Submaximal dose of trandolapril in the COOPERATE trial?

To the Editor: In the recent study published in *Kidney International* by Jacobsen et al [1], the authors considered the dose of angiotensin-converting enzyme inhibitor used in the COOPERATE trial [2] to be submaximal. With regard to this issue, however, we disagree with the authors. Trandolapril at a dose of 3 mg is sufficient. First, the baseline renal function of the enrollee was moderately reduced (mean serum creatinine level, 265 ± 12.5 mmol/L). In Japan, the recommended maximum dose of trandolapril is 2 mg, mainly for patients with uncomplicated essential hypertension. Thus, pharmacists strongly request us to reduce the dose in patients with renal dysfunction.

Second, during a run-in period, we had confirmed the individual maximal anti-proteinuric efficacy of trandolapril using an up-titration scale from 0.5 to 6.0 mg. Of 301 patients, 240 showed dose-response reactions up to 3 mg. Above this dose, however, no additional anti-proteinuric benefit was obtained. Third, the more a dose was increased, the higher the tendency for side effects, including hypotension, gastrointestinal symptoms, and acute renal decline or low compliance of the patients.

Fourth, compared with the previous study asking the efficacy of 4 mg trandolapril in chronic renal disease [3], the anti-proteinuric efficacy obtained in the COOPERATE was not less. Lastly, according to the official reports of pharmacokinetic and pharmacodynamic variables of trandolapril in Japanese patients with renal dysfunction [4], these variables after 7 days’ consecutive use of even 1 mg are three times greater than those of patients with congestive heart failure who have been treated with 4 mg trandolapril.

Naoyuki Nakao and Genjiro Kimura
Nagoya, Japan

References


4. Drugs in Japan: Ethical Drugs, 23rd edition, Tokyo, Japan Pharmaceutical Information Center, 2000

Reply from the Author

We appreciate the important additional information from the COOPERATE trial [1] in the letter by Dr. Nakao regarding the dose of trandolapril used. We recognize that 3 mg of trandolapril seems to be the optimal dose in this Japanese population with nondiabetic renal disease. This further supports the findings of an additional renoprotective effect of treatment with both ACE inhibitors (ACE-I) and angiotensin II receptor antagonists (ARB) in patients with renal disease found in our own study of diabetic nephropathy [2], as well as in the COOPERATE trial [1]. However, it should be mentioned that the maximal recommended dose of trandolapril is 4 mg daily in Europe and various renal diseases and ethnic groups [3] have different degrees of renal and systemic activation of...