Bioavailability of Trospium Chloride After Intravesical Instillation in Patients With Neurogenic Lower Urinary Tract Dysfunction: A Pilot Study

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Oral drug treatment of detrusor overactivity often causes undesirable side effects in other organs. For some patients, in particular those with neurogenically induced detrusor overactivity (detrusor hyperreflexia), the tolerance level for adverse effects is low and oral treatment may become ineffective.

Intravesical administration of the drug can diminish the side effects or increase treatment effectiveness in patients who are (partially) refractory to oral treatment because the relative concentration of the drug is increased in the target organ and decreased in the circulation.

Six men (19–34 years old) with traumatic spinal cord lesions between C2 and Th11 were randomized to intravesical instillation with 15 or 30 mg trospium chloride in 40 ml saline into the empty bladder. Catheterization was postponed until at least 3 h after instillation, and fluid intake was not allowed during the first 4 h. Blood samples were taken before and 11 times after instillation; the last sample 12 h post instillation.

Four positive samples were found in three patients: 0.10 ng/ml after 1 h and 0.13 ng/ml after 2 1/2 h in two patients with 15 mg, and 0.24 ng/ml after 30 min and 0.70 ng/ml after 6 h in one patient with 30 mg instilled trospium chloride. Three adverse effects were reported and were rated as probably not related to the drug.

It is concluded that intravesically instilled trospium chloride is not absorbed into the circulation in significant amounts and, thus, it may be expected that this mode of admin-

Abbreviations: AUC(0-t(last)), concentration-time relation from prior administration to last time of measurable plasma-concentration; Cₘₐₓ, maximum plasma concentration; tₘₐₓ, time of maximum plasma levels; MRT, mean residence time

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Pharmacotherapy with antimuscarinic drugs is widely accepted in the treatment of detrusor instability and hyperreflexia. Oral administration leads relatively often to antimuscarinic side effects such as dry mouth, difficulty in visual accommodation, gastrointestinal disturbances [Brown and Taylor, 1996; Yarker et al., 1995], and, in the case of tertiary amines, to additional effects in the central nervous system [Katz et al., 1998; Donnellan et al., 1997]. Comparative randomized double-blind trials carried out with oral oxybutynin hydrochloride and trospium chloride have demonstrated comparable clinical efficacy but significantly increased tolerance of trospium chloride [Madersbacher et al., 1995; Osca-Garcia et al., 1997]. Thus, there seem to be differences in tolerance between antimuscarinic drugs.

In order to improve the tolerance of antimuscarinic treatment, different modes of administration have recently been studied. Besides the use of transdermal delivery systems, the effects of direct instillation into the urinary bladder have primarily been investigated [for review, see Schwantes and Topfmeier, 1999]. Significant improvement of urodynamic parameters [Amarenco et al., 1992; Brendler et al., 1989; Buyse et al., 1995; Enzelsberger et al., 1995; Lace et al., 1994; Madersbacher and Jilg, 1991] and a good tolerance of the treatment have mainly been described after intravesical administration. Few data are available concerning the pharmacokinetic behaviour of antimuscarinic drugs after intravesical instillation. For oxybutynin hydrochloride, a tertiary amine, it was shown that the drug is absorbed in relevant amounts from the urinary bladder into the blood [Madersbacher and Knoll, 1995; Massad et al., 1992; Buyse et al., 1998], but nothing is known about the bioavailability of antimuscarinic molecules with a quaternary ammonium structure. Therefore, it was the purpose of the present study to investigate plasma levels of trospium chloride after it was directly instilled into the bladder by catheterization.

PATIENTS AND METHODS

Patients and Study Design

Six male patients with neurogenic bladder dysfunction consented for and were entered into the study after receiving full written and verbal information. Only those patients with complete visceromotor paralysis caused by a traumatic damage between spinal segments C2 and Th11 and an intact reflex path in the area of segments S2–S4 were included in the study. The patients also had to be accustomed to emptying their bladder by self- or third-party catheterization. Age had to be between 18 and 45 years and body weight ≤90 kg. The study was conducted as a randomized, open study. Premedication with antimuscarinic or spasmylic drugs, amantadine, tricyclic antidepressants, chinidine, antihistamines, disopyramide, and β-sympathomimetics had to be discontinued 7 days prior to entry in the study. The main exclusion criteria were alcohol consumption, medication and/or drug abuse, gastrointestinal stenosis, prostatic tumor, myasthenia gravis, narrow-angle glaucoma, tachyarrythmia, urinary tract
infection, and known intolerance to antimuscarinic drugs. Patients were hospitalized during the treatment and blood sampling periods. The study was reviewed by an independent ethical committee and conducted in accordance with the recommendations for biomedical research in humans stated in the revised Declaration of Helsinki (Hong Kong, September 1989) and the guidance concerning Good Clinical Practice laid down by the European Community.

