A Safety and Pharmacodynamic Study of the Highly Selective Aldosterone Synthase Inhibitor PB6440 in the Cynomolgus Monkey

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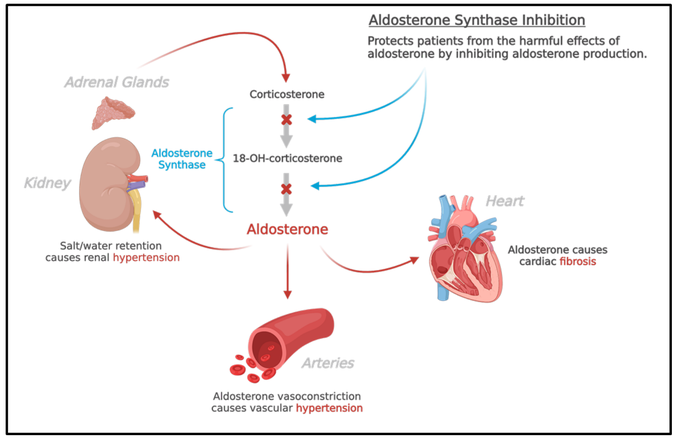
Background

Aldosterone is an important mediator of hypertension, particularly resistant hypertension, as well as heart failure (HF), and chronic kidney disease (CKD). Excess aldosterone activates the mineralocorticoid receptor (MR) and contributes to hypertensive heart disease, HF, and CKD. MR antagonists (MRAs) are effective in lowering blood pressure and improving cardiovascular outcomes in patients with HF and CKD but are associated with an increase in aldosterone levels. A significant obstacle to the development of aldosterone synthase (CYP11B2) inhibitors (ASIs) has been the identification of compounds which selectively inhibit CYP11B2 over the closely-related CYP11B1, the enzyme responsible for cortisol production. The serious complications associated with dysregulated cortisol production make inhibition of CYP11B1 a liability that must be avoided.

PB6440 is a potent inhibitor of aldosterone synthase with high selectivity over CYP11B1. In previous studies in cynomolgus monkeys, PB6440 exhibited excellent oral bioavailability and a marked suppression of aldosterone synthesis. Importantly, no effect was observed on cortisol production nor significant changes noted in plasma concentrations of the steroid precursors 11-deoxycortisol or deoxycorticosterone (DOC), which are dependent on CYP11B1 activity.



Objectives

The purpose of the current study was to assess the safety and pharmacodynamics of higher doses of PB6440 in the cynomolgus monkey in order to examine the effects on steroid concentrations as well as determine a therapeutic index prior to initiation of clinical studies in humans.

Methods

Male and female cynomolgus monkeys (2/sex/dose group) were administered 0, 10, 30 or 100 mg/kg PB6440 once-daily for 14 days by oral gavage. Assessment of safety was based on mortality, clinical observations, body weights, and clinical and anatomic pathology. Blood samples were collected for pharmacodynamic analysis, including aldosterone, cortisol, 11-deoxycortisol, DOC, and ACTH. Concentrations of plasma steroid hormones and concentrations of PB6440 in plasma were determined using a qualified LC/MS/MS protein precipitation analytical method.

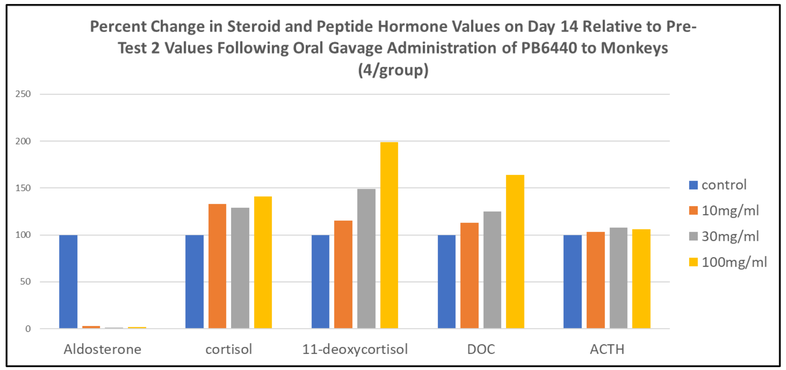
Results - Safety

PB6440 was well tolerated at all doses. There were no deaths and no reports of clinical observations at any dose level. Mild decreases in body weight were observed in PB6440-treated animals, which were likely due to the diuretic effects of the compound. PB6440 caused an increase in adrenal weights which was associated with hypertrophy of the adrenal zona fasciculata, a finding which has previously been observed with other aldosterone synthase inhibitors.

Results - Pharmacodynamics

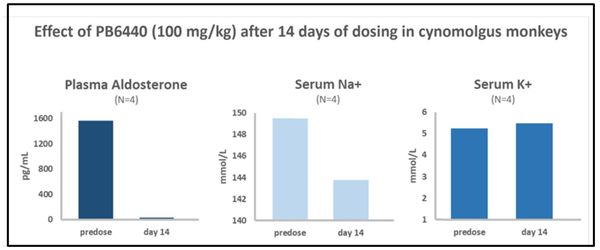
PB6440 led to marked declines in basal aldosterone levels of -97%, -99% and -98% from baseline at 10, 30 and 100 mg/kg/day, respectively, at 24-hours following the final dose. Despite these clear declines in circulating aldosterone levels, no meaningful changes in cortisol, 11-deoxycortisol or DOC were observed, supporting lack of CYP11B1 inhibition.

There were no remarkable changes in circulating peptide hormones including ACTH, renin, plasma renin activity and angiotensin II or steroids in the estrogen or androgen pathways.



Results – Pharmacodynamics (cont.)

PB6440 led to expected decreases in plasma sodium (up to 7 nmol/L at the high dose). No effect on plasma potassium levels were observed at any dose level.



Results - Pharmacokinetics

All monkeys had quantifiable concentrations of PB6440 in the first post-dose sample (0.5 hours post-dose) and PB6440 concentrations remained quantifiable through the last sample taken 24 hours following the last dose on Day 14. On both Day 1 and Day 14, mean PB6440 C_{max} and AUC_{0-24} values increased with dose over the entire dose range from 10 to 100 mg/kg/day although less than proportionally to the increase in dose.

Summary of Toxicokinetic Parameters

Day 7

Group	Dose Level (mg/kg/day)	Cmax (µg/mL)	Tmax (h) median value	AUC_{0-24} (µg·h/mL)
2	10	2.10	24.0	38.8
3	30	3.94	24.0	71.3
4	100	3.97	16.0	79.5

Day 14

Group	Dose Level (mg/kg/day)	Cmax (µg/mL)	Tmax (h) median value	AUC_{0-24} (µg·h/mL)
2	10	3.11	5.0	58.1
3	30	6.02	3.0	123
4	100	8.20	2.0	163

Conclusions

- PB6440 was well tolerated in the cynomolgus monkey at doses that are higher than needed for potent aldosterone suppression based on previous studies.
- At the highest dose level tested (100 mg/kg), which led to a 98% reduction in basal aldosterone levels, no evidence of significant CYP11B1 inhibition was observed. Despite the clear declines in circulating aldosterone levels no meaningful changes in cortisol, 11-deoxycortisol or DOC were observed, supporting a lack of CYP11B1 inhibition.
- The absence of an increase in serum potassium in the presence of a serum sodium decline merits further study.
- In conclusion, PB6440 is a highly CYP11B2 selective and novel ASI for the potential treatment of hypertension, HF and CKD.

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