



 HYPERTENSION, LIPIDS AND PREVENTION

HORMONAL AND ELECTROLYTE RESPONSES TO THE ALDOSTERONE SYNTHASE INHIBITOR LCI699 IN SODIUM DEPLETED HEALTHY SUBJECTS

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Background: Aldosterone is the principal mineralocorticoid in humans and a critical regulator of fluid and electrolyte homeostasis. It regulates blood pressure via sodium and potassium and excessive aldosterone levels are associated with cardiovascular and renal damage via tissue remodeling. The rate limiting enzyme for aldosterone biosynthesis is aldosterone synthase (AS).

Methods: In a double-blind, placebo-controlled study, we performed the first in-human study to assess the pharmacokinetics, pharmacodynamics and safety of ascending doses of LCI699, a potent and orally available AS inhibitor (ASI), in healthy normotensive males on a controlled salt diet. The mineralocorticoid receptor antagonist, eplerenone 100 mg qd, served as an active comparator.

Results: LCI699 was well tolerated following both single (0.5-200 mg) and multiple (0.5-10 mg) doses. LCI699 was rapidly absorbed (T_{max} 1 h) and demonstrated linear, dose-overproportional pharmacokinetics with an elimination half-life of ~4 h. After the first dose, plasma aldosterone (AUC 0-12 h) decreased dose dependently (35-41%). After 7 daily doses of LCI699 (1-10 mg), 24 h urinary aldosterone decreased by 22-83% and plasma aldosterone by 27-44%. In contrast, eplerenone increased urinary and plasma aldosterone by 88% and 38%, respectively. On Day 1 of treatment, LCI699 increased sodium excretion to a similar extent as eplerenone (~60-110%). All LCI699 doses and eplerenone resulted in small (0.2-0.4 mmol/L), transient increases in plasma potassium which returned to placebo levels by Day 7. Signs of hypoaldosteronism (postural tachycardia, decreased body weight and mild hyponatremia) were detected in some subjects at the 3 mg qd dose. Aldosterone inhibition by LCI699 (0.5-3 mg) was accompanied by a dose-dependent increase in trough plasma renin activity from 90-287% on Day 7 compared with eplerenone (56%).

Conclusions: LCI699 is a potent inhibitor of aldosterone synthase resulting in dose-dependent reductions in plasma and urinary aldosterone, and increases in plasma renin. These results support further evaluation of LCI699 for the treatment of cardiovascular disease.