STUDY OF INTESTINAL ABSORPTION OF A NEW QUINOLONE IN RATS

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Introduction

Many compounds belonging to different categories of drugs have been reported to be actively secreted by intestinal efflux systems as P-glycoprotein (P-gp)[1,2,3]. The existence of an intestinal secretion process for some fluorquinolones seems to be demonstrated in biological systems like Caco-2 cells[4,5].

The aim of this work is to go insight the absorption mechanism of CNV97100, a new quinolone and to establish the importance of the reported efflux process by in situ experiments.

Experimental Methods

The new Ciprofloxacin derivative was synthesized by CENAVISA S.A.[6] The structure is represented in Figure 1.

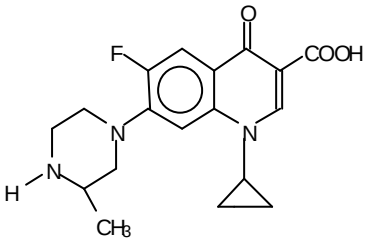

Figure 1

An intestinal in situ perfusion technique[7] was used to calculate permeability values, Peff of CNV97100 at 0.5, 5 and 50 µg/mL. The solutions were perfused in the whole intestine of the anesthetized male Wistar rats and samples were taken every 5 minutes over a period of 30 minutes.

Inhibition studies were performed using Verapamil, a mixed inhibitor of P-glycoprotein and Multidrug Resistance Associated protein. Verapamil was perfused at the concentration of 2 mM in the presence of 5 µg/mL of the quinolone.

Analysis of the samples was carried out by reverse phase HPLC technique and fluorimetric detection.

Peff was calculated by non- linear regression of the remaining concentration of quinolone in lumen versus time, using SIGMAPLOT 2.0.

Results and Discussion

Table 1 shows permeability values in every condition. The results are graphically outlined in Figure 2 for better comparison.

Perfusion Concentration	P_{eff} (cm/s) (SD)
50 µg/mL	$1.96 \cdot 10^{-5}$ ($2.50 \cdot 10^{-6}$)
5 µg/mL	$2.24 \cdot 10^{-5}$ ($9.30 \cdot 10^{-6}$)
0.5 µg/mL	$1.62 \cdot 10^{-5}$ ($7.45 \cdot 10^{-6}$)
5 µg/mL + Verapamil 2µM	$3.58 \cdot 10^{-5}$ ($6.57 \cdot 10^{-6}$)

Table 1

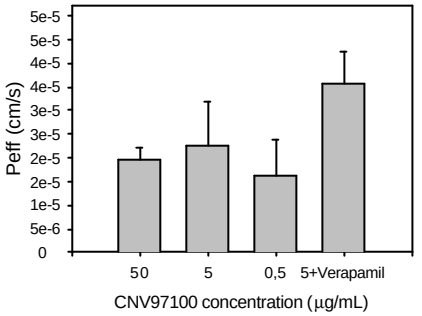

Figure 2

The one way analysis of variance ANOVA does not show statistical differences between the assayed concentrations, partially due to the large variability of Peff (around 30 % CV). The fact that there were no significant differences between the permeabilities obtained at the different concentrations of CNV97100 assayed suggests that absorption is a first order process, so that passive diffusion is the major transport mechanism or, if an active process exists, it is very far from saturation.

In order to study the relevance of a possible secretion process, the influence of Verapamil on the absorption of CNV97100 was checked.

Peff at the medium concentration of CNV97100, significantly increases in the presence of Verapamil ($p=0.005$).

This result demonstrates the existence of an active efflux mechanism.

Conclusion

The new quinolone CNV97100 seems to be passively absorbed in rat as no concentration dependence has been observed in the absorption process. Nevertheless the presence of a P-gp inhibitor significantly increased the permeability of the compound and therefore, the existence of an efflux process mediated by a P-gp-like mechanism could not be ruled out.

References

1. J. Hunter and B. H. Hirst. Adv. Drug. Deliv. Rev. 25 (1997)129-157.
2. A. Tsuji and I. Tamai. Pharm. Res. 13 (1996) 963-977.
3. T. Terao et al. J. Pharm. Pharmacol. 48 (1996) 1083-1089.
4. N.M. Griffiths et al. J. Pharmacol. Exp. Ther. 269 (1994) 496-502.
5. M.E. Cavet et al. Br. J. Pharmacol. 121 (1997) 1567-1578.
6. Cenavisa S.A. Spanish patent 8,901,480. 1989
7. V. Merino et al. J. Pharm. Sci. 84 (1995) 777-782.

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