

Objectives: The objective was to investigate the influence of two anticholinergic, propiverine and tolterodine on bladder contraction in a standardized in vivo model taking neurogenic innervation into account. In addition, standardized salivary flow measurements enabled the evaluation of hyposalivation, the most predominant anticholinergic side effects. Furthermore, the detrusor electromyogram was evaluated.

Material & Methods: 10 male mini pigs were anaesthetized. The carotic artery was cannulated for blood pressure control and the jugular vein for administration propiverine 0.4 mg/kg b.w and L(+)-tolterodine 0.06 mg/kg b.w. Doses were chosen according to the Defined Daily Dose (DDD). For stimulation-induced salivary flow measurements both lingual nerves were exposed and a cuff electrode was placed around the nerves. The bladder was then exposed and 2 electrodes were implanted under the serosa of the bladder dome to record the bladder EMG and a cystostomy was performed to assess cystometrographic measurements. A bilateral ureterocutaneostomy was performed in order to maintain a constant bladder volume during the trial. The urethra was then ligated to initiate isovolumetric bladder contractions during sacral anterior root stimulation (SARS).

Results: In all experiments, for each animal reproducible intravesical pressure values (pves) and salivary flow rates were elicited during electrostimulation before administration of the drug. **Bladder pressure (tab.):** After administration of *propiverine*, neurostimulation-induced rise in pves dropped about 64% from the initial value. After administration of *tolterodine* pves declined by about 60%. **Salivation:** After *propiverine* salivary flow dropped about 61%. Inhibition of salivary flow under *tolterodine* was about 54%. Similar results were obtained in **bladder EMG** recordings. Both propiverine and tolterodine increased the **heart rate** temporarily at a median of 18%. No change in **ECG** recordings was noted after administration of the test substances.

Conclusion: 1. The presented model allows comparative in vivo studies of pharmacological effects on bladder function. 2. Both drugs have similar effects on bladder inhibition in mini pigs. 3. Hyposalivation was comparable in both drugs. 4. The NANC innervation of the mini pig is about 10 to 15%.

| <i>propiverine hydrochloride</i> | | | | <i>tolterodine</i> | | | |
|----------------------------------|---------------------------------|--------------------------------|-----------------------------------|--------------------|---------------------------------|--------------------------------|-----------------------------------|
| No. | before [cm H ₂ O] | after [cm H ₂ O] | atropine [cm H ₂ O] | No. | before [cm H ₂ O] | after [cm H ₂ O] | atropine [cm H ₂ O] |
| 1 | 50 | 18 | 3 | 6 | 47 | 26 | 4 |
| 2 | 62 | 6 | 4 | 7 | 54 | 14 | 7 |
| 3 | 25 | 17 | 4 | 8 | 31 | 6 | 2 |
| 4 | 37 | 10 | 4 | 9 | 30 | 12 | 6 |
| 5 | 36 | 33 | 12 | 10 | 59 | 57 | 19 |
| median | 37 | 17 | 4 | | 47 | 14 | 6 |

Tab: Results of the stimulation-induced bladder pressure just before and 40 minutes after administration of propiverine hydrochloride (No. 1 to 5) and tolterodine (No. 6-10) as well as after administration of atropine at the end of the trial.

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RATIONALE FOR THE USEFULNESS OF TRANSDERMALLY ADMINISTERED OXYBUTYNIN IN THE THERAPY OF DETRUSOR INSTABILITY, BASED ON THE ANALYSIS OF MUSCARINIC RECEPTOR BINDING

Aims of Study. Antimuscarinic agent, oxybutynin, is widely used for the treatment of detrusor

instability (DI) or detrusor hyperreflexia which is characterized by symptoms of increased frequency of micturition and urge urinary incontinence [1]. However, the use of this drug is often limited by systemic side effects such as dry mouth known to occur frequently with orally administered oxybutynin. The incidence of dry mouth is expected to be lower with transdermal application of oxybutynin than oral administration. The transdermal therapeutic system (TTS) of oxybutynin (MM-801) has been currently developed and its usefulness is now under investigation. The therapeutic effect and dry mouth by oxybutynin in patients with DI are mainly based on the blockade of muscarinic receptors in the bladder and salivary gland, respectively. The analysis of drug-receptor binding in different tissues in relation to the pharmacokinetics is very useful in characterizing pharmacological specificity (potency, duration of action and tissue selectivity) of the drug [2]. To clarify the usefulness of transdermally administered oxybutynin in the therapy of DI, therefore, we characterized muscarinic receptor binding in rat tissues after the transdermal application of MM-801 in comparison with that after the oral administration of oxybutynin.

Methods. At 1 to 48 hr after the oral and transdermal administration of oxybutynin, rats were sacrificed by exsanguination 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- ^3H]scopolamine (NMS) as a radioligand, and binding constants of apparent dissociation constant (K_d) and maximal number of binding sites (B_{max}) for [^3H]NMS were estimated by Scatchard analysis [3,4]. The concentration of oxybutynin and its active metabolite, *N*-desethyloxybutynin (DEOB) in the plasma was also measured.

Results. Following the oral administration of oxybutynin (127 $\mu\text{mol/kg}$), there was a significant increase in K_d value for specific [^3H]NMS binding in the bladder, submaxillary gland, heart and colon of rats compared with the value of control rats, and a concomitant reduction of B_{max} value only in the submaxillary gland and heart. Such increase in K_d value in each tissue was seen at 1 and 3 hr after the oral administration of oxybutynin, but not at 12 and 24 hr. In contrast, a significant reduction of B_{max} value in the submaxillary gland and heart was maintained for at least 24 hr. The plasma concentration of oxybutynin and DEOB was maximal at 1 hr after the oral administration and it was extremely low at 12 and 24 hr later.

The transdermal application of MM-801 (one patch containing 33.6 μmol oxybutynin base/body) for 2, 4, 12, 24 and 48 hr brought about a significant increase in K_d value for specific [^3H]NMS binding in the bladder, submaxillary gland, heart and colon of rats, and there was little reduction of B_{max} value in each tissue. The increment of K_d value increased with the application time of MM-801, being maximal at 12 hr later. The plasma concentration of oxybutynin increased with the application time, 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. In rats at 8 hr after the removal of MM-801 following the 48 hr-application, the increase in K_d value for [^3H]NMS binding in each tissue was no longer seen and the plasma concentration of oxybutynin was markedly low.

Conclusions. These data suggest that the transdermally administered oxybutynin (MM-801) binds significantly to the muscarinic receptor in the bladder of rats and the binding to the receptor in the submaxillary gland is easily reversible by this TTS but not by the oral administration. Thus, the present study may provide a rationale for the usefulness of transdermal application of oxybutynin in the therapy of DI.