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PERSPECTIVES

Re-examining digoxin bioavailability after half a century: Time for changes in the bioavailability concepts

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In the late 1960s, it was realized that a variable or poor response to a therapeutic agent may not have its origin in the patient; it may be due to a formulation defect in the drug product administered [1]. The fact that difficulties of this type were occurring with certain lots of digoxin tablets on the market was discovered by the FDA through a systematic testing program inaugurated in April 1970. These observations coupled with several similar ones, e.g., the 1968 Australian outbreak of diphenylhydantoin (phenytoin) intoxication [2], the tremendous differences found in plasma levels of oral generic formulations in the USA market [3] prompted FDA to introduce and establish the concept of bioavailability [4] on January 7, 1977; "Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action".

Recently, the finite time absorption concept was developed and successfully applied to the analysis of gastrointestinal drug absorption data [5-7]. Besides, it was shown that the absolute bioavailability of highly soluble, highly permeable drugs, e.g., theophylline, can be estimated using oral data exclusively [7]. It should be noted that the finite time absorption concept is embedded in modern physiologically-based pharmacokinetic (PBPK) models by giving a physiological time frame for each segment of the intestine [8]. Undoubtedly, PBPK modeling is a powerful tool for the analysis of complex absorption data; the interested reader can find detailed PBPK models for digoxin pharmacokinetics incorporating P-glycoprotein-mediated efflux in the literature [9, 10].

All above findings prompted us to re-examine digoxin bioavailability data [11] published prior to the definition of bioavailability [4] *vis a vis* a bioequivalence digoxin study [12] carried out under the FDA guidelines and analyzed in FDA in 2002, Fig. 1.

Figure 1A shows the concentration–time profile in three subjects upon administration of a digoxin tablet under fasting or fed conditions [11]. According to the authors "… when measured by peak serum digoxin concentration as well as by area under the serum digoxin concentration–time curve, the bioavailability of digoxin appeared to be higher in the fasting state than in the fed state. However, when measured by cumulative five-day urinary excretion of digoxin bioavailability was identical in both conditions". We find the same result by looking at the ratio of pertinent AUCs; in fact, by applying the trapezoidal rule we get $(AUC)_{0-1\,(fasted)}/(AUC)_{0-3\,(fed)} = 0.76/0.8345 = 0.90$. This means that digoxin absorption has ceased at 1 and 3 h in fasted and fed state, respectively, which is in agreement with the finite time absorption concept [6, 7]. In other words, this observation reveals that the AUCs calculated up to the termination of drug absorption can be used as indicators of digoxin extent of absorption.

The same exercise was repeated with the 2002 bioequivalence data [12], Fig. 1B. Here, again the absorption is more rapid in fasted conditions ($t_{max} = 1$ h),

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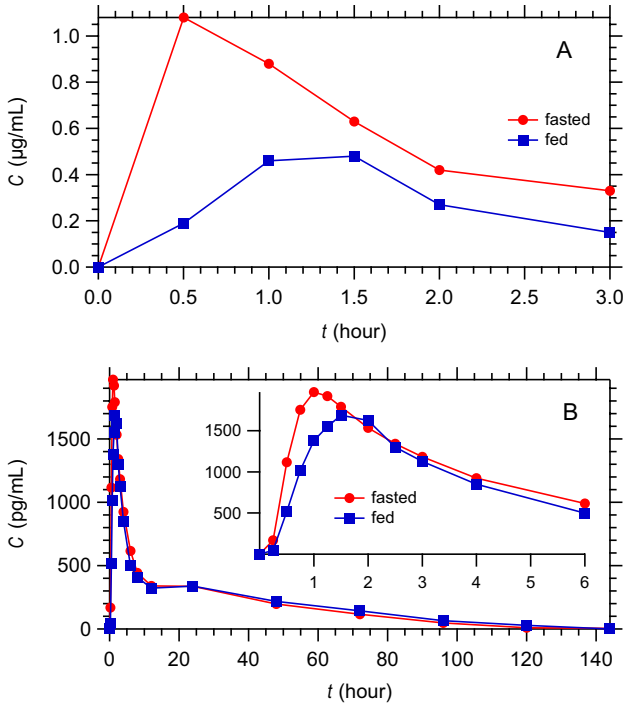

