

Letter to the Editor

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Response to Aliskiren Therapy Will Have Minimal Effect on Intracellular Renin of Renin-Producing Cells

We appreciate Campbell's¹ thoughtful comments on our recently published cell culture data.² From our results, we deduced that the intracellular aliskiren concentrations are $\approx 1\%$ of the extracellular levels. Given the in vivo plasma concentrations of aliskiren at therapeutic doses, combined with its putative high plasma protein binding ($\approx 95\%$), he concluded that the "free" plasma concentrations of aliskiren would be < 10 nmol/L, ie, too low to allow meaningful cellular accumulation of aliskiren. In fact, according to this concept, tissue aliskiren levels, being dependent on free plasma aliskiren, would never exceed plasma aliskiren levels. Yet, after a 2-week treatment of Sprague-Dawley rats with either a low or a high dose of aliskiren, extensive partitioning of aliskiren was observed in the kidney, its renal tissue levels being ≤ 63.7 times those in plasma.³ The cell type in which aliskiren was localized could not be determined in this study. Given the virtual absence of renal clearance of aliskiren ($< 1\%$),⁴ it is, however, unlikely that such accumulation relates to clearance mechanisms. Furthermore, in a comparable study in double-transgenic rats harboring the human genes for renin and angiotensinogen, at 3 weeks after stopping aliskiren treatment (when the drug could no longer be detected in blood plasma), the renal tissue aliskiren levels were still in the range of its IC_{50} .⁵ Similarly, in hypertensive patients, both blood pressure and plasma renin activity remained suppressed for several weeks after stopping aliskiren treatment.⁶ This is too long to be attributed to the in vivo half life of aliskiren (≈ 40 hours³) and, thus, may also point to an aliskiren reservoir outside the blood compartment. Finally, the high plasma protein-binding percentage reported by Campbell¹ needs to be interpreted with care, because it was calculated on the basis of data from 3 different laboratories, each applying their own specific assay conditions. In fact, a considerably lower percentage ($\approx 50\%$) was reported by

Vaidyanathan et al.⁴ Therefore, significant (renal) tissue accumulation of aliskiren appears to be possible, and future studies should now determine its precise cellular accumulation site(s), as well as the mechanism of such accumulation, particularly in view of the possibility that $\geq 50\%$ of aliskiren in blood plasma is protein bound.

Disclosures

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Manne Krop

A.H. Jan Danser

*Division of Pharmacology, Vascular and Metabolic Diseases
Department of Internal Medicine
Erasmus MC
Rotterdam, The Netherlands*

1. Campbell DJ. Aliskiren therapy will have minimal effect on intracellular renin of renin-producing cells. *Hypertension*. 2009;53:e17.
2. Krop M, Garrelds IM, de Bruin RJA, van Gool JMG, Fisher NDL, Holtenberg NK, Danser AHJ. Aliskiren accumulates in renin secretory granules and binds plasma prorenin. *Hypertension*. 2008;52:1076–1083.
3. Feldman DL, Jin L, Xuan H, Contrepas A, Zhou Y, Webb RL, Mueller DN, Feldt S, Cumin F, Maniara W, Persohn E, Schuetz H, Danser AHJ, Nguyen G. Effects of aliskiren on blood pressure, albuminuria, and (pro)renin receptor expression in diabetic TG(mREN-2)-27 rats. *Hypertension*. 2008;52:130–136.
4. Vaidyanathan S, Jarugula V, Dieterich HA, Howard D, Dole WP. Clinical pharmacokinetics and pharmacodynamics of aliskiren. *Clin Pharmacokinet*. 2008;47:515–531.
5. Feldman DL, Jin L, Persohn E. Aliskiren accumulates in the kidney: does it matter? *J Renin Angiotensin Aldosterone Syst*. 2008;9:S7. Abstract.
6. Oh BH, Mitchell J, Herron JR, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. *J Am Coll Cardiol*. 2007;49:1157–1163.

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Manne Krop and A.H. Jan Danser

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