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# THE EFFECT OF HEPATIC DISEASE ON THE PHARMACOKINETICS OF TROSPIUM CHLORIDE

## Hypothesis / aims of study

To describe and compare the single 40 mg dose pharmacokinetics of trospium chloride (TCl) in subjects with impaired hepatic function and normal healthy subjects.

## Study design, materials and methods

This was a single-center, open-label, single dose study in subjects with impaired hepatic function and normal healthy subjects. Plasma and urine samples were collected at specified times up to 72 hours after dosing. Hepatically impaired male and female subjects between the ages of 18 and 65 years inclusive and gender-, age-, and weight-matched healthy subjects were eligible for participation in the study.

A minimum of 24 subjects were enrolled into 3 groups: 1 group of healthy normal subjects and 2 groups of hepatically impaired subjects. A single dose of TCl, 40 mg, was administered to 8 subjects with mild hepatic dysfunction (Child-Pugh score of 5-6), 8 subjects with moderate/severe hepatic dysfunction (Child-Pugh score of 7-12), and 8 subjects with normal hepatic function.

Blood samples were collected prior to dosing and at 1, 2, 4, 6, 8, 10, 12, 18, 24, 48, and 72 hours after dosing for determination of trospium concentrations in plasma. All urine voided was collected from 0 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after dosing for determination of trospium concentrations. Pharmacokinetic parameters were calculated.

## Results

Overall, 19 men (79%) and 5 women (21%) were enrolled in the study. The mean age of all enrolled subjects was 55.25 ±4.84 years (range 48 to 63 years). The 2 groups of hepatically impaired subjects were well matched in terms of gender, age, and weight with the healthy subject group. There were 3 females (19%) and 13 males (81%) in the combined hepatically impaired groups and 2 females (25%) and 6 males (75%) in the healthy subject group. The range of Child-Pugh scores was 5 to 8 in the 2 groups of hepatically impaired subjects with a range of 5 to 6 for Group 2 (mild impairment) and a range of 7 to 8 for Group 3 (moderate impairment).

Mean oral (CLpo) and renal ($CL_R$) clearance were 5% and 7% higher, respectively, in subjects with mild hepatic impairment and 17% and 51% higher, respectively, in subjects with moderate/severe hepatic impairment compared to healthy subjects. Only the difference in $CL_R$ between subjects with moderate/severe hepatic impairment and healthy subjects was statistically significant.

**Results – Pharmacokinetics**

| | Group [a] | N | Geometric LS Mean | Pair | Ratio (%) | 90% CI | p-value (Comparison to Group 1) |
|---|---|---|---|---|---|---|---|
| $C_{max}$ | 1 | 8 | 3.721 | - | - | - | - |
| (ng/mL) | 2 | 8 | 4.159 | 2/1 | 111.76 | (54.65-228.54) | 0.7918 |
| | 3 | 8 | 6.083 | 3/1 | 163.45 | (79.93-334.25) | 0.2505 |
| AUC(0-∞) | 1 | 8 | 64.30 | - | - | - | - |
| (ng*h/mL) | 2 | 7 | 60.94 | 2/1 | 94.77 | (56.8-158.11) | 0.8582 |
| | 3 | 8 | 54.96 | 3/1 | 85.47 | (52.13-140.14) | 0.5900 |
| $CL_{po}$ | 1 | 8 | 570.8 | - | - | - | - |
| (L/h) | 2 | 7 | 601.9 | 2/1 | 105.45 | (63.2-175.96) | 0.8599 |
| | 3 | 8 | 667.0 | 3/1 | 116.86 | (71.26-191.65) | 0.5929 |
| $CL_R$ | 1 | 5 | 13.52 | - | - | - | - |
| (L/h) | 2 | 7 | 14.41 | 2/1 | 106.59 | (77.93-145.77) | 0.7260 |
| | 3 | 6 | 20.44 | 3/1 | 151.25 | (109.42-209.09) | 0.0406 |

[a] Group 1 = Normal hepatic function; Group 2 = mild hepatic impairment; Group 3 = moderate/severe hepatic impairment.

The most frequently reported adverse events were headache in 5 subjects and dry mouth in 4 subjects.

**Interpretation of results**

Although higher mean maximum trospium plasma concentrations and lower mean area under the concentration-time curves were observed in subjects with hepatic impairment, these changes were not statistically significant. Renal clearance increased to compensate for the hepatic impairment in subjects. Also, no clear relationship was observed between Cmax and AUC (0-∞) versus severity of hepatic impairment.

**Concluding message**

Overall, a single, oral dose of 40 mg trospium chloride administered to normal healthy, mildly hepatically impaired, or moderately/severely hepatically impaired female and male subjects was considered to be generally safe and well tolerated. These pharmacokinetic results do not suggest a need for dose adjustment in patients with hepatic impairment, and are consistent with the limited role of hepatic metabolism (versus renal excretion) in the elimination of trospium.

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