BIOPHYSICAL MODEL APPLYING TO PREDICT INTESTINAL ABSORPTION OF SARAFLOXACIN AND SPARFLOXACIN

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Introduction

The aim of the study was to determine the in situ permeability (Peff) of Sarafloxacin and Sparfloxacin and to compare the result with the predicted values utilizing the Higuchi-Ho model based on the use of lipophilicity indexes. Prediction of the permeability values for both quinolones was based on a previously established absorption-partition correlation for a series of Norfloxacin and Ciprofloxacin derivates [1].

Experimental Methods

The determination of the intestinal Permeability coefficient was made by a method of perfusion in situ without recirculation described by Doluisio and adapted to our experimental conditions. The animals used were male Wistar rats weighting between 270-300 grams. For the predictions lipophilicity was quantified by means of n-octanol partition-coefficient at pH 7.00. The analysis of the samples was made by liquid chromatography (HPLC) with fluorimetric detection. The absorption rate coefficients were obtained by nonlinear fitting of a monoexponential equation to the luminal concentrations versus time data. These absorption rate coefficients were transformed into permeability values (Peff) with the following equation: Peff= (Ka*R)/2 where R is the effective intestinal radius calculated from the perfused volume and the intestinal segment length.

Permeability coefficient of Sparfloxacin was detemined at two perfusion concentrations: 120 and 10 µg/mL. For Sarafloxacin the study was carried out at three different concentrations: 50, 5 and 0.5 µg/mL .

Results and Discussion

The permeability values of Sarafloxacin and Sparfloxacin in the different conditions are displayed in Figure 1.

The one way analysis of variance (ANOVA) showed statistically significant differences between the Permeability values at the different concentrations for Sarafloxacin whereas no differences were found between the two permeability values for Sparfloxacin.

The previously obtained absorption-lipophilicity correlation for homologous derivatives of Ciprofloxacin and Norfloxacin is represented in Figure 2. The Permeability values of Sarafloxacin and Sparfloxacin are superimposed in the graph.

The Permeability value experimentally obtained for Sparfloxacin is very similar (included in the 95% confidence interval) to the predicted value by the Higuchi-Ho model. For this compound it is possible to predict its intestinal Permeability in rat from its partition-coefficient and to consider its absorption as an apparent passive process in the range of concentrations assayed.

The experimental Peff for Sarafloxacin is quite lower than the predicted value from the Higuchi-Ho model at all the concentrations assayed. The first posibility to explain this deviation from the absorption-lipophilicity correlation was to consider the existence of an efflux process since the permeability obtained experimentaly is lower than the predicted by the equation used.

Nevertheless, the results obtained at different concentrations showed an apparent active absorption mechanism since the permeability values decrease when concentration increase.

Other authors have reported similar results with other quinolones as Ofloxacin [2]. More experimental results, however, are needed to clarify the exact nature of the transport mechanism and whether it will have any relevance in vivo.

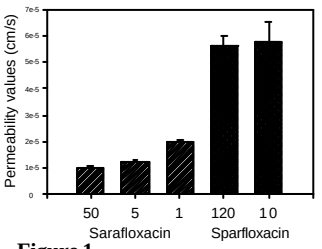

Figure 1

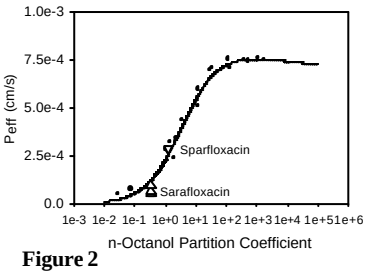

Figure 2

Conclusion

The absorption partition correlation found for the homologous series of quinolones is a useful tool for predicting permeability values from partition coefficient when the absorption mechanism is passive diffusion even for heterologous compounds. The deviations from this correlation can help to detect active components in the absorption process

References

1. V. Merino et al. *J. Pharm Sci* 84 777-782. (1995)
2. L. Rabbaa et al. *Antimicrob. Agents. Chemother*. 41(10):2274-2277. (1997);