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GENDER SPECIFICITY OF TOLTERODINE ON MICTURITION AND DIURNAL VARIATION OF URINE PRODUCTION OF THE CONSCIOUS RAT

AIM OF STUDY

To evaluate the effect of oral Tolterodine administration on the micturition characteristics of the rat. The focus of this study is placed on the examination of the effects of Tolterodine on the diurnal variation of the micturition characteristics of male and female conscious rats. In addition we propose to examine the influence of Tolterodine on water consumption and urine production and their possible contribution in modulating urinary tract function.

MATERIALS & METHODS

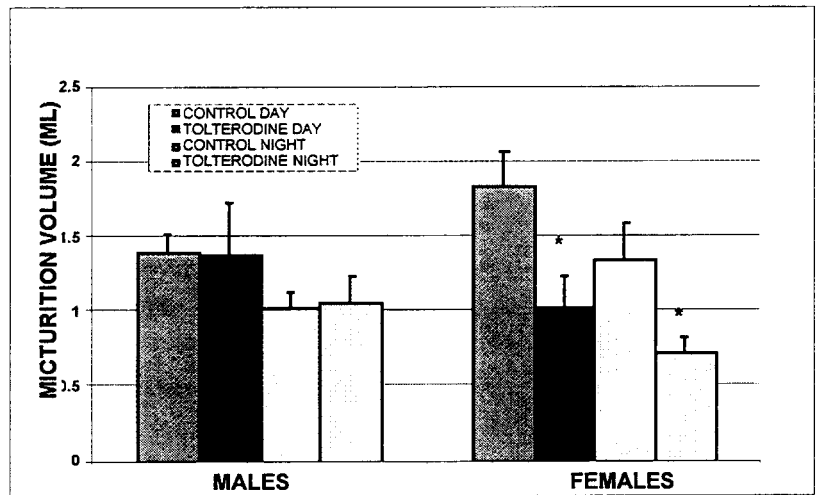
Baseline values of the micturition volume and frequency of 9 male and 10 female SD adult rats was initially evaluated over a 24 hr time period. To standardize initial hydration conditions an 5-ml oral dose of water was administered and rats placed in a metabolism chamber with free access to water. Micturition f/v characteristics were derived from the measurements of voided volume detected by a digital balance placed below the metabolism cage and connected to a PC. The total volume of water consumed over the 24 hour was also measured. Two separate control studies were initially done followed by the administration of a single dose of 1 mg/ml of Tolterodine dissolved in 5 ml of water. Analysis of data was made by normalizing numerical values of volume to kg of rat body weight. Mean frequency of micturition and mean volume voided per micturition were computed in 3 hour time bins and represented over the 24 hr period. In addition the mean values of the number of micturitions and mean micturated volumes during the day/dark cycle were evaluated. Statistical comparisons were made using the paired t-test and values are given as mean \pm SE. A probability of $p < 0.05$ was taken as a criterion of significance.

RESULTS

Baseline data show that females consistently consume significantly larger amounts of water (83%) than male rats. Tolterodine does not significantly affect water consumption in the males but significantly reduces water consumption in female rats by 42%; a value equivalent to male controls.

Tolterodine does not significantly affect the amount of urine produced

by male rats but significantly reduces the total amount of urine production in female rats by 26%. Tolterodine did not change significantly the number of micturitions of male rats in comparisons to controls during the day or night cycle but increased significantly 56% the number of micturitions of female rats in comparison to controls during the day but not during the dark cycle. More significantly, Figure, Tolterodine does not produce a significant effect on the volume voided per micturition in male rats either during the dark or light cycle but significantly decreases the mean volume voided per micturition in female rats.



CONCLUSIONS

On the basis of the results of this single dose Tolterodine trial it is concluded that Tolterodine suppresses the demand of water consumption by females but not by males and consequently decreases urine production by females but not in males. Tolterodine does not decrease the frequency of micturition of either the male or female rat or increase the amount of urine volume voided per micturition. While gender and diurnal variation are contributing factors affecting the results previous experimental evidence suggests that there are gender differences in the metabolite profiles of Tolterodine which may partly account for the observed results in the volume of micturition. Finally this study focuses attention on the mechanism of action of Tolterodine on micturition and the implications of modulation in the state of hydration of the female rat.