Pharmacokinetic evaluation of tolterodine hydrogels in rabbits

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ABSTRACT SUMMARY

The aims of this study were to develop transdermal gel formulation for tolterodine and evaluate its pharmacokinetic properties in rabbits.

INTRODUCTION

Tolterodine, a competitive muscarinic receptor antagonist, is used as a safe and effective treatment for patients with urinary incontinence in recent years [1]. Tolterodine, although it acts on all types of muscarinic receptors, has fewer side effects than oxybutynin as tolterodine exhibits a selectivity for the bladder over salivary glands [2]. After oral administration, tolterodine is metabolized in the liver, resulting in the formulation of the 5-hydroxymethyl derivative (DD01), a major pharmacologically active metabolite [3,4]. Tolterodine hydrogels were designed to provide consistent plasma tolterodine levels with daily application, favorably altering DD01:tolterodine ratio, and to utilize a biocompatible delivery system, thus reducing both the antimuscarinic adverse effects of oral formulations and the application-site skin reactions associated with other available forms of transdermal delivery.

EXPERIMENTAL METHODS

Gel dosage forms of tolterodine were prepared using a serial mixture of deionized water and ethanol as the vehicle and a gelling agent of carbomer 940 at a concentration of 1.5% (w/w). After complete hydration of carbomer 940 by deionized water, 3% (w/w) drug dissolved in 10% (w/w) ethanol, 5% (w/w) N-methyl pyrrolidone (NMP), glycerol and triethanolamine were added and mixed completely, and then deionized water was added to give a total weight of 10 g.

In vitro skin permeation experiments were carried out using a Franz diffusion cell. The skin of Kunming mice was mounted on the receptor compartment with the SC-side facing upwards into the donor compartment. The receiver side was filled with 5 ml of pH 7.4 phosphate buffer.

New Zealand white rabbits, weighing 1.5 to 2.0 kg, had free food and water before and during the sampling time. Dorsal part of the hair was gently cut and removed by hair clippers without causing any skin damage and the area was marked (radius of the circular area was 4.0 cm). Tolterodine aqueous was i.v. administrated and gel formulations (1 g) were applied to the skin. Blood samples were collected from the ear vein into a tube containing heparin pre-dose (0 min) and then at 0.17, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 h after post-dose. Plasma was separated by centrifugation for 10 min at 13,000 rpm. The serum samples were frozen and stored at -80°C until analysis. The contents of tolterodine in the serum samples were determined by a LC-MS/MS (SCIEX API4000 triple–quadrupole mass spectrometer) and expressed as concentrations obtained in ng/ml and cumulative release percentage of plasma at various time points.

RESULTS AND DISCUSSION

The results of in vitro transdermal delivery experiment showed that the relationship of the steady accumulative percutaneous amount ($Q$, µg·cm$^{-2}$) of tolterodine hydrogels and time was $Q_{4-12h} = 770.19t^{1/2}$-966.99. Tolterodine permeated at the steady-state speed of 770.19 µg cm$^{-2}$ h$^{-1}$ and its release coincided with Higuchi Equation.

The time course of the plasma concentrations of tolterodine and DD01 after the administration of tolterodine and tolterodine hydrogels was summarized in Fig. 1. The pharmacokinetic parameters calculated from the plasma drug concentration vs. time profiles were listed in Tab. 1. After i.v. injection of tolterodine, the Cmax of tolterodine, DD01 were
1274 ± 230 ng/ml and 5.60 ± 3.00 ng/ml, respectively. The drugs were exhausted after 24 h.

CONCLUSION
Previous study showed that tolterodine is preferentially metabolized to an active metabolite DD01 in the liver after oral administration. Due to the differences in metabolic capacity, there was no dose-dependent clinical efficacy and the absolute bioavailability of tolterodine was highly variable, ranging from 10 to 70% after oral administration. Moreover, it has been reported that a significant inhibition of the metabolism of tolterodine resulted in an approximate 2.5-fold increase in area under curve (AUC).

From the above analysis it is quite evident that tolterodine hydrogels may offer a possibility to avoid the first pass effect, resulting in a single active compound of tolterodine in plasma, which may profit the patient in the dose control and the reduction of potential adverse effect from two active compounds in body.

REFERENCES

ACKNOWLEDGMENTS
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Fig.1. Plasma concentration-time profiles for tolterodine and DD01 after administration of (A) tolterodine (20 mg/kg, i.v.) and (B) tolterodine hydrogels (20 mg/kg).

Tab. 1 Pharmacokinetic evaluation of the rabbit plasma data (mean ± S.D., n = 3).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>AUC$_{0-24h}$ (ng·h/ml)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolterodine (i.v.)</td>
<td>6398±2665</td>
<td>0.25</td>
<td>10675.65</td>
<td>—</td>
</tr>
<tr>
<td>Tolterodine hydrogels</td>
<td>218±185</td>
<td>1.00</td>
<td>1223.97</td>
<td>11.47</td>
</tr>
</tbody>
</table>

Each point represents mean ± S.D. (n = 3).