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Letter to the Editor

Crossover Design in Tamoxifen Bioequivalence: a Borderline Situation

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According to operating guidelines (EU note for guidance 1992; Federal register 1997), in bioavailability–bioequivalence trials the AUC (area under the plasma-concentration–time curve) value used must be the AUC extrapolated to infinity from $AUC_{0-tlast}$ as follows:

$$AUC = AUC_{0-tlast} + C_{last}/\beta \quad (1)$$

where C_{last} is the last measurable concentration measured at time t_{last} and β is the slope of the plot of the last log-transformed plasma concentrations against time. Half-life ($t_{1/2}$) is evaluated from:

$$t_{1/2} = 0{\cdot}693/\beta \quad (2)$$

However, with these studies the above guidelines specifically require not more than 20% of extrapolated AUC to be added to $AUC_{0-tlast}$ in the extrapolation procedure. This means that plasma concentrations must be followed for an adequate period, which in most cases can be empirically assessed as 3 times the half-life (Marzo 1997).

A problem arises for drugs with long terminal half-lives, such as amiodarone ($t_{1/2} \cong 35$ days), digitoxin ($t_{1/2}$ 6–8 days), chloroquine ($t_{1/2}$ 9 days) and for drugs that are biotransformed into active metabolites with long half-lives (Marzo 1997). In planning bioequivalence studies the investigator usually uses information from the literature. However, the value of $t_{1/2}$ reported in the literature might occasionally be misleading and produce unexpected results.

The author would like to discuss a typical case from his own experience with tamoxifen bioequivalence, involving data obtained with reference Nolvadex 10-mg tablets administered as a single dose in two different trials each performed on 18 healthy female volunteers.

In the first pivotal study, on the basis of data published elsewhere (Lønning et al 1992), the author assumed the half-lives of tamoxifen and its main active metabolite desmethyltamoxifen to be in the 4–11 day range, and a blood sampling period of 4 weeks and a wash-out lasting 8 weeks were thus incorporated in a two-period, two-formulation, two-sequence study using a single dose. On average, the data showed a half-life of 8·6 days for tamoxifen and 14·1 days for its metabolite. In the extrapolation procedure >20% was added in 4 cases with tamoxifen and in 11 cases with its metabolite (Table 1).

In a further pivotal trial the blood sampling period was prolonged to 5 weeks (Figure 1) and wash-out to 12 weeks. In the extrapolation of AUC > 20% was added in two cases with

Table 1. Mean values of the half-life and the extrapolated area under the plasma-concentration–time curve (AUC) and number of subjects for whom the AUC was extrapolated by more than 20% in two bioequivalence studies on 18 volunteers treated with 10 mg Nolvadex as a single dose.

		Half-life (days)	Extrapolated AUC (%)	No. volunteers for whom extrapolation was >20%
First study	Tamoxifen	8·6 (6·0–13·5)	13·2 (6·2–30·3)	4
Blood sampling period 4 weeks	Desmethyltamoxifen	14·1 (7·8–27·5)	25·0 (9·1–52·0)	11
Second study	Tamoxifen	7·4 (3·9–16·5)	14·4 (9·2–21·6)	2
Blood sampling period 5 weeks	Desmethyltamoxifen	12·8 (6·5–56·3)	12·9 (3·3–64·8)	3

The figures in parentheses are minimum and maximum values.

tamoxifen and in three cases with the metabolite. An exceptional case was encountered of a volunteer for whom 64·8% extrapolation of AUC was required for the metabolite, whereas for the other two cases this value was 23·9 and 23·0% (Table 1).

The case of tamoxifen should be considered as being on the borderline between two different approaches, one related to the crossover design, the other to two parallel groups. Despite the difficulties encountered, the author would prefer the crossover approach with tamoxifen bioequivalence as fewer subjects are needed and more statistical power is achieved, assuming that the 5 weeks of blood sampling and 12 weeks for wash-out between two treatments cannot be shortened.

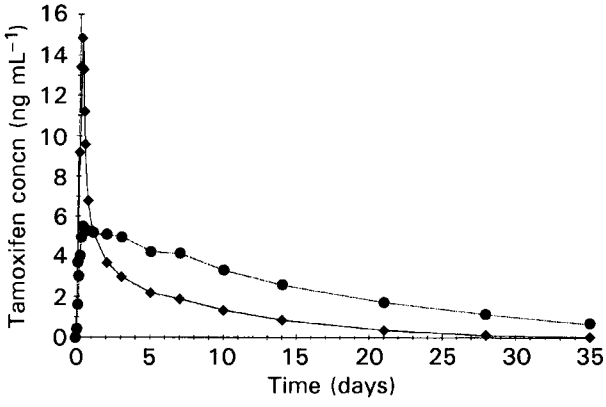

Figure 1. Mean plasma concentrations of tamoxifen (◆) and its metabolite desmethyltamoxifen (●) in 18 female healthy volunteers treated with Nolvadex (10 mg).

For drugs with longer half lives, however, a design with parallel groups should be preferred, because a crossover trial would last longer than 4 months, which is too long, inter alia because a statistically significant period effect could be encountered. In addition, possible drop-outs could prolong the trial by an additional 3–4 months.

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