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Open questions on bioequivalence: the case of multiple peak phenomenon

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Open questions on bioequivalence are defined as experimental situations not clearly resolved by operating guidelines and requiring tailored protocols (Marzo 1995, 1998, 2003). Examples are some of the so-called open questions: drugs with a wide acceptable pharmaceutical titre, drugs with a high variability, drugs with prevalent active metabolites, endogenous substances, drugs cleared with long half-lives and drugs that cannot be given to healthy volunteers (Marzo 1998; Marzo et al 2000). In this paper an additional open question is discussed, namely that related to the multiple peak phenomenon.

Some drugs, when administered orally, produce two peaks caused by an enterohepatic circulation, the first appearing within 1–2 h and the second within 6–12 h of administration. Piroxicam is a typical example (Fourtillan & Bubourg 1983; Brogden et al 1984). In these cases the C_{max}/t_{max} coupled parameters of the first peak are usually considered for evaluating bioequivalence. However, reporting these parameters for the second peak as descriptive behaviour could facilitate the interpretation of results.

Diclofenac as is or salified, administered orally, produces in most cases two peaks. The second one (seen at about 2–3 h) is too fast to be attributed to enterohepatic circulation (Reiner et al 2001) (Figure 1). The second peak phenomenon, after administration of aqueous solutions or dispersible formulations of diclofenac sodium salt, has been described in various reports (Chan et al 1990; Terhaag et al 1991, 2000; Macià et al 1995). Macià et al (1995) attributed it to a pH-dependent dissolution profile of the dosage form within the gastrointestinal tract.

In a comparative bioavailability study of a new very fast-acting formulation of diclofenac potassium salt carried out on 24 healthy volunteers, Reiner et al (2001) reported that the second peak was absent when the first peak appeared early and was substantial. In most cases diclofenac reached its C_{max} at 10 min and in one case at 5 min after dosing with the very fast-acting formulation.

Recently Bettini et al (2000) have found that diclofenac sodium salt in tablets, when immersed in water, is transformed at a relatively slow kinetic rate into the tetrahydrate of diclofenac sodium salt, which is less soluble than diclofenac sodium salt. Although no data are available on other diclofenac salts, it is likely that the same process of hydration can occur with other diclofenac salts as with diclofenac (Bettini et al 2000). A comparison of the two kinetic processes – diclofenac hydration and its enteral absorption – suggests the following possibility. When enteric absorption is rapid, the drug is absorbed in the stomach and duodenum, and no second peak appears. However, if enteral absorption is slower, a substantial amount of diclofenac is transformed into the tetrahydrate, which is less soluble and is absorbed in subsequent tracts of the intestine, thus producing the second peak.

We have conducted several bioequivalence trials with diclofenac sodium or potassium salts, and found that the AUC and t_{max} complied with the bioequivalence requirements, whereas C_{max} produced 90% confidence intervals outside the stipulated range of 0.80–1.25. This was caused by the two-peak phenomenon. Terhaag et al (2000) reported a similar result, namely bioequivalence assessed with AUC and not assessed with C_{max} for multiple peak phenomenon with diclofenac sodium salt.

According to the current regulatory view, the bioequivalence of test and reference substances could not be fully demonstrated in these situations. Taking a less restrictive view, in these cases one could conclude for bioequivalence if the values of C_{max} for the test and reference substances raised no safety or activity problems. This would be acceptable

