

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 bioavailability¹.

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 and the proton dependence (pH=7.00 versus pH=8.00) of the absorption of triamterene 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 technique². The solutions were perfused in the whole intestine of the anesthetized 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 parameters values were obtained by nonlinear regression of effective permeabilities versus concentration using the following equation³:

$$P_{eff} = \frac{P_c}{1 + C/K_m} + P_m \quad \text{Equation 1}$$

where P_c is the carrier permeability ($=J_{max}/K_m$), K_m is the Michaelis constant, P_m 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 triamterene 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 concentrations at pH=7.0 ($p=0.02$). Figure 1 shows the plot of P_{eff} versus concentration and the best fit line. Parameters and statistical figures associated are listed in Table 2.

Conc. (mg/mL)	P_{eff} (cm/s) (SD) pH=7.0	P_{eff} (cm/s) (SD) pH=8.0
0.008	$3.12 \cdot 10^{-5}$ ($9.6 \cdot 10^{-6}$)	$1.42 \cdot 10^{-5}$ ($1.5 \cdot 10^{-6}$)
0.08	$2.33 \cdot 10^{-5}$ ($5.6 \cdot 10^{-6}$)	
0.8	$1.84 \cdot 10^{-5}$ ($3.5 \cdot 10^{-6}$)	$1.42 \cdot 10^{-5}$ ($3.7 \cdot 10^{-6}$)
4	$1.73 \cdot 10^{-5}$ ($1.9 \cdot 10^{-6}$)	
8	$1.67 \cdot 10^{-5}$ ($4.1 \cdot 10^{-6}$)	$1.34 \cdot 10^{-5}$ ($1.8 \cdot 10^{-6}$)

Table 1

Parameter	Value
J_{max} (µg/s·cm ²)	$8.32 \cdot 10^{-7}$ ($0.13 \cdot 10^{-7}$)
K_m (µg/mL)	$5.07 \cdot 10^{-2}$ ($7.87 \cdot 10^{-3}$)
P_c (cm/s)	$1.64 \cdot 10^{-5}$ ($6.61 \cdot 10^{-7}$)
P_m (cm/s)	$1.70 \cdot 10^{-5}$ ($2.55 \cdot 10^{-7}$)
R^2	0.9978

Table 2

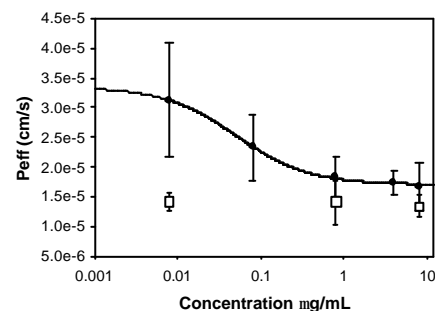


Figure 1

The results obtained at pH=7.00 demonstrate a significant decrease in P_{eff} when the concentration increases, probably due to an active absorption

process. Passive and carrier permeability have approximately the same magnitude. K_m value obtained indicates that low concentrations in the lumen produce a saturation of the carrier system.

There are no statistical differences between P_{eff} when pH 8.00 is used. Furthermore, these values are not significantly different from the estimate of the passive component at pH=7.0. This finding implies that the absorption at pH 7.0 is probably mediated by a H⁺-dependent carrier whose contribution is negligible at pH 8.

For a dose of 2mg/kg that represents a concentration in lumen around 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 an effective permeability of $1.67 \cdot 10^{-5}$ cm/s in rat⁴.

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 fashion⁵.

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 its low and variable bioavailability.

References

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