STUDY OF THE ABSORPTION MECHANISM OF TRIAMTERENE IN RATS.

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Introduction

Triamterene is currently used as a diuretic in therapeutics and has a low bioavailability[1].

This study intends to go insight the intestinal absorption mechanism of triamterene in rat to find possible causes to its bioavailability problems and in order to make further comparison with the absorption of solid formulations.

Experimental Methods

The concentration dependence of the absorption was studied by perfusion of five different concentrations of triamterene ranging from 0.08μg/mL to 8 μg/mL, using an intestinal in situ perfusion technique[2]. The solutions where perfused in the whole intestine of the anesthesized rats and samples of the luminal content were taken every 5 minutes over a period of 30 minutes. Permeability values, P_{eff}, were calculated in every condition by non linear regression of the remaining concentration of triamterene in lumen versus time.

Kinetic values were obtained by nonlinear regression of effective permeabilities versus concentration using the following equation[3]:

$$P_{eff} = \frac{P_C}{1 + C/K_m} + P_m \qquad \textbf{Equation 1}$$

where Pc is the carrier permeability (=Jmax/Km), Km is the Michaelis constant, Pm is the nonsaturable membrane permeability and C is the initial perfusion concentration. The fitting was made with the aid of SIGMAPLOT 2.0.

Results and Discussion

The permeability values of triamterere in each condition are listed in Table 1. The one way analysis of variance (ANOVA) showed statistically significant differences between P_{eff} values in the different conditions (p=0.02). In Figure 1 shows the plot of P_{eff} versus concentration and the best fit line. Parameters and the statistical figures associated are listed in Table 2.

Concentration μg/mL	Peff (cm/s) (SD)
0.008	$3.12 \cdot 10^{-5}$ ($9.6 \cdot 10^{-6}$)
0.08	$2.33 \cdot 10^{-5}$ ($5.6 \cdot 10^{-6}$)
0.8	$1.84 \cdot 10^{-5}$ ($3.5 \cdot 10^{-6}$)
4	$1.73 \cdot 10^{-5}$ ($1.9 \cdot 10^{-6}$)
8	$1.67 \cdot 10^{-5}$ ($4.1 \cdot 10^{-6}$)

Table 1

Parameter	Value
Jmax (μg/s·cm^2)	$8.32 \cdot 10^{-7}$ ($0.13 \cdot 10^{-7}$)
Km (μg/mL)	$5.07 \cdot 10^{-2}$ ($7.87 \cdot 10^{-3}$)
Pc (cm/s)	$1.64 \cdot 10^{-5}$ ($6.61 \cdot 10^{-7}$)
Pm (cm/s)	$1.70 \cdot 10^{-5}$ ($2.55 \cdot 10^{-7}$)
R^2	0.9978

Table 2

Figure 1

From the results obtained an active transport of triamterene in the rat intestinal tract can not be ruled out. Nevertheless the passive permeability is about the same magnitude than the carrier permeability. Km value obtained indicates that low concentrations in the lumen produce a saturation of the carrier system. For a dose of 2mg/kg that represents a concentration in lumen about 1.2 mg/mL, the bioavailability of the compound is approximately 70% (data not shown). This value is in accordance with the expected bioavailability for a compound with a passive permeability of $1.67 \cdot 10^{-5}$ cm/s in rat[4]. The carrier system involved in the transport of triamterene could be the responsible of the absorption of folic acid derivatives since triamterene is structurally related with this compound and it has been demonstrated that triamterene inhibits the intestinal absorption of folic acid in a dose dependent fashion[5].

Conclusion

A combined kinetic of passive and carrier mediated mechanism describes the absorption process of triamterene in small intestine of rat. The low permeability at the higher luminal concentrations could be partially responsible of the low and variable bioavailability.

References

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