Pharmacokinetics and Brain Distribution of Tetrahydropalmatine and Tetrahydroberberine after Oral Administration of DA-9701, a New Botanical Gastroprokinetic Agent in Rats

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Purpose
DA-9701, a new botanical gastroprokinetic agent, has potential for the management of delayed gastric emptying in Parkinson's disease if it has no central anti-dopaminergic activity. To assess the safety of using DA-9701 in patients with Parkinson's disease, this study describes the pharmacokinetics of the DA-9701 components with dopamine D₂ receptor antagonising activity, tetrahydropalmatine (THP) and tetrahydroberberine (THB).

Methods
We examined the pharmacokinetics of THP and THB after oral administration of various doses (80-328 mg/kg) of DA-9701. The distribution of THP and THB to the brain and/or other tissues was also evaluated after single or multiple oral administrations of DA-9701.

Results
Oral administration of DA-9701 yielded dose-proportional AUC and Cmax values for THP and THB, indicating linear pharmacokinetics. THP and THB’s large tissue-to-plasma concentration ratios indicated considerable tissue distribution. High concentrations of THP and THB in the stomach and small intestine suggest an explanation for DA-9701’s potent gastroprokinetic activity. The brain-to-plasma concentration ratios of both THP and THB were also greater than unity (approximately 2~4) at all time points studied after single and multiple oral administration of DA-9701. The maximum concentrations of THP and THB in brain following multiple oral DA-9701 for 7 days (150 mg/kg/day) was observed at 30 min after the last oral DA-9701 treatment: 131 ± 67.7 ng/g for THP and 6.97 ± 4.03 ng/g for THB.

Conclusion
Although both THP and THB pass through the blood-brain barrier, oral administration of DA-9701 at the effective dose in humans is not expected to lead to sufficient brain concentrations to exert central dopamine D₂ receptor antagonism.