S38-2 Discovery research of Conivaptan hydrocholide, a novel arginine vasopressin receptor antagonist

◯Hiroyuki KOSHIO[1]

[1]Astellas Pharma Inc.

Hyponatremia (HypoNa) is the disease in which decrease in plasma sodium concentration caused an excess of water relative to solute. Arginine vasopressin (AVP) is the primary regulator of renal electrolyte-free water reabsorption and excessive AVP secretion independent of serum osmolality frequently causes excessive water retention, which is the etiological basis of HypoNa. The effectiveness of conventional therapies for HypoNa is inconsistent, and the rapid correction of plasma sodium level is thought to result in the occurrence of neurological complications. In order to solve these problems, we have attempted to develop a new series of AVP antagonists. We have aimed at compound that has high affinities and antagonistic activities in V_{1A} and V_2 receptors and has dissolubility for intravenous administration as profile. As a result of synthetic study, it was found that the bisaryl moiety was effective in increasing the binding affinity potential and the solubility was improved by introduction of imidazole moiety. Eventually, YM087 (Conivaptan hydrochloride) has discovered. In animal studies, YM087 produced an aquaretic effect and a correction of plasma sodium level. In addition, in HypoNa patients, intravenous infusion of YM087 demonstrated significant efficacy. YM087, the first drug in this class, was approved in the USA in 2005 for euvolemic HypoNa.