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**Title:** RATIONALE FOR THE USEFULNESS OF INTRAVESICAL AND TRANSDERMAL OXYBUTYNIN IN THE THERAPY OF DETRUSOR INSTABILITY, BASED ON THE ANALYSIS OF MUSCARINIC RECEPTOR BINDING

**Aims of Study.**

Urinary incontinence and other symptoms of lower urinary tract dysfunction are prevalent among the rapidly growing population. Oral anticholinergic agents such as oxybutynin (Oxy) have been used effectively in managing detrusor instability (DI) or detrusor hyperreflexia in patients with neurogenic bladder and urge urinary incontinence [1]. However, there are some patients who do not respond to oral anticholinergic agents or who cause frequently systemic side effects as dry mouth with orally administered Oxy [2]. In an effort to avoid the side effects of oral agents and to treat patients who are refractory to oral pharmacotherapy, the intravesical instillation of Oxy has been reported to be effective and safe in most patients [3]. Furthermore, the transdermal therapeutic system (TTS) of Oxy (MM-801) has been currently developed and its usefulness is now under investigation. The therapeutic effect and dry mouth by Oxy in patients with DI are mainly mediated through the blockade of muscarinic receptors in the bladder and salivary gland, respectively. Our current studies have highlighted the usefulness of in vivo analysis of drug-receptor binding in relation to the pharmacokinetics for characterizing pharmacological specificity (potency, duration of action and tissue selectivity) of the drug [4-5]. Therefore, we investigated comparatively muscarinic receptor binding in the bladder and other tissues of rats, in relation to the plasma concentration of Oxy and its active metabolite (N-desethyloxybutynin: DEOB), after the intravesical, transdermal and oral administration of Oxy.

**Method.**

At 0.5 to 48 hr after the intravesical, transdermal and oral administration of Oxy, rats were sacrificed by exsanguinations from the descending aorta, and the bladder, submaxillary gland, heart and colon were dissected. The muscarinic receptor in each tissue was measured by a radioreceptor binding assay with [N-methyl-$^{3}$H]scopolamine (NMS) as a radioligand, and binding constants of apparent dissociation constant (Kd) and maximal number of binding sites (Bmax) for [$^{3}$H]NMS were estimated by Scatchard analysis. The concentration of Oxy and DEOB in the plasma was also measured.

**Result.**

Following the oral administration of Oxy, there was a significant increase of Kd value for specific [$^{3}$H]NMS binding in the bladder, submaxillary gland, heart and colon of rats compared with the value of control rats, and a concomitant reduction of Bmax value only in the submaxillary gland and heart. Such increase of Kd value in each tissue was seen only at 1 and 3 hr after the oral administration of Oxy, but a significant reduction of Bmax value in the submaxillary gland and heart was maintained for more than 24 hr. The plasma concentration of Oxy and DEOB was maximal at 1 hr after oral administration and it was extremely low at 12 and 24 hr later.

The transdermal application of MM-801 brought about a significant increase of Kd value for specific [$^{3}$H]NMS binding in the bladder, submaxillary gland, heart and colon of rats, and there was little reduction of Bmax value in each tissue. The increment of Kd value increased with the application time of MM-801, being maximal at 12 hr later. The plasma concentration of Oxy increased with the application time of MM-801, and the maximal level

was seen at 12 hr and maintained until the application time of 48 hr. DEOB was not detected in the plasma of MM-801-administered rats.

The intravesical instillation of Oxy brought about a significant increase of Kd value for specific [$^{3}$H]NMS binding only in the bladder and submaxillary gland of rats, and there was little reduction of Bmax value in each tissue. Such increase of Kd value in the bladder was much greater and of longer duration than that in the submaxillary gland. Following the intravesical instillation of Oxy, the plasma concentration of Oxy was markedly low, and DEOB was not detected in the plasma.

**Conclusions.**

These data suggest that the intravesical, transdermal and oral administration of Oxy produces a significant blockade of muscarinic receptors in the bladder of rats and that the blocking potency of the receptor in the submaxillary gland is much weaker by the intravesical and transdermal administration than by the oral administration. Thus, the present study may provide a rationale for the usefulness of intravesical and transdermal administration of Oxy in the therapy of DI.

**References.**

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