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Letter to the Editor

Pharmacokinetic Analysis, Bioavailability and Operating Guidelines

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In some cases, bioavailability and bioequivalence dossiers which have been criticized by companies interested in a joint venture or rejected by regulatory authorities at the NDA or ANDA stage, have been submitted for my attention for constructive criticism. As they suffered from inappropriate pharmacokinetic analysis, I suggested that they should provide a reanalysis and generally be reissued in an updated form. The most common shortcomings I have encountered include the following.

Compartmental vs non-compartmental analysis

In the original dossier aimed at assessing the bioequivalence of two pharmaceutical formulations, pharmacokinetic parameters were obtained according to standard compartmental models, without giving detailed information about how good the fitting was, or the weighting ascribed to the experimental data in the fitting procedure and presentation showing how the model interpolated experimental data. In a reanalysis of the data, some cases proved to fit the one-compartmental model, others the two-compartmental model, others both models, while some did not fit at all. In some cases, the peak plasma concentration occurred at the first or second blood sampling.

In the revised form, the parameters were obtained with non-compartmental analysis and statistics were carried out as specified in the following section. Most dossiers were useable, as the analysis suggested by the operating guidelines suggested bioequivalence. However, in one case, the non-compartmental analysis produced confidence intervals outside the accepted range, whereas the analysis originally performed by the authors would have indicated bioequivalence. Such discrepancies can occur when confidence intervals lie on the borderline of the accepted range (Rescigno et al 1996).

The preference for non-compartmental models in evaluating pharmacokinetic parameters in bioequivalence trials, clearly required by the operating guidelines (Anonymous 1992, 1997), results from the following calculations performed in our facility. Using mean plasma concentrations of verapamil obtained after the administration of the drug as a delayed-release formulation in volunteers, compartmental and non-compartmental analyses were performed and the results
compared (Marzo & Ceppi Monti 1997). Major differences were encountered; the C_{max} and AUC ranged from 4 to 14%, and with β slope and t½ ranging from 18 to 52% the AUC extrapolation was markedly affected. Additionally the lag-time ranged from 77 to 92% (Table 1).

Additive vs multiplicative models

In the original form, the authors used non-log-transformed parameters (multiplicative model) and symmetrical confidence intervals in assessing bioequivalence (Westlake 1976) and justified this choice by analysing the distribution of the parameters, which proved to be normal. This procedure was criticized because of the need for hundreds of values to demonstrate normal distribution, whereas the bioequivalence trial was carried out on only eighteen subjects. In addition, both US FDA and European guidelines specifically request C_{max} and AUC to be log-transformed and tested through 90% confidence intervals in the 0·80–1·25 range (the additive model), to overcome possible abnormal distribution of the parameters, irrespective of whether they are normally distributed (Anonymous 1997, 1992; Steinijans & Hauschke 1993; Marzo & Balant 1995).

Table 1. Pharmacokinetic parameters of verapamil obtained with non-compartmental, one-compartmental and two-compartmental models giving various weights (w) to plasma concentrations.

		One compartment			Two compartments		
Parameter	Non-compartmental	$w=1$	$w=1/y$	$w=1/y^2$	$w=1$	$w=1/y$	$w=1/y^2$
C_{max} (ng mL^{-1})	83·78	80·16	79·41	78·97	73·14	79·43	78·87
		(−4·3)	(−5·2)	(−5·7)	(−12·7)	(−5·2)	(−5·9)
AUC (ng mL^{-1} h)	858	760	786	796	738	786	795
		(−11·4)	(−8·4)	(−7·2)	(−14·0)	(−8·4)	(−7·3)
β (h^{-1})	0·126	0·192	0·166	0·154	0·184	0·167	0·160
		(+52·4)	(+31·7)	(+22·2)	(+46·0)	(+32·5)	(+27·0)
t½ (h)	5·49	3·61	4·18	4·51	3·78	4·14	4·34
		(−34·2)	(−23·9)	(−17·9)	(−31·1)	(−24·6)	(−20·9)
Lag time (h)	5·00	9·58	9·57	9·58	8·85	9·57	9·58
		(+91·6)	(+91·4)	(+91·6)	(+77·0)	(+91·4)	(+91·6)

Values in parentheses represent the percentage differences between compartmental and non-compartmental analyses.

In the revised form, correct analysis confirmed the bioequivalence previously claimed by the authors.

Conclusions

Attention needs to be drawn to situations of the kind described above, since, although reanalysis according to proper operating guidelines salvaged the trials, the sponsors involved in these cases wasted considerable time and in some cases lost opportunities. I conclude that operators involved in this kind of trial should study and follow the appropriate guidelines before selecting the type of pharmacokinetic and statistical analysis to be carried out.

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Letter to the Editor

It May Be the Caffeine in Extra Strength Excedrin that is Effective for Migraine

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It was announced in the US Federal Register for June 16 that a meeting of the Nonprescription Drugs Advisory Committee would be held on July 15 to hear presentations and discuss data submitted regarding New Drug Application 20–802, Excedrin Extra Strength, 250 mg paracetamol, 250 mg aspirin and 65 mg caffeine, for the pain of migraine (Friedman 1997). A description of the test procedure and results was given by the director of one of the three studies (Lipton 1997). The meeting was held and approval is currently pending.

Research that I have carried out indicates that the effective ingredient for migraine in Excedrin may be the caffeine. I suffer from migraine-type headaches, which I believe to be vascular in nature. My migraines are caused by numerous foods and food components. This was confirmed by a double-blind test using tyramine hydrochloride. I see auras on average twice a month, which is a classical sign for migraine.

I have used every non-prescription analgesic on the US market for my headaches, including aspirin, paracetamol, ibuprofen, ketoprofen, naproxen sodium, Excedrin and aspirin-free Excedrin; only the last two have been effective. I have also tested caffeine alone (100 mg) in the form of Nodoz; it too is effective. Since the other two ingredients of Excedrin alone (aspirin and paracetamol) have no effect, I concluded that the reason the two versions of Excedrin are effective for my headaches is that they contain caffeine.

I therefore undertook a study of the analgesic properties of caffeine in a single human subject, namely me. In an experiment, my blood was analysed every hour following a single 100-mg dose of pure caffeine. After two and a half hours, I consumed 250 mg monosodium glutamate in 90 g ricotta cheese. A headache began five and a quarter hours after the dose of caffeine; this is the period of effectiveness of 100 mg caffeine.

Assuming first-order kinetics for the decay of caffeine in blood (Renner et al 1984), the blood concentrations were used to extrapolate an initial caffeine value of 3·82 mg mL^{-1}, with the value at the start of the headache being 1·97 mg mL^{-1}. The half-life was calculated to be 5·48 h.

I found a 50-mg dose to have no effect on my headaches. This agrees with the results of Laska et al (1984) of 10 000 patients taking analgesics containing caffeine as an adjuvant. A minimum of 60 mg caffeine was required for effective results. The adult dose for Excedrin recommended by the manufacturer as an analgesic provides 130 mg caffeine (two caplets).

Because of the relatively long half-life of caffeine in the blood, I also observed that if a headache returned after taking caffeine, an additional 50-mg dose was sufficient to maintain the analgesic effect for another two hours. Keeping the dose low then avoided causing nervousness and usually did not prevent me sleeping.

I conclude the unique effectiveness of caffeine is that, unlike other analgesics I tested, it is a vasoconstrictor (Rall 1985).

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