**Drugs and Blood Sampling**

After complete bladder emptying, a solution containing either 15 mg/40 ml or 30 mg/40 ml trospium chloride (Dr. R. Pfleger GmbH, Germany) was instilled by catheter (MedicoPlast® CH12, Tiemann, Germany) into the urinary bladder of each patient in two parallel groups as a single-dose application. The temperature of the solution was 37°C. Discharge of urine had to be avoided during the first 3 h after administration. Blood sampling was carried out at baseline prior to and 11 times during the 12 h following instillation (immediately before and 30 min, 60 min, 90 min, 2 h, 2½ h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h after instillation). Samples were collected using an indwelling venous catheter, immediately centrifuged for 5 min at 4,000 rpm and deeply frozen (−20°C). The plasma trospium chloride concentrations were analyzed using a validated gas chromatographic method (limit of quantitation LOQ: 0.10 ng/ml).

**Adverse Effects**

Each patient was queried after the last blood sampling time about the occurrence of adverse events. Specifically, they were asked about dryness of mouth, abnormal heart rate, gastrointestinal disorders, sweat secretion problems, accommodation disturbances, and “other unusual symptoms.” Hematology and blood chemistry were assessed before and after treatment (maximum 4 days before and 4 days after treatment). Quick’s test and urinary laboratory parameters (protein, glucose, erythrocytes/hemoglobin, and leucocytes) were used as additional safety variables.

**Data Analysis**

For statistical analysis the AUC\((0-t_{\text{last}})\), defined as the concentration-time relation from prior administration to the last time of measurable plasma concentration, was intended to be used as the main parameter. Moreover, the individual and mean maximum plasma concentrations (\(C_{\text{max}}\)), the time of maximum plasma levels (\(t_{\text{max}}\)) and the mean residence times (MRT) should also be calculated. Owing to the limited number of patients in this pilot study, all parameters should be evaluated statistically using merely descriptive methods.

**Power of the Trial and Randomization**

Since no reliable data concerning pharmacokinetic variables after intravesical instillation of trospium chloride were available for sample size calculation, the trial was carried out as a pilot study. A total of six patients (three in each group) were enlisted in order to achieve valid data on the pharmacokinetic parameters on one hand and to minimize the number of participating patients on the other hand.
RESULTS

All six patients who were enrolled completed the study and were included in the data analysis. Both treatment groups were comparable with respect to demographic data (Table I). This becomes obvious when the given doses are correlated to the individual body weights and body surfaces (Table II). In two of the three patients treated intravesically with 15 mg/40 ml trospium chloride, plasma concentrations were measured only at two different times. In one patient (1) the plasma trospium chloride level was 0.13 ng/ml 2 1/2 h after intravesical instillation. In another patient (6), a plasma level of 0.10 ng/ml was observed 1 h after administration. Trospium chloride could not be detected in the plasma at any of the other sampling times (Table III). After administration of 30 mg/40 ml, plasma trospium chloride levels were measurable in only one of the three patients (5) 30 min (0.24 ng/ml) and 6 h (0.70 ng/ml) after instillation (Table III). Altogether, very low plasma trospium chloride levels were found only in 4 of 72 plasma samples. The plasma trospium chloride levels were not related to dosage, because two of the three patients with measurable plasma concentrations belonged to the 15 mg/40 ml dosage group.

Questioning of the patients concerning adverse events resulted in three reports. One patient (4) reported a reduced temperature sensation in the left foot and another (2) reported increased spasticity of the legs. Both adverse events were related to the underlying paraplegia, in particular, since no measurable plasma trospium chloride levels occurred in either of these patients at any time of the investigation. The third patient (1) reported a slight dryness of the mouth. Since patients were not allowed to drink during the first 4 h after drug instillation and this patient drank less than usual during the treatment phase, the relevance of this event could not be established. Moreover, because a very low plasma trospium chloride level was detected in this patient only at the 2 1/2 h sampling time, a systemic effect on the salivary gland seems improbable.

