Absolute and Relative Bioavailability

Khaled Abo-EL-Sooud

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Abstract

Attaining desired blood drug concentration and, consequently, augmenting the bioavailability of poorly absorbed drugs have always been an essential aspect for the pharmaceutical agency. The achievement of this target gives positive economic benefits as reducing drug dosage and medical impacts in decreasing toxicity and bacterial resistance in case of antimicrobials. Various factors may reduce the availability of drugs. There are numerous ways to estimate bioavailability. Various software's models have been developed to simplify such analyses. The newly developed programs should provide a range of modules for pharmacokinetic and pharmacodynamic analysis with a more user-friendly interface.

Attaining desired blood drug concentration and, consequently, augmenting the bioavailability of poorly absorbed drug molecules have always been an essential aspect of development plans for the pharmaceutical agency. The achievement of this target gives positive economic benefits as reducing drug dosage and frequency and medical impacts in decreasing toxicity and bacterial resistance in case of antimicrobials. A drug may be well absorbed orally because of good lipid solubility and yet not has a good oral bioavailability because of extensive presystemic loss. Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. There are numerous ways that are

K. Abo-EL-Sooud (✉)
Pharmacology Department, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt
e-mail: kasooud@cu.edu.eg

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followed to estimate bioavailability. To simplify such analyses, various software's models have been developed. The newly developed programs should provide a range of modules for pharmacokinetic and pharmacodynamic analysis with a more user-friendly interface. Factors that reduce the availability of drugs prior to their entry into the systemic circulation should be considered during prescription. Understanding the difference between absolute and relative bioavailability and be able to convert between these values is an essential issue. Relative bioavailability is one of the significant measures used to assess bioequivalence between several drug products.

Purpose and Rationale

The part of parent drug that absorbed, i.e., reached, the systemic circulation (blood). It is symbolized by the letter **F** (expressed in percent). The dosage form and molecular size of the drug determine to a great extent how much of a drug reaches the systemic circulation (Musther et al. 2014).

The rate and extent to which a drug is absorbed and available at the site of action are of the concerns of the bioavailability (Zweig et al. 2007). Rate means "how fast" the drug is absorbed per time unit. The extent means the amount of the dose enters systemic circulation from the site of administration.

Regulatory decisions concerning marketed drugs depend upon their ability to achieve the C_{max} of the generic product and T_{max} (Endrenyi and Yan 1993). Therefore, it is recommended that the 90% confidence limits for the percentage ratio of the C_{max}/AUC (area under the curve) values of two drug products should be (based on their logarithmic averages or medians) between 75% and 133%.

The overall drug exposures are markedly higher after administration of solution as compared to capsule (De Beule and Van Gestel 2001). Consequently, FDA guidelines clearly state that the two formulations should not be used correspondently. The mean relative bioavailability of itraconazole capsule was 85% that of the solution, but drug absorption was variable, and overall drug concentrations were similar between formulations. Mean elimination half-lives of both formulations were nearly identical at approximately 33 h (Hasbach et al. 2017). The consequences of failing to recognize a potential difference could be substantial and include avoidable cost, increased risk of toxicity, inadequate tissue drug concentrations, and treatment failures.

Relative bioavailability is one of the measures used to assess bioequivalence between two drug products. For FDA approval, a generic manufacturer must demonstrate that the 90% confidence interval for the ratio of the mean responses (usually of AUC and, C_{max}) of its product is within the limits of 80–125% (Chow and Liu 2009).

Some drugs administered orally are poorly bioavailable as they readily undergo first-pass metabolism and incomplete absorption. Drug efficacy can be severely limited by poor aqueous solubility, and some drugs also show side effects due to their poor solubility (Chaudhary et al. 2012). Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their bioavailability. Many natural compounds from medicinal plants have the capacity to augment the bioavailability when co-administered with another drug (Tatiraju et al. 2013).