Fig. 1 Concentration–time data from a bioavailability study (A) and a bioequivalence study (B) (11, 12). Insert in (B) shows an expanded view of the first 6 h of the data

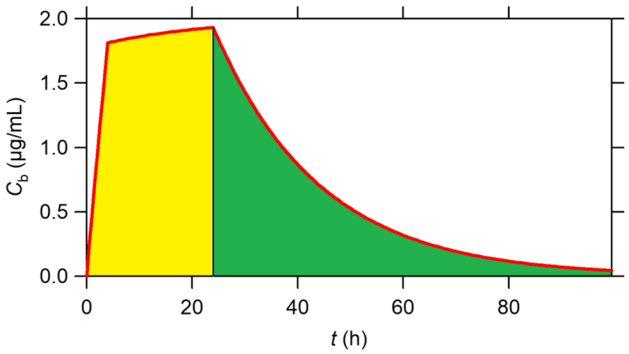

Fig. 2 A schematic for a drug absorbed in finite time, τ. The areas $(AUC)_0^\tau$(on the left, yellow area) and $(AUC)_\tau^\infty$ (on the right, green area) are depicted. The C_b, t profile was generated based on a drug following one compartment model disposition and two successive constant input rates [7]. The following parameter values were used in the simulation: $F_1D/V_d = 2$ μg/mL, $F_2D/V_d = 2$ μg/mL, $\tau_1 = 4$ h, $\tau_2 = 20$ h, $k_{el} = 0.05$ h^{-1}

while the t_{max} is observed at 1.5 h under fed conditions. Clearly, t_{max} for the fed state is different in this study compared to the 1973 work [11] which was prior to establishment of strict guidelines concerning the feeding conditions for such studies. Analysis of the data using the finite time models [6] assuming zero- (z) or first-order (1st) absorption and one-compartment model disposition gave the following estimates for the finite absorption time τ: (fasted, test): 0.94 ± 0.076 h (z), 0.96 ± 0.17 h (1st), (fasted, ref): 0.94 ± 0.073 h (z), 0.96 ± 0.16 h (1st), (fed, mean1): 1.42 ± 0.11 h (z), 1.43 ± 0.17 h (1st), (fed, mean2): 1.33 ± 0.10 h (z), 1.33 ± 0.14 h (1st). These values are very close to the experimental t_{max} values 1 and 1.5 h, respectively. The corresponding ratios of areas under the curve, calculated from zero up to the experimental t_{max} observed are as follows, [AUC 0–1 h, fasted, test]/ [AUC 0–1 h, fasted, ref] = 1.01 and [AUC 0–1.5 h, fed, test] /[AUC 0–1.5 h, fed, ref] = 0.954. These results are quite similar with the classical comparison of AUCs calculated up to the very end of the sampling scheme (144 h) and infinity, namely, $(AUC)_{0-144}$ and $(AUC)_{0-\infty}$, reported in the FDA document [12]. Indeed, the arithmetic mean of the test/ref ratios for $(AUC)_{0-144}$ were 1.10 ± 0.49 and for $(AUC)_{0-\infty}$ 1.05 ± 0.36 for the single dose fasting bioequivalence study, while the arithmetic mean of the test/ref ratios for $(AUC)_{0-144}$ were 1.04 ± 0.37 and for $(AUC)_{0-\infty}$ 1.03 ± 0.28 for the single dose post-prandial bioequivalence study [12].

Thanks to the insightful suggestion of an anonymous reviewer, we were reminded that Lovering et al. [13] analyzed in 1975 comparative bioavailability studies using truncated blood level curves. Their conclusions [13] based on ten drugs including digoxin analyses are in full agreement with the finite time of absorption concept. This work [13] also contains a simple pharmacokinetic method for the estimation of the termination of the absorption process.

