Enrasentan, an Antagonist of Endothelin Receptors

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ABSTRACT

Endothelins are powerful vasoconstrictor agents produced by endothelial cells and identified by Yanagisawa et al. in 1988. Two types of receptors for endothelins have been identified: \( \text{ET}_A \) receptors are located on smooth muscle cells of the vascular wall and are responsible for endothelin-induced vasoconstriction while \( \text{ET}_B \) receptors are located on endothelial cells and induce these cells to release NO and prostacyclin. Moreover, these peptides not only cause a potent and prolonged vasoconstriction but are also known to enhance cell proliferation and to stimulate extracellular matrix accumulation. High levels of plasma or tissue endothelins have been found in patients with heart failure, diabetes, stroke, primary pulmonary hypertension, liver cirrhosis and other diseases. Given these effects of endothelins, blocking their receptors might be a new way to reduce blood pressure and to treat other illnesses. Accordingly, many endothelin antagonists have been developed and evaluated in animals and humans. Enrasentan is a mixed \( \text{ET}_A \) and \( \text{ET}_B \) receptor antagonist with a higher affinity for \( \text{ET}_A \) receptors, although it cannot be considered a selective antagonist. In an animal model of hypertension and cardiac hypertrophy the drug has reduced blood pressure, prevented cardiac hypertrophy and preserved myocardial function. In rats with hyperinsulinemia and hypertension enrasentan normalized blood pressure and prevented cardiac and renal damage. In rats with stroke the drug reduced the ischemic area in the brain. Enrasentan has been added to conventional treatment in patients with heart failure (NYHA Class 2–3) and no addictive effect of the drug has been observed. This is in contrast with results obtained in animal models and still has not been explained. In conclusion, many possible clinical applications can be suggested for this drug, but further studies are necessary to better evaluate its therapeutic efficacy.