STUDY OF THE ABSORPTION OF A NEW FLUOROQUINOLONE IN RATS: POSSIBLE INVOLVEMENT OF P-GLYCOPROTEIN EFFLUX MECHANISM

Bermejo M, González-Álvarez I, Fernández-Teruel C, Ruiz-García A*, Merino V, Garrigues TM, Plá-Delfina JM.

Departamento de Farmacia y Tecnología Farmacéutica. Facultad de Farmacia. Universidad de Valencia. Av. Vicente A. Estellés sn Burjassot 46100 Valencia. España.

*Department of Pharmaceutics, University of Washington,

Box 357610 HSB H272 Seattle, WA 98195-7610

Introduction

Numerous compounds including fluoroquinolones have been reported to be actively secreted (by efflux systems as P-glycoprotein) when they are studied in vitro models as Caco-2 cultured cells [1], but the relevance of this process in situ or in vivo is not always significant.

The aim of the study was to determine the influence of Pin situ intestinal alycoprotein on absorption of а new 6fluoroquinolone (CNV97100), synthesised by Cenavisa Laboratories (Spain), that has shown higher in vitro antibacterial activity than the parent compound [2].

Experimental Methods

The Ciprofloxacin derivative was synthesised by CENAVISA S.A Laboratories The structure is represented in Figure 1.



Figure 1

The study was carried out on male Wistar rats, weighing 250-300 g, maintained in perfect housing conditions. The in situ absorption rate coefficient (ka) of CNV97100 was determined in the whole intestine of the rat at five different concentrations ranging from 500 μ g/ml to 0.05 μ g/ml in presence and in absence of Verapamil 4 mM as P-glycoprotein inhibitor. The quinolone solutions were perfused in the intestine of anesthesized rats and samples of luminal content were taken over a period of 30 mins.

Apparent first order absorption coefficients ka, were calculated in every condition by non-linear regression of the remaining concentration of quinolone versus time [3,4].

The one-way analysis of variance showed statistically significant differences among the apparent first order absorption coefficients determined at different concentrations. The remaining luminal concentrations in every conditions were fitted to a system of differential equations of a combined passive and Michaelis-Menten kinetics with the aid of Winnonlin v.01 software.

$$\frac{\partial C}{\partial t} = -k_d + \frac{V_m \cdot C}{K_m + C} = Eq (1)$$

This allows to obtain the passive $(k_{\rm d})$ and active $(K_{\rm m}$ and $V_{\rm m})$ parameters.

Results and Discussion

The apparent first order absorption coefficients of CNV97100 in presence and in absence of Verapamil were represented in Figure 2. The remaining experimental concentrations in lumen versus time and the fitted curves to eq (1) are represented in Figure 3. The fitting parameters are displayed in Table 1.

The presence of Verapamil in the perfused solution produces an increase in the apparent absorption coefficient to a maximum value of 1.2 h⁻¹, that corresponds approximately with the passive component.



Conclusion

These results show for the new compound that the efflux process is relevant not only in vitro (data not shown) but also in situ in rats. When the upper concentration of CNV 97100 is used, the active component seems to be saturated. Moreover, Verapamil is able to inhibit the efflux process. The influence in the in vivo situation will be further studied.

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