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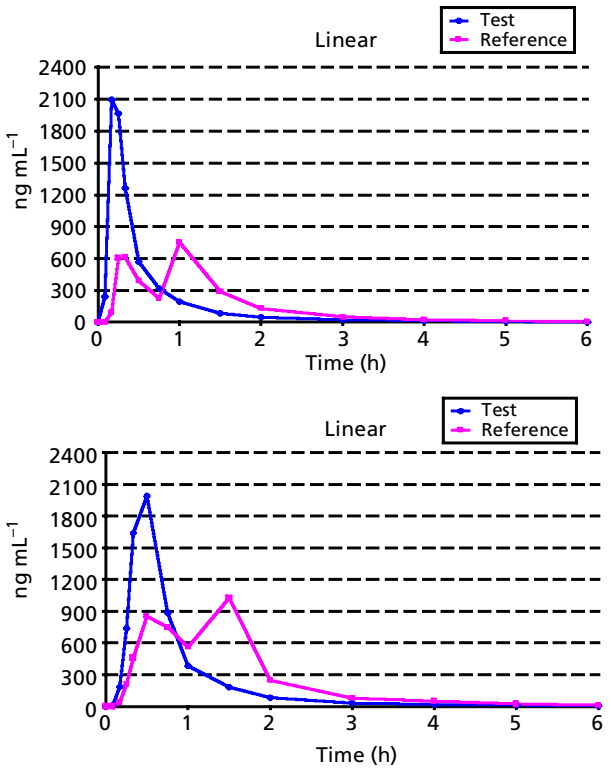

Figure 1 Typical examples of the multiple-peak phenomenon with diclofenac in two volunteers given a fast-acting test (diclofenac potassium salt, film-coated tablets formulation patented by APR) and reference tablet of diclofenac potassium salt (Voltarene Rapide), 50 mg in both cases.

for drugs with a wide therapeutic window, when the various C_{max} values would fall within the range of active concentrations.

However, the specific case of the multiple peak phenomenon is not considered, and consequently no waiver is available under the current regulatory guidelines (Anonymous 2001). The multiple peak phenomenon must therefore be considered an additional open question in bioequivalence.

References

Anonymous (2001) EU note for guidance on the investigation of bioavailability and bioequivalence. CPMP/EWP/QWP/1401

Bettini, R., Giordano, F., Donini, C., Massimo, G., Castellani, P. L., Colombo, P. (2000) Swelling force development as a result of hydrate formation in diclofenac sodium or nitrofurantoin tablets. *S.T.P. Pharm. Sci.* **10**: 335–339

Brogden, R. N., Heel, R. C., Speight, T. M., Avery, G. S. (1984) Piroxicam. A reappraisal of its pharmacology and therapeutic efficacy. *Drugs* **28**: 292–323

Chan, K. H., Mojaverian, P., Ziehmer, B. A., John, V. A. (1990) Application of radiotelemetric technique in evaluating diclofenac sodium absorption after oral administration of various dosage forms in healthy volunteers. *Pharm. Res.* **7**: 1026–1032

Fourtillan, J. B., Bubourg, D. (1983) Etude pharmacocinétique du piroxicam chez l'homme sain, après administration d'une dose égale à 20 mg par voie orale. *Thérapie* **38**: 163–170

Macià, M. A., Frias, J., Carcas, A. J., Guerra, P., Valiente, R., Lucero, M. L. (1995) Comparative bioavailability of a dispersible formulation of diclofenac and finding of double plasma peaks. *Int. J. Clin. Pharmacol. Ther.* **33**: 333–339

Marzo, A. (1995) Open questions on bioequivalence. *Pharmacol. Res.* **32**: 237–240

Marzo, A. (1998) Crossover design in tamoxifen bioequivalence: a borderline situation. *J. Pharm. Pharmacol.* **50**: 1433–1434

Marzo, A. (2003) Bioequivalence behind the scenes. *Pharm. Dev. Reg.* **1**: 179–189

Marzo, A., Vuksic, D., Crivelli, F. (2000) Bioequivalence of endogenous substances facing homeostatic equilibria: an example with potassium. *Pharmacol. Res.* **42**: 523–525

Reiner, V., Reiner, A., Reiner, G., Conti, M. (2001) Increased absorption rate of diclofenac from fast acting formulations containing its potassium salt. *Arzneimittelforschung* **51**: 885–890

Terhaag, B., Gramatte, T., Hrdlcka, P., Richter, K., Feller, K. (1991) The influence of food on the absorption of diclofenac as a pure substance. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **29**: 418–421

Terhaag, B., Hoffmann, A., Barkworth, M., Vens-Cappell, B. (2000) Bioavailability of a new effervescent tablet of diclofenac. *Int. J. Clin. Pharmacol. Ther.* **38**: 546–551