Procedure

The absolute bioavailability is the dose-corrected AUC of extravascular route divided by AUC intravenous. For example, the formula for calculating **F** for a drug administered depends upon the calculated $AUC_{0-\infty}$ using the linear trapezoidal rule according to the following equations (Abo-EL-Sooud et al. 2017):

$$\mathbf{F} = [\text{mean } AUC_{\text{NON-IV}} / \text{mean } AUC_{\text{IV}}] \times 100.$$

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 100% ($\mathbf{F} = 1$), whereas drugs given by other routes usually have an absolute bioavailability of

less than one. When the bioavailability of extravascular route is very close to unity, this indicates that the absorption of the tested drug from this site is nearly completed. If we compare the two different dosage forms having same active ingredients and compare the two-drug bioavailability, it is called relative bioavailability (Gray and Jones 2004).

Relative Bioavailability and Bioequivalence

In pharmacology, relative bioavailability measures the bioavailability (estimated as the AUC) of a formulation (A) of a certain drug when compared with another formulation (B) of the same drug, usually an established standard or through administration via a different route. When the standard consists of an intravenously administered drug, this is known as absolute bioavailability (Shargel et al. 2004).

While the mechanisms by which a formulation affects bioavailability and bioequivalence have been extensively studied in drugs, formulation factors that influence bioavailability and bioequivalence in nutritional supplements are largely unknown (Cuiné et al. 2008). As a result, in nutritional sciences, relative bioavailability or bioequivalence is the most common measure of bioavailability, comparing the bioavailability of one formulation of the same dietary ingredient to another.

Evaluation

The pharmacokinetic analysis is performed using compartmental and noncompartmental models. From both models, the obtained AUC is the unique parameter for bioavailability estimation. Noncompartmental analysis (NCA) used to calculate pharmacokinetic parameters does not assume the number of compartments (Foster 2007). The compartmental analysis (CA) describes the decline in blood drug concentration as a function of time and predicts the drug concentrations at any time. This type classify the body to central (blood) and peripheral compartments (tissues). Drug that is in the peripheral compartment can return to the central compartment or other different tissues. The model may be best described by the compartmental open model which may be mono-exponential or bi-exponential or tri-exponential (Okusanya et al. 2007).

Biexponential expression

$$\mathrm{Cp} = \mathrm{A}e^{-\alpha t} + \mathrm{B}e^{-\beta t}$$

where Cp is the drug concentration in serum at time T; A and B are the intercepts of the distribution and elimination phases, respectively, with the concentration axis expressed as μg/ml; α and β are the distribution and elimination rate constants, respectively, expressed in units of reciprocal time (h^{-1}); and e is the natural logarithm base. The pharmacokinetic parameters and AUC are calculated according to Baggot and McKellar (1994).

The noncompartmental parameters are calculated by using the statistical moment theory (Wolfsegger and Jaki 2009). The elimination half-life ($T_{½el}$) is calculated as $\ln 2/\beta$. The AUC was calculated according to the trapezoidal rule. The mean residence time (MRT) is calculated as AUMC/AUC, where AUMC is the area under the first moment curve and AUC is the area under the curve.

There are numerous ways that are followed to estimate bioavailability. Site-specific analysis can offer essential information that can influence a risk assessment. Bioavailability can likewise be resolved for other extravascular courses of the organization, for example, intramuscular, subcutaneous, rectal, and sublingual (Morris et al. 2011). Sublingual and rectal routes are commonly used to avoid hepatic first-pass impact (Narang and Sharma 2011). Bioavailability of most small molecular weight drugs administered intramuscularly alternately subcutaneous injections depends upon the mechanism and the rate of transport to general circulation. High molecular weight formulations administered enter the blood to a limited extent through the lymphatic pathway (Khan et al. 2013).

The AUC is one of the essential pharmacokinetic parameters used to calculate others such as clearance or bioavailability. The AUC tells us how much drug is in the body and has units of concentration*time (e.g., mg*h/L). There are several methods to calculate AUC, ranging from more complex but more accurate methods like the integration of the equation that describes the pharmacokinetic profile to an easier, but less accurate method is called the trapezoidal method. This latter method is commonly used because of its ease and is based on the idea of calculating the area of a trapezoid (Persky 2012).