All above results demonstrate that the extent of digoxin absorption can be equally well estimated relying on the calculation of the area $(AUC)_0^\tau$, where τ denotes the end of drug absorption process. In fact, one can write a mass balance equation for the absorption of drug terminated at time, τ assuming one-compartment model disposition for any type of absorption kinetics, Fig. 2:

$$Q_\tau = FD - Q_{el(0-\tau)} \tag{1}$$

where Q_τ is the amount of drug in the body at time τ, F is the bioavailable fraction of the drug dose D and $Q_{el(0-\tau)}$ is the amount of drug eliminated from the body between time zero and τ. The corresponding equation for the areas depicted in Fig. 2 assuming one-compartment model disposition of volume V_d and elimination rate constant k_{el} is as follows:

$$(AUC)_0^\tau = (AUC)_0^\infty - (AUC)_\tau^\infty = \frac{FD}{V_d k_{el}} - \frac{FD - Q_{el(0-\tau)}}{V_d k_{el}} = \frac{Q_{el(0-\tau)}}{V_d k_{el}} = \frac{FD - Q_\tau}{V_d k_{el}} \tag{2}$$

Equation 2 reveals that $(AUC)_0^\tau$ is proportional to FD corrected in terms of the amount of drug in the body at time τ, Q_τ; the latter quantity is not only related to absorption characteristics of the formulation, but also

to drug elimination characteristics, Eq. 1. Thus, the area $(AUC)_0^\tau$ can be used as an indicator of the extent of drug's absorption. In the same vein, Eqs. 3 and 4 were derived for two-compartment model drugs following zero- and first-order absorption, respectively.

$$(AUC)_0^\tau = \frac{FD}{V_d\tau}\left[\frac{k_{21}-\alpha}{\alpha^2(\beta-\alpha)}(\alpha\tau + e^{-\alpha\tau} - 1) + \frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}(\beta\tau + e^{-\beta\tau} - 1)\right] \quad (3)$$

$$(AUC)_0^\tau = \frac{k_a FD}{V_d}\left[\frac{(k_{21}-\alpha)(1-e^{-\alpha\tau})}{\alpha(k_a-\alpha)(\beta-\alpha)} + \frac{(k_{21}-\beta)(1-e^{-\beta\tau})}{\beta(k_a-\beta)(\alpha-\beta)} + \frac{(k_{21}-k_a)(1-e^{-k_a\tau})}{k_a(\alpha-k_a)(\beta-k_a)}\right] \quad (4)$$

where α and β are the distribution and elimination hybrid rate constants, k_a is the first-order absorption rate constant, τ is the duration of drug absorption and k_{21} the rate constant of drug transfer from the peripheral to the central compartment. Again, $(AUC)_0^\tau$ is proportional to FD; in this case, the amount of drug, in the body at time τ, Q_τ will be present in the central and peripheral compartment too. Lovering et al. [13] also discussed ways to avoid prolonged sampling times and to ensure reduced risk comparing areas from different times.

All above lead to several interesting observations. First, they show the paramount importance of τ in both the absorption process and the associated estimation of drug bioavailability. Moreover, they demonstrate that for such drugs a sampling scheme for the determination of bioavailability can be kept quite brief causing less inconvenience to volunteers and expediting derivation of results, by avoiding prolonged sample collection.

Drug absorption time is finite because absorption takes place mainly in the upper part of the gastrointestinal tract [6, 7, 14]; in some cases, drug can be also absorbed in the colon in finite time [6, 7, 14]; Fig. 2 shows such an example where drug absorption has ceased in the colon after $\tau = 24$ h. Consequently, τ is determined by human physiology (transit time in the lumen) and biopharmaceutical drug properties (e.g., solubility, permeability). Plausibly, the digoxin observations can be extended to other drugs too.

It is worthy to mention that the use of the maximum drug concentration in blood, C_{max} as a sole regulatory indicator of a drug's rate of absorption, has been criticized extensively and repeatedly [15-19]. Although C_{max} is always being used as a rate parameter in all bioequivalence guidelines, its numerical value is more important since it provides the maximum concentration of the drug in blood. A detailed discussion for the relative magnitude of C_{max} and the drug concentration at the end of the absorption process $C_b(\tau)$, is discussed in [7]. Accordingly, implications associated with the potential use of the finite absorption time, τ, in bioavailability/bioequivalence studies or even the potential replacement of the "rate" concept with the "duration" concept in the definition of bioavailability [4] can be considered by regulatory Agencies. The analysis of digoxin data coupled with our previous results [6, 7] demonstrate that the extent of absorption and the duration of the absorption process are inextricably linked. Undoubtedly, these considerations are of extreme importance and further research is required before any changes are implemented. Only time can tell.

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Declarations

Conflict of interest The authors declare no competing interests.

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