ORAL BIOAVAILABILITY PREDICTION IN THE RAT: OFLOXACIN

G. Sánchez, A. Ruiz-García, M. Bermejo, V. Merino, T. Garrigues, J.M. Plá-Delfina
Department of Pharmacy and Pharmaceutics, Valencia University, SPAIN.

Objetive

To predict oral bioavailability (F) of ofloxacin from: a) first-order absorption rate constants k_a obtained by "in situ" intestinal perfusion of a drug solution or b) n-octanol partition coefficients; and to compare the results with those obtained "in vivo" (F).

Materials and Methods

Ofloxacin was donated by Hoechst. In all the experiments Male Wistar rats were used.

Absorption rate constant, k_a, was determined in the whole intestine (n=6) by a non-circulating method[1].

Oral bioavailability (F) was calculated by two-compartment pharmacokinetic analysis of the plasma level versus time curves obtained after 4mg intravenous infusion (n=10) and 4 mg oral administration (n=10) of ofloxacin. IV infusion and blood sampling were carried out by means of cannulae placed in the jugular vein 24 h before the experiment[2].

Partition coefficients were obtained between n-octanol and phosphate buffer pH 7.00 and (n=6).

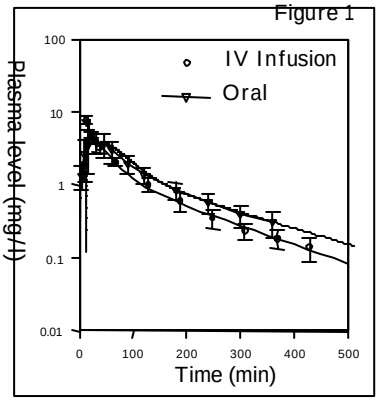
Quantification of all the samples was achieved by fluorimetry after HPLC.

One and two-compartment open models were fitted to plasma level versus time data with the program PCNONLIN 4.2.

Results

Mean plasma levels are shown in Figure 1, where predicted plasma level versus time curves are also depicted.

Figure 1



The two-compartment open model describes more accurately the pharmacokinetic profile of ofloxacin in the rat. Parameters are shown in Table 1.

Table 1

	Infusion	Oral
V_c (L)	0.47 (0.14)	0.48 (0.02)
$V_{d(ee)}$ (L)	0.88 (0.07)	1.00 (0.05)
K_a (h^{-1})		2.58 (0.12)
Kel (h^{-1})	1.08 (0.06)	0.93 (0.03)
Cl (L/h)	0.51 (**)	0.45 (**)
a (h^{-1})	1.9 (0.1)	1.90 (0.04)
b (h^{-1})	0.36 (0.03)	0.30 (0.01)
F		111.5 (3.5)

Ofloxacin distributes to an important volume of the rat, nevertheless it is not retained in the periferic compartment.

The calculated F is 111.5 (3.5). The ofloxacin partition coefficient was shown to be 0.43 (0.03); "in situ" ka value is 0.98 (0.08) h-1.

Conclusions

The value of k_a obtained "in situ" is very close to the one predicted by the biophysical model[3] from P values (1.16(0.21)h^{-1}).

The hyperbolic relationship established between F and k_a in a previous work[1] underestimates F of ofloxacin (predicted F value=61.3 (3.33)%).

Acknoledgements

This work is part of the SAF96-1710 Project of the MEC- Spain. A. R.G. and G. S. participated with MEC grants.

References

[1]Merino, V., J. Freixas, M. V. Bermejo, T. M. Garrigues, J. Moreno and J. M. Plá-Delfina. 1995. J. Pharm. Sci. 84:777-782.

[2]Peris-Ribera J. E., F. Torres-Molina, M. C. García-Carbonell, J. C. Aristorena and J. M. Plá-Delfina. 1991. J. Pharmacokin. Biopharm. 19:647-665.

[3]Bermejo M. V., V. Merino, T. M. Garrigues, J. M. Plá-Delfina, A. Mulet, P. Vizet, G. Trouiller and C. Mercier. 1999. J. Pharm. Sci. 88(4):398-405.