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

To the Editor:

Krop et al\(^1\) reported an interesting study of the effects of aliskiren on intracellular renin and concluded that aliskiren accumulates in renin granules of renin-producing cells. There is, however, concern about the relevance of these data to subjects receiving aliskiren therapy.

Krop et al\(^1\) incubated renin-producing leukemic mast cells in the presence of varying concentrations of aliskiren for 7 days and studied the inhibition by aliskiren of renin in the incubation medium, renin in the cell lysate, and renin released by the cells after stimulation by forskolin. Aliskiren at 0.1 nmol/L had no effect on renin activity in the incubation medium and is, therefore, the most appropriate comparator for evaluation of the effects of higher aliskiren concentrations. Aliskiren at 1 nmol/L produced \(\sim 50\%\) inhibition, and 10 nmol/L produced nearly complete inhibition of renin activity in the incubation medium. By contrast, for renin in the cell lysate and for renin released after stimulation by forskolin, the effects of 10 nmol/L of aliskiren were similar to the effects of 0.1 nmol/L of aliskiren: 100 nmol/L was required to produce \(\sim 50\%\) inhibition, and 1 \(\mu\)mol/L was required to produce nearly complete inhibition of renin activity. These data show that \(\sim 100\)-fold higher aliskiren concentrations were required to inhibit intracellular rather than extracellular renin. Conversely, these data suggest the aliskiren concentration to which intracellular renin was exposed was only \(\sim 1\%\) of the extracellular concentration.

Interpretation of the effects of aliskiren therapy on intracellular and extracellular renin must take account of the extensive binding of aliskiren to plasma proteins. Wood et al\(^2\) reported an IC\(_{50}\) of 0.6 nmol/L for pure renin, similar to the IC\(_{50}\) reported by Krop et al\(^1\) for renin in the incubation medium. By contrast, the IC\(_{50}\) value for the inhibition of renin in human plasma is reported by 2 different laboratories to be 10 to 14 nmol/L,\(^3,4\) indicating that \(\sim 95\%\) of plasma aliskiren is bound to plasma proteins. Given that plasma total aliskiren concentrations are only transiently \(>100\) nmol/L in subjects receiving chronic aliskiren therapy,\(^5\) “free” aliskiren levels are likely to be much less than 10 nmol/L. Therefore, according to the data of Krop et al\(^1\) cited above, aliskiren therapy will have only a minimal effect on intracellular renin of renin-producing cells, such as renal juxtaglomerular cells.

Sources of Funding

D.J.C. is recipient of a Senior Research Fellowship from the National Health and Medical Research Council of Australia (grant 395508) and grant support from the National Heart Foundation of Australia.

Disclosures

D.J.C. has had research contracts with Solvay Pharmaceutical Company and Novartis in the last 5 years and has been a member of an advisory board for Novartis.

Duncan John Campbell

St Vincent’s Institute of Medical Research and Department of Medicine

University of Melbourne

St Vincent’s Hospital

Fitzroy, Victoria, Australia

Aliskiren Therapy Will Have Minimal Effect on Intracellular Renin of Renin-Producing Cells
Duncan John Campbell

Hypertension. 2009;53:e17; originally published online January 5, 2009;
doi: 10.1161/HYPERTENSIONAHA.108.126722
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/53/2/e17

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at: http://hyper.ahajournals.org//subscriptions/