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Letters to the Editor

Brain as an eliminating organ?

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In a recent article (Lapka 1991) data concerning easy brain entry of a novel nootropic agent, alaptide, in mice, rats and rabbits have been presented. However, when trying to model the data, an erroneous model has been applied which led to a conclusion that the brain was an eliminating organ. In fact, by multiplying the brain elimination rate constant, k_{BO} (Table 1 in Lapka (1991)), by the brain volume of distribution used by that author (0·0145, 0·0075 and 0·0039 L kg^{-1} for mice, rats and rabbits, respectively) a value for brain clearance equal to 0·06, 0·015 and 0·00096 L h^{-1} kg^{-1} for mice, rats and rabbits, respectively, can be calculated. This corresponds to more than 10% of the total clearance of alaptide, according to the author's kinetic data. In general, this could be possible if the brain contains enzymes which metabolize alaptide, but the author has shown that no metabolites of this drug were formed.

The model used was suggested on the basis of the effect-compartment modelling approach (Sheiner et al 1979), successfully applied to correlate pharmacokinetics and pharmacodynamics in cases of non-instantaneous transport of drugs to sites of their action when the latter are not available for sampling. The basic assumption of this approach is the negligible volume of distribution of a drug in the effect compartment so that it cannot influence the drug pharmacokinetics. It is evident that in the case of alaptide the situation is quite the opposite. First, there were no pharmacodynamic data. The task was purely pharmacokinetic and the use of effect-compartment modelling seemed illogical. The brain received a substantial part of the dose and, moreover, the drug concentration in the brain was monitored, so there were no obstacles for the use of a standard compartmental model which would include the brain as a (non-eliminating) compartment. The best way to apply the model would be to fit it to both data sets (plasma and brain concentrations) simultaneously. This would provide real information on alaptide distribution kinetics into the brain and may help in explaining the interspecies differences in brain-to-plasma partition coefficients reported by Lapka (1991).

References

Lapka, R. (1991) Pharmacokinetics and brain entry of alaptide, a novel nootropic agent, in mice, rats and rabbits. J. Pharm. Pharmacol. 43: 874–876

Sheiner, L. B., Stanski, D. R., Vozeh, S., Miller, R. D., Ham, J. (1979) Simultaneous modelling of pharmacokinetics and dynamics: application to *d*-tubocurarine. Clin. Pharmacol. Ther. 25: 358–371

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Brain as an eliminating organ? A reply

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The aims reported in my article (Lapka 1991) were multiple: to present the pharmacokinetics of the nootropic agent alaptide with special attention to its entry into brain; to compare its pharmacokinetic parameters obtained by different models (a three-compartment model with brain as a third compartment (model 1), a two-compartment model with the brain as a linked compartment (model 2), and a non-parametric assessment of k_{BO} (model 3)); and to draw attention to development of the effect-compartment approach for pharmacokinetic modelling in compartments with relatively small volumes of distribution such as brain. Unfortunately, the second aim was obscured by the referee's intervention and only the linked compartment model appeared in the published article.

Table 1. Pharmacokinetic parameters of alaptide in mice based upon models 1 and 2.

Model	Parameter					
	V_c (L kg^{-1})	k_{10} (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{1B} (h^{-1})	k_{BO} (h^{-1})
1	0·774 (6·7)	0·595 (17·5)	0·284 (31·3)	0·187 (78·5)	0·0228 (20·0)	3·53 (26·3)
2	0·783 (6·6)	0·607 (17·1)	0·266 (33·5)	0·168 (86·9)	0·0268 (19·8)	4·19 (23·9)

Values are expressed as mean (% asymptotic coefficient of variation).

Table 1 demonstrates the comparison of pharmacokinetic parameters based on models 1 and 2 in mice. It is evident that model 2 (Fig. 1 in Lapka (1991)) gave similar results to the more appropriate model, model 1. Total clearances based upon models 1 and 2 (0·461 and 0·475 L $h^{-1}kg^{-1}$, respectively) are indistinguishable. Even the approximate model (model 3) gave a similar value for k_{BO} (3·66 h^{-1}). Results in two other animal species were similar.

Although brain clearance of alaptide constitutes about 10% of total clearance, as stated by Piotrovskij (1992), the use of the effect-compartment model, originally developed for pharmacokinetic/pharmacodynamic modelling, led to clear pharmacokinetic parameter estimates. The only reason for application of the effect-compartment model was to call attention to its potential not only in pharmacokinetic/pharmacodynamic modelling but also in evaluating drug concentration-time courses in compartments having very small volumes of distribution. The conclusion in the title of Piotrovskij's letter (Piotrovskij 1992) is his own and was not stated in my original article (Lapka 1991).

References

Lapka, R. (1991) Pharmacokinetics and brain entry of alaptide, a novel nootropic agent, in mice, rats and rabbits. J. Pharm. Pharmacol. 43: 874–876

Piotrovskij, V. K. (1992) Brain as an eliminating organ? J. Pharm. Pharmacol. 44: 946