performed in crossover fashion using four of the dosage forms. Two of the dosage forms gave essentially the same average concentrations - namely, an emulsion when the drug was dissolved in the oil phase of Lipomul Oral Emulsion and a soft elastic capsule with the drug dissolved in the surfactant Polysorbate 80. The emulsion and soft elastic capsule dosage forms increased the bioavailability about 14-fold over that produced by the powder-filled capsule. Hence the composition of a dosage form of a drug and how the dosage form is manufactured are most important in determining the intensity of the pharmacologic effect.

We found that sodium cyclamate, the sweetening agent present in two experimental pediatric lincomycin syrups, reduced the bioavailability of lincomycin to about 25% of that in the absence of the sweetening agent. Since sodium and calcium cyclamates, at that time, were sold as ingredients in diet beverages, I wished to know if the interaction would occur if mixing occurred in the human stomach as well as in the medicine bottle. I did a 3-way crossover study in 6 subjects. The control was lincomycin HCl given alone in aqueous solution. The next group consisted of the administration of the lincomycin solution followed by a 1 molar equivalent (247.5 mg) of sodium cyclamate in 2 fl. ox. of water. The third group was given lincomycin solution followed by 1/2 bottle (8 fl. ox.) of Diet-Rite Cola which contained 0.25% sodium cyclamate equivalent to 2.39 molar equivalents of sodium cyclamate per mole of lincomycin. Hence, if the cyclamate was given in a soft drink and mixed with the lincomycin in the human stomach, the drug interaction occurred and the absorption of lincomycin was severely impaired.

For many years textbooks said that ethyl alcohol was eliminated from the body at a constant, zero order, rate. We did an 8-subject 4-way crossover study in which doses of 15, 30, 45 and 60 ml of 95% alcohol were administered under fasting conditions. The results in one of the subjects and results in the other 7 subjects were similar. If the metabolism of ethanol was zero order, then the downslope lines would all be parallel. But this is not so. The slope is greater, as the dose of alcohol increases from 0.034, 0.071, 0.173 and 0.190. In fact, a plot of the reciprocal of the slope, $1/k_o$, versus the reciprocal of the initial concentration, $1/C_o$, at the start of each linear segment. This type of plotting is in conformity with Michaelis-Menten, not zero order, elimination kinetics.

Left: John G. Wagner Right: Albert A. Belmonte