When a bioavailability study is carried out, at least two dosage forms are administered to each subject. One dosage form is the product to be tested, while the other dosage form is a standard or reference dosage form. This may be an IV dose, oral solution, or most commonly the original manufacturer's product. The doses are given with sufficient time between administrations for the drug to "wash out" or are completely eliminated. We usually assume that each subject eliminates each dosage form at the same rate (Toutain and Bousquet-Mélou 2004).

Relative Bioavailability

The relative bioavailability is concerned with the extent to which an extravascular drug product (e.g., a generic drug product) is absorbed in comparison with the trade name, or currently marketed drug product. This is usually determined by comparing the AUC of the plot of plasma drug concentration vs. time of the new product to that of the trade name product, i.e.,

$$\text{relative F} = \text{AUC}_{\text{generic}}/\text{AUC}_{\text{trade name}}$$

In case of evaluating pharmacokinetic interactions, the AUC $_{0-\infty}$ is calculated using the linear trapezoidal rule alone or with co-administered drug, and relative bioavailability is calculated according to the following equations (Abo-EL-Sooud et al. 2017):

$$F_{rel} = \left[\frac{\text{mean AUC}_{\text{with co-administered}}}{\text{mean AUC}_{\text{without co-administered}}}\right] \times 100.$$

Critical Assessment of the Method

A drug may be well absorbed orally because of good lipid solubility and yet not has a good oral bioavailability because of extensive presystemic loss. While the intravenous bioavailability of drugs is always 100%, the oral bioavailability is usually less than 100% because of incomplete absorption and/or first-pass elimination (Sim 2015).

The absolute bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e., $\mathbf{F} < 100\%$). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. Whether a drug taken with or without food will also affect absorption, other drugs taken concurrently may alter absorption and first-pass metabolism, intestinal motility alters the dissolution of the drug, and may affect the degree of chemical degradation of the drug by intestinal microflora (Guerville and Boudry 2016).

Factors affecting bioavailability:

Physical properties of the drug molecules
The form pharmaceutical formulation (short- or long-acting)
The presence of food in the stomach
Gastric emptying rate
Drug-drug and drug-food interactions
Gastrointestinal tract integrity
Microsomal enzymes inducers or inhibitors
First pass effect enterohepatic circulation, diet, gender
Disease condition especially hepatorenal functions

In clinical trials, interindividual variation is a critical measurement used to assess the bioavailability differences from patient to patient in order to ensure predictable dosing (Howgate et al. 2006).

Table 1 Residual analysis for drug concentrations after intravenous input

Time	Conc	Ln(Conc)	Conc_pre	Residual	Weight
0.25	1.64	0.49469624	1.63994069	5.931E-05	1
0.5	1.139	0.13015068	1.13988013	−0.0008801	1
1	1.06	0.05826891	1.03101809	0.02898191	1
2	0.81	−0.210721	0.92523711	−0.1152371	1
4	0.78	−0.2484614	0.74587998	0.03412002	1
6	0.77	−0.2613648	0.60129125	0.16870875	1
8	0.52	−0.6539265	0.48473103	0.03526897	1
10	0.221	−1.5095926	0.39076598	−0.169766	1

Table 2 Compartmental analysis of plasma data after intravenous input

Parameter	Unit	Value
A	μg/ml	5.219348692
Alpha	1/h	9.204329903
B	μg/ml	1.147722998
Beta	1/h	0.107742638
Parameter	Unit	Value
k10	1/h	0.567500333
k12	1/h	6.997086385
k21	1/h	1.747485823
t1/2Alpha	h	0.075306642
t1/2Beta	h	6.433360013
C0	μg/ml	6.36707169
V	(mg/kg)/(μg/ml)	0.785290357
CL	(mg/kg)/(μg/ml)/h	0.445652539
V2	(mg/kg)/(μg/ml)	3.144371412
CL2	(mg/kg)/(μg/ml)/h	5.494744465
AUC 0-t	μg/ml*h	7.59265674
AUC 0-inf	μg/ml*h	11.219503
AUMC	μg/ml*h^2	98.9310014
MRT	h	8.817770398
Vss	Mg/kg/(μg/ml)	3.929661769

Modifications of the Method

Tiresome mathematical calculations, optimization algorithms, and graph plotting are essential for pharmacokinetic data analysis. To simplify such analyses, different software's models have been developed. Many of these commercially available packages are expensive or have a steep learning curve.

