Dual ACE and NEP Inhibitors: 
A Review of the Pharmacological Properties of MDL 100,240

Gian Paolo Rossi

Department of Clinical & Experimental Medicine, 
University of Padova, Italy

Key Words: Angiotensin—Cardiovascular disease—Hypertension—Kininase II—Neutral endopeptidase—Vasoactive peptides.

ABSTRACT

The Angiotensin I converting enzyme (ACE, EC 3.4.14.1, kininase II) and neutral endopeptidases (NEP, NEP 24.11) are mechanistically related metallopeptidases. They play a key role in the regulation of blood pressure, body fluid homeostasis and cell growth. Therefore, they are implicated in the pathogenesis of arterial hypertension, congestive heart failure, left ventricular remodeling after myocardial infarction and other cardiovascular diseases. Furthermore, since these two metallopeptidases possess some subsite and substrate similarities, as indicated by their interaction with certain mercaptoalkanoyl inhibitors, they are regarded as an important common target for pharmacological inhibition with a single drug. MDL 100,240 is a pro-drug that, upon conversion to MDL 100,173, acts as a potent dual inhibitor of ACE and NEP with a balanced activity on both enzymes. Only very limited pharmacokinetic studies with MDL 100,240 have been published. These studies used a high pressure liquid chromatography method with UV absorbance detection to quantify the drug. According to the studies in dogs the terminal $t_{1/2}$ of MDL 100,173 was 35.7 h. The area under the curve for total MDL 100,173 was nearly 10-fold greater than the sum of the areas under the curve for MDL 100,240 and for unconjugated MDL 100,173. These results support the hypothesis that MDL 100,240 is hydrolyzed in plasma to the active thiol, MDL 100,173, which is rapidly conjugated with endogenous plasma thiols thus providing a pathway for elimination. Studies in vivo in experimental models of hypertension and congestive heart failure confirmed the vasodilatory and natriuretic effects of MDL, which appear to be independent of the degree of activation of the renin-angiotensin-aldosterone system. In addition, MDL 100,240 showed an impressive effectiveness both in preventing and in regressing hypertension-induced vascular remodeling and cardiac hypertrophy. Accordingly, MDL 100,240 is being developed for the treatment of cardiovascular diseases, including hypertension and congestive heart failure. If the promises of this novel therapeutic strategy are fulfilled, clinical trials are expected to demonstrate advantages of MDL 100,240 over pure ACE inhibitors.