No relevant changes in the pre- and post-treatment blood, Quick and urinary parameters were observed in any of the patients.

DISCUSSION

Hardly any trospium chloride is absorbed into the blood after intravesical instillation. No measurable plasma levels could be detected at any time in three of the six patients, and measurable trospium chloride concentrations were detected in the other three patients only at one or two of the eleven sampling times. Moreover, plasma levels were very low compared to those occurring after oral administration, where mean maximum plasma trospium chloride concentrations of 6.9 ng/ml have been observed after doses of 45 mg (Schürer et al., 1993, unpublished). Since the validated
analytical method used has a minimum detection limit of 0.10 ng/ml for trospium chloride, the positive results in the present study have to be considered as realistic. Single-dose instillation of trospium chloride leads to a significant increase in bladder capacity [Fröhlich et al., 1998]. These results raise interesting questions concerning the mode of action of trospium chloride and other antimuscarinic drugs after intravesical administration. For example, oxybutynin hydrochloride is clearly absorbed when administered intravesically, reaching plasma levels comparable to those observed after oral administration [Madersbacher and Knoll, 1995; Massad et al., 1992; Buyse et al., 1998]. This indicates a systemic antimuscarinic mechanism of action. In contrast, systemic effects of trospium chloride seem to be widely excluded when the drug is administered intravesically. The question of whether direct musculotropic effects are involved in the triggering of smooth muscle relaxation in the urinary bladder wall should be the subject of further investigations. Trospium chloride as well as oxybutynin hydrochloride have been shown to exert direct musculotropic effects in several in vitro studies [Eckert et al., 1995; Yarker et al., 1995].

Antimuscarinic side effects such as dry mouth, disturbances in accommodation etc. are related to the systemic availability of these drugs. Thus, the occurrence of these side effects could be expected after intravesical instillation of oxybutynin. Although most of the trials carried out with intravesically instilled oxybutynin found the frequency and intensity of side effects to be very low [Amarenco et al., 1992; Brendler et al., 1989; Buyse et al., 1995; Enzelsberger et al., 1995; Lace et al., 1994], Palmer et al. [1997] and Krishnan et al. [1996] have shown that intravesical oxybutynin produces side effects that represent the normal spectrum of peripheral (dry mouth) and central nervous drug effects. Furthermore, in the study of Kaplinsky et al. [1996], 25% of the patients did not tolerate intravesical treatment with oxybutynin due to antimuscarinic side effects. In this connection, intravesical treatment with trospium

### Table II. Individual Doses Referring to Body Weight and Body Surface

<table>
<thead>
<tr>
<th>Random no.</th>
<th>Dose (absolute) (mg)</th>
<th>Dose (mg/kg body weight)</th>
<th>Dose (mg/m² body surface)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>0.18</td>
<td>0.0005</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>0.40</td>
<td>0.0009</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>0.35</td>
<td>0.0009</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>0.17</td>
<td>0.0004</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>0.48</td>
<td>0.0009</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>0.22</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

### Table III. Four Blood Samples Positive for Trospium Chloride

<table>
<thead>
<tr>
<th>Positive samples</th>
<th>Dosage (mg)</th>
<th>Time</th>
<th>Concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>1</td>
<td>2.5 hr</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>30 min</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6 hr</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1 hr</td>
<td>0.10</td>
</tr>
</tbody>
</table>

The other 68 samples were all negative.
chloride could make it possible, to limit such antimuscarinic effects on salivary glands, the gastrointestinal tract, the eye and the central nervous system, particularly in patients requiring regular catheterization.

CONCLUSIONS

Based on the data of the present study, it can be concluded that intravesically administered trospium chloride is not absorbed into the blood in relevant amounts. Hence, improvement of tolerance of antimuscarinic therapy can be expected in patients who show low tolerance for these adverse effects, provided that efficacy can be shown for the intravesical instillation of trospium chloride, which requires further adequately powered placebo controlled studies. Intravesical administration of antimuscarinic agents is feasible in particular in patients who require intermittent catheterization for bladder emptying.

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REFERENCES


