Evaluating Drug Absorption After Oral Administration. Some Problems and Some Solutions

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Summary. Quantitative assessment of drug absorption remains a difficult task, because the multiple-compartment disposition of a drug may not be obvious after oral administration (the problem of the vanishing exponential) and the macroconstants are indistinguishable. For these reasons, proper analysis of the drug absorption based on the apparent behavior of oral data without intravenous reference curve rarely provides absorption information useful for in vivo – in vitro correlations. When intravenous reference curve is available, compartment model used for analysis of the oral data should be corresponding to the iv data such as the Loo-Riegelman method. The model independent statistical moments method is one of the preferable alternatives because of its ease of computation and its potentially smaller error, if absorption can be assumed to be first-order.

Key words: drug absorption, statistical moments method; vanishing exponential, indistinguishable macroconstants, Wagner-Nelson method, Loo-Riegelman method, first order absorption kinetic

Despite the advances in pharmacokinetic analysis of data during the past decade, methods to evaluate the absorption kinetics of a drug, particularly after oral administration, remain controversial. Nevertheless, interest in the rigorous analysis of absorption data is still high in some quarters. Regulatory agencies often require a quantitative assessment of absorption data as part of the pharmacokinetic characterization of new drugs. The pharmaceutical industry finds it necessary to comply. The industry has an additional interest in the evaluation of drug absorption, to establish in vitro – in vivo correlations. Correlations between gastrointestinal absorption and dissolution rate may permit rapid screening of new dosage forms, and serve as a quality control tool to quickly assess the potential effects of small changes in processing or composition, or of age, on the bioavailability of drug from the dosage form. This report examine some problems associated with the assessment of absorption data, and some limited strategies to overcome these problems.

Background

Many methods to evaluate absorption data are available. Clinical investigators usually find it sufficient to compare the times required to reach the peak concentration of drug in blood after oral administration. However, it is often difficult to define the peak time precisely because of limited opportunities to take blood samples. Accordingly, this approach may be insufficiently sensitive for some needs. Ronfeld and Benet (1977) have demonstrated that, with normal biologic and experimental variability, it may be impossible to differentiate, on the basis of peak times, two dosage forms that differ in their release rates of drug by a factor of two.

The most commonly used methods to assess absorption kinetics require compartmental analysis, or assumptions regarding the compartmental characteristics of the biologic model. Several problems are encountered in their application. The first is that the compartmental character of a drug depends on how we give the drug. Almost all drugs require multicompartiment characterization to describe disposition after rapid intravenous injection. The same drug, after oral administration, may show the same multicompartiment disposition (i.e., the characteristic nose seen in Curve 2 of Fig.1) or may not. The multicom-
compartment characteristics of a drug after oral administration in one dosage form may vanish when the drug is given in a second dosage form. The same oral dosage form may yield different compartmental characteristics from one patient to the next, or even in the same patient from one administration to the next. In other words, a drug that requires a two-compartment model to characterize its pharmacokinetics after rapid intravenous injection may require either a one- or two-compartment model after oral administration, depending on the absorption kinetics of the drug. This phenomenon of vanishing exponential terms has been described by Wagner (1976). While the oral data is adequately described by a simpler one-compartment model, problems arise when this simpler model was used to evaluate the drug absorption.

The representative equation for the usual two-compartment model after oral administration (assuming first-order absorption) is:

$$C = \frac{k_{a2}FD}{V_1} \left[ \frac{(k_{21}-k_{a2})}{(\alpha-k_{a2})} e^{\alpha t} + \frac{(k_{21}-\alpha)}{(\beta-\alpha)(k_{a2}-\alpha)} e^{-\alpha t} \right] + \frac{(k_{21}-\beta)}{(\alpha-\beta)(k_{a2}-\beta)} e^{-\beta t}$$

where $C$ is drug concentration in blood or plasma, $FD$ is available dose, $k_{a2}$ is the absorption rate constant for the model, $V_1$ is the volume of the central compartment, $k_{21}$ is the exit rate constant from the peripheral compartment, and $\alpha$ and $\beta$ are the macro-constants describing the disposition of the drug; $\alpha > \beta$.

Ronfeld and Benet (1977) have shown that when $k_{a2}$ approaches $k_{21}$, the first term inside the brackets of Eq. (1) goes to zero and the triexponential equation reduces to a biexponential equation. The blood level-time curve appears to reflect a drug with one-compartment characteristics, absorbed in a first-order fashion. Analysis of the data with methods appropriate to a one-compartment model yields an absorption rate constant not equal to $k_{a2}$ but equal to $\alpha$. In their simulations, Ronfeld and Benet (1977) found that smaller value of $k_{a2}$ also yielded a curve consistent with a one-compartment model, but that larger values of $k_{a2}$ yielded curves that suggested a two-compartment model.

Even when there are no vanishing exponentials after oral administration, proper analysis of oral data, in the absence of an intravenous reference curve, is difficult, because of the investigators inability to differentiate $k_{a2}$ from $\alpha$ or $\beta$. For a given drug, one of the following conditions will apply: $k_{a2} > \alpha > \beta$, $\alpha > k_{a2} > \beta$, or $\alpha > \beta > k_{a2}$. An arbitrary assumption of one of these conditions is required to analyze the data.

When a drug exhibits apparent one-compartment characteristics after oral administration, it is common to find the Wagner-Nelson method (Wagner and Nelson 1963), applied to the data to assess absorption kinetics. This is usually undertaken without knowledge of the compartmental characteristics of the drug's disposition. The Wagner-Nelson method would seem to apply only to drugs with one-compartment disposition characteristics; this limitation challenges the usual strategy. The situation is further complicated by a report claiming that the Wagner-Nelson method can be applied to data that obey the two-compartment open model with first-order absorption to estimate $k_{a2}$ (Wagner 1974).

A rigorous and unambiguous way of overcoming many of the problems found in evaluating absorption data is to evaluate the oral data corresponding to the intravenous reference curve such as the Loo-Riegelman method (Loo and Riegelman 1968). The reference curve avoids the problems of vanishing exponential terms and undifferentiated macro-constants, particularly when oral and intravenous data are obtained simultaneously, by means of isotope methodology. However, the calculation of Loo-Riegelman method is tedious and requires computer fitting to the intravenous curve, and simpler methods are sought. One alternative, potentially applicable to the case of first-order absorption, is the statistical