Several models and add-in programs have previously been constructed for diverse applications (Meineke 2000; Brown 2006). The pharmacokinetic analysis has been adopted for such NCA computation (Dansirikul et al. 2005; Jaki and Wolfsegger 2012) and bioavailability/bioequivalence trials (Abdallah and Ludden 1995; Chow et al. 2011). However, several programs have only one type of analysis mostly NCA calculation functions or need a specific spreadsheet templates with limiting input data.

Therefore, it is valuable exploring the possibility of cost-effective and easy-to-use alternatives for pharmacokinetic and pharmacodynamic analysis. PKSolver is an available menu-driven add-in program used Microsoft Excel in Visual Basic for Applications (VBA) (Zhang et al. 2010). The program provides a range of modules for pharmacokinetic and pharmacodynamic analysis other than NCA, including CA (Watabe et al. 2006), pharmacodynamic modeling (Felmlee et al. 2012), multiple absorption sites (Plusquellec et al. 1999; Kota et al. 2007; Abo-EL-Sooud et al. 2017), and enterohepatic circulation (Gabrielsson and Weiner 1999; Roberts et al. 2002; Abo-El-Sooud et al. 2016), which were developed for fitting the double-peak concentration-time profile based on the classical one-compartment model (Tables 1, 2, 3, and 4). The parameters estimated with PKSolver are satisfactory. In conclusion, the PKSolver simplified the pharmacokinetic and pharmacodynamic data analysis process and its output could be generated in Microsoft Word in the form of an integrated report. The program provides pharmacokinetic researchers with a fast and easy-to-use tool for routine and basic pharmacokinetic and pharmacodynamic data analysis with a more user-friendly interface.

Table 3 Noncompartmental analysis of plasma data after extravascular input

Parameter	Unit	Value
Lambda_z	1/h	0.118444235
t1/2	h	5.85209726
Tmax	h	1
Cmax	μg/ml	29
Tlag	h	0
Clast_obs/Cmax	μg/ml	0.155172414
AUC 0-t	μg/ml*h	88
AUC 0-inf_obs	μg/ml*h	125.9925626
AUC 0-t/0-inf_obs	μg/ml*h	0.698453926
AUMC 0-inf_obs	μg/ml*h^2	1160.299044
MRT 0-inf_obs	h	9.209266163
Vz/F_obs	(mg)/(μg/ml)	55.28344692
Cl/F_obs	(mg)/(μg/ml)/h	6.548005555

Table 4 Compartmental analysis of enterohepatic circulation model after oral dose input

Parameter	Unit	Value
Ka	1/h	1.1651223
k10	1/h	0.698827735
k1 g	1/h	0.466307328
Ttom	h	5.557105687
V/F	Mg/(μg/ml)	0.321034708
Parameter	Unit	Value
t1/2 ka	1/h	0.594913668
t1/2 k1 g	1/h	0.991871309
t1/2 k10	1/h	1.486459979
D_rec	Mg	7.912095782
D_rec/dose	Mg	0.395604789
Tmax1	h	0.858274297
Cmax1	μg/ml	22.9182339
Tmax2	h	6.415379984
Cmax2	μg/ml	9.330701874
AUC 0-t	μg/ml*h	74.52201017
AUC 0-inf	μg/ml*h	74.62153654
AUMC	μg/ml*h^2	128.0914937
MRT	h	1.716548594
CL/F	(mg)/(μg/ml)/h	0.268019139

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