Revising the assessment of bioequivalence in the light of finite absorption time (FAT) concept: The axitinib case

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Objectives: Pharmacokinetics since its inception (1) in 1953 has been built on the notion of an infinite time for oral drug absorption; in fact, this is like a dogma in contemporary pharmacokinetics and software. FDA founded the relevant fields of bioavailability and bioequivalence in January 7, 1977 relying on this notion; thus, the relevant current FDA (2) and EMA (3) bioequivalence guidelines utilize the gold standard metric for the extent of absorption, namely, the area under the blood drug concentration curve extrapolated to infinite time $(AUC)_{0-\infty}$, as a logical consequence of this dogma. However, this parameter implies infinite time for absorption, which never happens in the real world. In parallel, the highest drug concentration C_{max} observed in plasma is used in bioequivalence testing as a rate of absorption metric.

However, the infinite time for oral drug absorption has been questioned (4). The physiologically sound finite absorption time (FAT) concept and the relevant physiologically based finite time pharmacokinetic (PBFTPK) models for the analysis of concentration, time data were developed (5-8). The PBFTPK models are based on i) the passive drug diffusion mechanism under the sink conditions principle ii) the rate limiting role of the drug's properties solubility and permeability and iii) the relevant restrictions associated with the gastrointestinal transit times of drug in the stomach, the small intestines and the colon. Based on these principles, the PBFTPK models developed have up to three drug successive input functions of constant rate operating for a total time τ (8). It has been also shown that the ratio of the areas $(AUC)_{0-\tau}$ for the test and reference formulations ,where τ denotes the end of the absorption process, was found to be a reliable metric of the relative digoxin bioavailability in two studies analyzed (7). It is worthy to note that one of the digoxin studies was carried out in 1973 and the late Lewis Sheiner was one of the authors of the study.

In this work we aim to develop a non-compartmental methodology based on the finite absorption time (FAT) concept for the assessment of bioequivalence. To this end, we

utilize axitinib data from a pilot bioequivalence study of a creek company based on two tests (T1,T2) and one reference (R) formulations (9).

Methods:

PBFTPK model fittings. We fitted the model equations (8) to axitinib mean concentration, time data to find the best fitting results and derive estimates for τ for each one of the formulations studied. The PBFTPK software used in all model fittings relies on user defined functions in Igor programming environment. In this implementation we adapted its versatile built-in least squares algorithm which allows, among other features, restrictions to parameter values, the use of statistical weights and data sub-sets, calculation of parameter covariance matrix, and easy graphical representation of results. Due to the complex form of the model equations and the convoluted shape of the resulting x^2 hypersurface in parameter space with numerous local minima, the determination of initial trial parameter values was crucial and required their manual adjustments.

Development of a noncompartmental methodology for the assessment of bioequivalence. We calculated using the trapezoidal rule the ratio of the cumulative areas (T1/R and T2/R) of the blood concentration versus time curves for each one of the sampling points of the study. These ratios exhibit a nonlinear increase as a function of time reaching a plateau. According to the FAT concept the ratio (T1/R or T2/R) reaches a plateau when the absorption processes of both the test and reference (T1 and R or T2 and R) formulations have ceased (10). The plateau value of this ratio is a measure of the relative bioavailability of the two formulations.

Results:

PBFTPK model fittings. The best fit results, based on R^2 and χ^2 values, for the analysis of the mean values (from 24 volunteers) of T1, T2 and R concentration, time data, correspond to a one-compartment model with two successive constant input rates and a first-order elimination. In all cases the fitting results were superior to those derived from the fittings using the conventional one-and two-compartment models with first-order absorption. The estimates for the total duration, τ of axitinib absorption were 2.96±0.33, 3.32±0.28, 3.32±0.29 h for T1, T2 and R, respectively; the elimination rate constant estimates were 0.46±0.06, 0.50±0.06, 0.50±0.06 h^{-1} for T1, T2 and R, respectively. These results demonstrate that these formulations exhibit similar absorption and disposition characteristics. The observed mean t_{max} values for T1, T2 and R formulations were 1.33, 2, and 2.33 h, respectively.

Development of a non-compartmental methodology for the assessment of bioequivalence. The ratios (T1/R, T2/R) of the cumulative areas using the sampling points of the study of the blood concentration, time curves applying the trapezoidal rule (numerical integration) were calculated. Then, the ratios were plotted as a function of time; in all cases the ratios increased as a function of time reaching a plateau value. This pattern was observed in all cases examined, i.e., for each one of the volunteers as

well as for the mean values of the three formulations examined. The plateau values for T1/R and T2/R were found to be equal to 1.23 and 1.27, respectively and correspond to the relative bioavailability of the two formulations, i.e., T1 versus R and T2 versus R. Visual inspection of the plots reveals that both curves reach the plateau at 4 h, which is the upper end of the time interval 3-4 hours of the numerical integration; this is in full agreement with the estimates for τ reported above, since all of them (estimate ±2SD) lie in the time interval 3-4 hours. This analysis clearly demonstrates that axitinib absorption takes place in the small intestine and terminates at a finite time. Accordingly, the plateau values 1.23 and 1.27 represent reliable estimates for the relative bioavailability of T1 versus R and T2 versus R, respectively. In other words, the area up to time τ, $(AUC)_{0\text{-}\tau}$ is an ideal metric for the extent of drug absorption.

For all three formulations, the observed values for t_{max} were found to be smaller than the corresponding estimates for τ. This means that the corresponding values for C_{max} do not represent a true rate metric since the absorption of drug continues beyond t_{max} and ceases at time τ. These observations do not substantiate the use of C_{max} as a rate metric.

Conclusions:

The results obtained are an additional piece of evidence that oral drugs are absorbed in finite time. Accordingly, the use of $(AUC)_{0\text{-}\tau}$ for the assessment of bioequivalence is in full agreement with the physiologically sound FAT concept.

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