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

To the Editor:

Krop et al1 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 al1 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 ≈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 ≈50% inhibition, and 1 μmol/L was required to produce nearly complete inhibition of renin activity. These data show that ≈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 ≈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 al2 reported an IC_{50} of 0.6 nmol/L for pure renin, similar to the IC_{50} reported by Krop et al1 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 ≈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 al1 cited above, aliskiren therapy will have only a minimal effect on intracellular renin of renin-producing cells, such as renal juxtaglomerular cells.

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