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Title (type in CAPITAL LETTERS): **TOLTERODINE AND ITS METABOLITES SHOW VERY LOW PENETRATION INTO THE CENTRAL NERVOUS SYSTEM**

Aims of Study: Tolterodine is a novel muscarinic receptor antagonist that has been shown to exhibit a selectivity for bladder over salivary glands in vivo {1}. Tolterodine is effective and well tolerated in patients with overactive bladder. The aims of this study were to investigate the tissue distribution of radiolabeled tolterodine in the mouse. The pharmacokinetics and metabolism of tolterodine in the mouse are similar to those in humans, including formation of the major active metabolite 5-hydroxymethyl (5-HM, labcode DD 01).

Methods: Mice were treated with single or repeated oral doses of ^{14}C- or ^{3}H-tolterodine (at doses of 4 to 40 mg/kg). Tissue distribution of radioactivity was determined by tissue dissection studies and whole body autoradiography.

Results: The distribution of radioactivity in most tissues was rapid, with peak concentrations attained within 1 hour postdose. Highest concentrations of radioactivity were found in the elimination organs: gallbladder, liver, kidney, lung (tissue/blood ratios: >100-6). Lowest concentrations were found in the brain (tissue/blood ratio: 0.1-0.3). The distribution patterns were similar after single and repeated dosing, but the elimination was somewhat slower after repeated administration.

Conclusions: Tolterodine and its metabolites were rapidly distributed into tissues. However, penetration of the blood brain barrier was low. This may be related to the comparatively low lipophilicity of tolterodine (Log D 1.83) and particularly that of 5-HM (Log D 0.74). Thus, as a result of different degrees of serum protein binding, the unbound (active) fraction of 5-HM is higher than that of tolterodine both in the mouse (4.5-fold) and in humans (10-fold). Together with the results of the present study, this suggests that the risk of deleterious effects on cognitive functions may be lower with tolterodine than with more lipophilic antimuscarinic drugs.

Reference

1. *Eur J Pharmacol.* 1997;327:195-207.

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