BIOAVAILABILITY PREDICTIONS FROM IN SITU PERMEABILITY: 6- FLUOROQUINOLONES

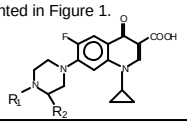
M Bermejo, A. Ruíz-García, G. Sánchez-Castaño, V. Merino, TM. Garrigues, J.M. Plá-Delfina.
Departamento de Farmacia y Tecnología Farmacéutica. Facultad de Farmacia. Universidad de Valencia.
Av. Vicente A. Estellés sn Burjassot 46100 Valencia. España.

Introduction

In the early stages of drug development a method to obtain information about oral bioavailability of new candidates could help to simplify the initial screening and focus on more absorbable derivatives. One of these methodologies consists of predicting the fraction of dose absorbed from intestinal pemeability[1]. In this work the relationship between the *in situ* permeability values (P_{eff}) and oral bioavailability (F) determined in rat of some antibacterial quinolones is being investigated. Preliminary data corresponding to two new Ciprofloxacin derivatives are presented.

Experimental Methods

Two Ciprofloxacin derivatives were synthesised by CENAVISA S.A[2] Laboratories The structures are represented in Figure 1.



R_1	R_2	Name
H	CH_3	CNV97100
CH_2CH_3	CH_3	CNV97102

Figure 1

The study was carried out on male Wistar rats, weighing 250-300 g, maintained in perfect housing conditions. The *in situ* absorption experiments were performed on six animals, using a closed loop technique on the whole intestine of the animal, as previously described[3].

Bioavailability studies were carried out on non-anestethised rats. The animals were cannulated on the yugular vein the day before to the experiment. Intravenous administration of was carried out by means of the yugular cannula and the intra-gastric administration was made using a gavage needle. Blood samples were taken from the cannula at selected times.

The analysis of the samples was carried out by HPLC with a fluorimetric detection. Analysis procedures were validated for every compound.

Mean plasma levels of five animals were used to estimate the pharmacokinetic parameters describing the profile versus time and to calculate the area under the curve AUC by trapezoidal rule.

The fitting equation used for permeability-bioavailability correlations was:

$$F_{abs} = 1 - e^{-(\frac{P_{eff} \cdot 2}{R} \cdot T)}$$

where R is the intestinal radious and T the effective intestinal transit time for absorption. The fitting procedures were made by means of PCNONLIN 4.0.

Results and Discussion

In Table 1 the permeability values obtained *in situ* and the bioavailabilities determined *in vivo* are shown for the two new quinolones along with other experimental results previously reported.[3,4,5] In Figure 2 the relationship between permeability *in situ* values and oral bioavailability is graphically outlined.

The predictive performance of the model was evaluated using a "leave-one-out" procedure and computation of both the mean prediction error (ME showing the prediction bias) and the squared root of the mean squared prediction error (sqMSE showing the prediction accuracy). Considering these parameters there is a good relationship between Peff and bioavailability (ME=7.8% and sqMSE=17%).

As regards absorbing transit time, T, the value obtained (1.2 h) is very closed to the referenced.[5,6]

Compound	Peff (cm/s) (SD)	$F_{trap.}$%
CNV97100	$1.86 \cdot 10^{-5}$ ($1.49 \cdot 10^{-6}$)	73.5
CNV97102	$7.99 \cdot 10^{-5}$ ($8.47 \cdot 10^{-6}$)	86.5
Norfloxacin[3,4,5]	$1.05 \cdot 10^{-5}$ ($1.74 \cdot 10^{-6}$)	33.8
Pefloxacin[3,4,5]	$4.78 \cdot 10^{-5}$ ($4.98 \cdot 10^{-7}$)	85.5
N'-Propyl-norfloxacin[3,4,5]	$1.01 \cdot 10^{-4}$ ($9.96 \cdot 10^{-6}$)	92.8

Table 1

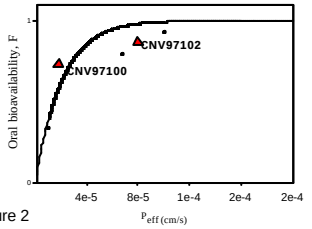


Figure 2

Conclusion

A good relationship could be established in our experimental conditions between *in situ* permeability and *in vivo* bioavailability. A new set of quinolone derivatives must be assayed in order to perform the external validation of the correlation to check its predictive potentialities.

References

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Acknowledgements

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