30PE-13

DISTRIBUTION MECHANISM OF OTERACIL POTASSIUM TO SMALL INTESTINE IN RATS.
Kunihiro Yoshisue and Sekio Nagayama
Pharmacokinetics Research Lab., Taiho Pharmaceutical Co., Ltd, 224-2 Ebisuno, Hiraishi, Kawauchi-cho Tokushima, 711-0194, Japan

Oteracil potassium (Oxo), which inhibits the phosphorylation of 5-FU by orotate phosphoribosyltransferase, is added to S-1, a novel 5-FU derivative anticancer agent, to reduce the gastrointestinal (GI) toxicity of this agent. Oxo is distributed to small intestinal mucosa at high concentration following oral administration of S-1, but is not to tumor. However, the mechanism of distribution of Oxo to small intestine remains unclear. In this study we investigated the distribution mechanism of Oxo to small intestine in rats. In transcellular transport studies with the Ussing chamber method, although no clear directional transport of Oxo between the mucosal and serosal membranes was noted, directional accumulation of Oxo in tissues from the mucosal membrane was observed. And although transport of Oxo from the mucosal to serosal side was higher than that of mannitol, saturation of transcellular transport of Oxo was not observed at concentrations of 0.001 – 10 mM, and uptake of Oxo from mucosal membrane did not saturate at concentrations of 0.001 – 3 mM. On the other hand, in the efflux studies with the Ussing chamber method, Oxo was, when taken up into cells from the mucosal side, rapidly released to the mucosal side. These findings suggest that the permeability of Oxo in mucosal membrane is much higher than that in basal membrane, and the membrane transport of Oxo in the mucosal side is non-saturable manner and bi-directional transport can occur depending on the concentration of Oxo in the GI tract and the GI cells. We concluded that Oxo was distributed to small intestinal tissues at high concentrations following oral administration, because the permeability of Oxo in basal membrane is much less than that of Oxo in mucosal membrane, and Oxo, which was distributed to small intestine, was released from cells to the luminal side of intestine when the concentration of Oxo in GI content was decreased by movement of GI content distally.

30PE-14

MECHANISM OF STOMACH DISTRIBUTION OF A NOVEL GASTROPROKINETIC AGENT, ACOTIAMIDE HYDROCHLORIDE (Z-338/YM443) IN RATS
Kazuyoshi Yoshii, Yoshihiro Kawabata, Masamichi Hirayama, Ryoko Toda, Junko Hasegawa, Mineo Takei and Yukinori Mera
ZERIA Pharmaceutical Co., Ltd., 2512-1, Numagami, Oshikiri, Kumagaya-shi, Saitama, Japan

Acotiamide hydrochloride (Z-338/YM443) is a member of new class prokinetic agents currently being developed for the treatment of functional dyspepsia. It’s thought acotiamide ameliorates symptoms of functional dyspepsia by improvement of delayed gastric emptying based on inhibition of acetylcholinesterases in stomach. However, acetylcholinesterases distribute in various tissues such as muscle and brain. To examine whether specific distribution of acotiamide into stomach would be observed, the tissue to plasma concentration ratio (K_p) were determined by constant rate infusion of acotiamide. K_p in vivo (K_p in vivo) for stomach was 4.1±0.3 at the lowest infusion rate and 2.4±0.3 at the highest infusion rate, indicating a dependency on plasma concentrations. K_p in vivo of skeletal muscle was independent on plasma concentrations, showing ca 0.8. It was considered the distribution to stomach involved in a saturable mechanism. Initial uptake clearances for stomach, skeletal muscle, liver, kidney and brain were evaluated by an integration plot method. The initial uptake clearance for stomach was the third highest after kidney and liver. These phenomena may occur by binding to proteins in stomach tissue, K_p in vitro (K_p in vitro) value for stomach was estimated from plasma and stomach tissue protein binding. K_p in vitro was calculated as 2.5 from free fractions of plasma and stomach tissue. Though the K_p in vitro was consistent with the K_p in vivo at the highest infusion rate, it’s likely that acotiamide was distributed to stomach by other mechanisms including active transport systems. Taken together, these results were indicating that acotiamide might distribute into stomach specifically via active transport systems.