THE MUSCARINIC RECEPTOR ANTAGONIST PROPIVERINE BINDS TO HUMAN (1-ADRENOCEPTORS AND RELAXES THE HUMAN PROSTATE

Hypothesis / aims of study
There is growing interest in the concomitant use of \( \alpha_1 \)-adrenoceptor and muscarinic receptor antagonists in the treatment of male lower urinary tract symptoms (LUTS). Propiverine, and some of its metabolites, are muscarinic receptor antagonists and primarily used to treat symptoms of overactive bladder (OAB). Apart from blocking muscarinic receptors, propiverine and some of its metabolites also directly block L-Type Ca\( ^{2+} \) channels [1]. Here we have explored whether antagonism of \( \alpha_1 \)-adrenoceptors may additionally contribute to therapeutic effects of propiverine.

Study design, materials and methods
Effects on the tone of human isolated prostate and porcine isolated bladder trigone were assessed by adding propiverine or other drugs to tissue strips pre-contracted with 10 \( \mu \)M of the \( \alpha_1 \)-adrenoceptor agonist phenylephrine. In porcine bladder trigone, additional phenylephrine concentration-response curves (CRC) were generated in the absence and presence of various concentrations of propiverine. A direct interaction with \( \alpha_1 \)-adrenoceptors was explored in competition radioligand binding experiments using cloned human \( \alpha_1 \)-adrenoceptor subtypes expressed in Chinese hamster ovary cells, \(^{[3]H}\)-prazosin as the radioligand, and propiverine as well as its metabolites M-5 (2,2-diphenyl-2-propoxy-acetic acid [1-methyl-piperid-4-yl]-ester-N-oxide-trans), M-6 (2,2-diphenyl-2-hydroxy-acetic acid [1-methyl-piperid-4-yl]-ester-N-oxide-trans) and M-14 (2,2-diphenyl-2-propoxy-acetic acid [piperid-4-yl]-ester) were used as competitors. All data are shown as means \( \pm \) SEM of \( n \) experiments.

Results
Propiverine concentration-dependently reduced the tone of human prostate strips which had been pre-contracted with 10 \( \mu \)M phenylephrine. The relaxing potency of propiverine (\(-\log EC_{50} \) [M]) was 4.8 \pm 0.1 (\( n \)=4). Under the same conditions, the \(-\log EC_{50} \) of tamsulosin was 10.5 \pm 0.04 (\( n \)=5). Similar potencies were calculated when effects of these two drugs were studied in porcine bladder trigone: propiverine 5.0 \pm 0.1 (\( n \)=5), tamsulosin 11.0 \pm 0.04 (\( n \)=5). The propiverine metabolite M-14 at concentrations >10 \( \mu \)M also reduced \( \alpha_1 \)-adrenoceptor-mediated contractions in porcine trigone, while M-5 and M-6 did not.

Table 1 \(-\log EC_{50} \) [M], negative logarithm of phenylephrine for the half maximum effect during the 1\textsuperscript{st} and 2\textsuperscript{nd} CRC and \( E_{\text{max}} \) [%], maximum contraction during the 2\textsuperscript{nd} CRC expressed in percent of the maximum effect during the 1\textsuperscript{st} CRC (=100%); * \( p < 0.05 \) ** \( p < 0.01 \) (compared to time-matched control - TMC).

<table>
<thead>
<tr>
<th>Compound</th>
<th>( n )</th>
<th>( \alpha_1A )</th>
<th>( \alpha_1B )</th>
<th>( \alpha_1D )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC</td>
<td>8</td>
<td>5.96 \pm 0.18</td>
<td>5.82 \pm 0.19</td>
<td>58 \pm 9</td>
</tr>
<tr>
<td>Propiverine</td>
<td>10 ( \mu )M</td>
<td>6.22 \pm 0.29</td>
<td>5.46 \pm 0.38</td>
<td>39 \pm 6</td>
</tr>
<tr>
<td></td>
<td>30 ( \mu )M</td>
<td>6.02 \pm 0.16</td>
<td>5.48 \pm 0.28</td>
<td>28 \pm 6*</td>
</tr>
<tr>
<td></td>
<td>100 ( \mu )M</td>
<td>5.82 \pm 0.10</td>
<td>5.90 \pm 0.22</td>
<td>9 \pm 2**</td>
</tr>
</tbody>
</table>

In a second series of experiments, two subsequent phenylephrine CRCs were generated in porcine trigone, the first in the absence and the second in the presence of inhibitor. In time-matched control (TMC) experiments, the second phenylephrine CRC exhibited the same phenylephrine potency as the first curve but a lowered maximum effect (\( E_{\text{max}} \)). Several concentrations of propiverine did not significantly alter the potency of phenylephrine but concentration-dependently and significantly reduced its \( E_{\text{max}} \) when compared to TMC (Table 1).

In radioligand competition binding experiments propiverine exhibited similar affinity for all three \( \alpha_1 \)-adrenoceptor subtypes (Table 2). Its metabolite M-14 had similar affinity at all three subtypes as its parent compound propiverine, whereas the metabolites M-5 and M-6 did not substantially inhibit radioligand binding to any \( \alpha_1 \)-adrenoceptor subtypes within the tested concentration range (Table 2).

Table 2: \(-\log K_i \) [M] values at the three human \( \alpha_1 \)-adrenoceptor subtypes. Phentolamine was used as an internal control.
Interpretation of results
Propiverine concentration-dependently relaxed isolated human prostate and pig bladder trigone strips both pre-contracted with the $\alpha_1$-adrenoceptor agonist phenylephrine. The latter effect was shared by the propiverine metabolite M-14 but not by the metabolites M-5 or M-6. These data on prostate and trigone muscle tone function do not allow to differentiate whether inhibition of $\alpha_1$-adrenoceptor-mediated contraction was due to functional antagonism by blocking Ca$^{2+}$ channels or to direct $\alpha_1$-adrenoceptor-receptor antagonism. Our radioligand binding studies demonstrated affinities for propiverine at all three $\alpha_1$-adrenoceptor subtypes, which are consistent with the potency to inhibit contraction. This was also mimicked by M-14 but not by M-5 or M-6. Our data suggest that direct antagonism of $\alpha_1$-adrenoceptors contributes to the observed inhibition of contraction. However, the potency of propiverine to inhibit human prostate and porcine trigone contraction by phenylephrine and its affinity at the human $\alpha_1$-adrenoceptors are about one order of magnitude lower to its reported affinities at muscarinic receptors [2], but its potency to inhibit muscarinic receptor- or neuronal mediated human detrusor contraction as well as L-type Ca$^{2+}$ channels [2,3] is similar to the observed binding properties to $\alpha_1$-adrenoceptors.

Concluding message
In contrast to other drugs used for treatment of OAB, propiverine is not only a muscarinic receptor antagonist but also an inhibitor of L-type Ca$^{2+}$ channels [3] and, as shown here, of $\alpha_1$-adrenoceptors. As all three effects functionally occur in similar concentration ranges, we conclude that direct $\alpha_1$-adrenoceptor antagonist activity may contribute to the clinical effects of propiverine, particularly in male LUTS.

References

Specify source of funding or grant
The study was funded by APOGEPHA Arzneimittel GmbH Dresden, Germany.

Is this a clinical trial?
No

What were the subjects in the study?
HUMAN

Was this study approved by an ethics committee?
Yes

Specify Name of Ethics Committee
Ethics Committee of the University Clinics, Medical Faculty, Dresden University of Technology, Germany

Was the Declaration of Helsinki followed?
Yes

Was informed consent obtained from the patients?
Yes