[S3-2] *[4/21/2000 (Fri) 14:10~14:50/Byulkwan Auditorium, Bldg 26]*

A Novel Acid Pump Antagonist, YH1885

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YH1885 is a new gastric antisecretory agent discovered and being developed by Yuhan Research Center. In contrast of irreversible proton pump inhibitors (PPI), YH1885 provides a lot of advantages over PPI owing to its reversible mode of action on acid pump(H^+/K^+-ATPase), the final mediator of acid secretion.

YH1885 is a reversible and competitive acid pump antagonist with respect toactivating K^+-cation (Figure 1). YH1885 is over 100 times more selective for acid pump in hog stomach to its related enzyme, Na^+/K^+-ATPase in rabbit and dog kidney.

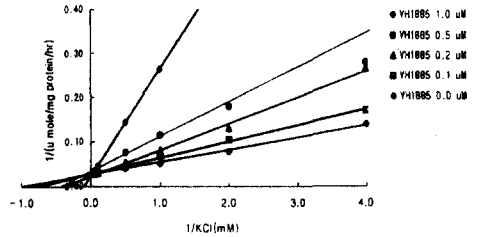

Figure 1. Competitiveness of YH1885 on H^+/K^+-ATPase

YH1885 exhibited three times stronger potency than omeprazole against basal acid secretion in pyrous ligated rat (Figure 2). YH1885 has potent antisecretory activity against several stimulant-induced acid secretion in animals.

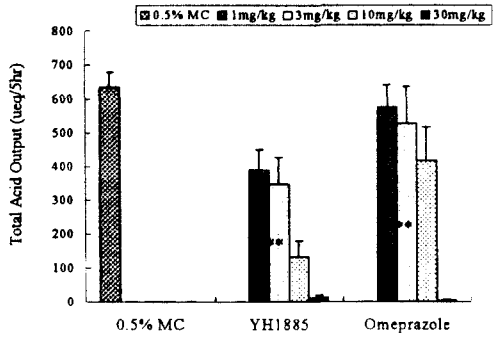

Figure 2. Inhibitory effects of orally dosed YH1885 and omeprazole on basal acid secretion in pylorus-ligated rats.

Moreover, YH1885 did not show the sustained hypergastrinemia in rats and dogs. Plasma gastrin levels in all dosed groups in rats and dogs had never reached to steady state during the whole treatment period (Figure 3). In case of PPI, blood gastrin levels do not return to normal range implicating the sustained hypergastrinemia.

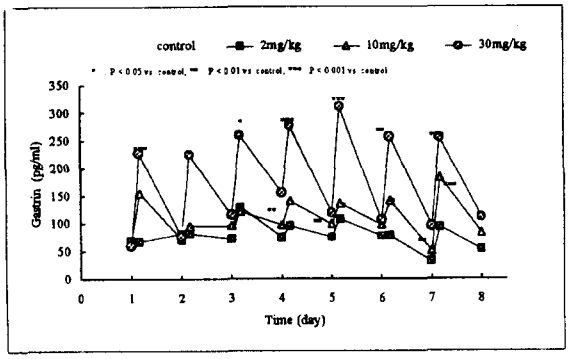

Figure 3. Plasma gastrin levels in dogs for 7-days treatment

YH1885 showed the favorable pharmacokinetic profiles in animals. The compound was distributed well throughout the body and especially with the higher level in the stomach tissue. YH1885 showed high metabolic stability in human liver microsome and would have no drug-drug interactions. In repeated dose study, our compound revealed minimal target organ toxicity except some pharmacologically related effect, but with fast recovery. In genotoxicity study, there was no genotoxic potential in 3 standard battery tests. In fertility and early development study, there was no effect on male reproductive system up to 180 mg/kg. In embryo-fetal development study, there was no major external, visceral, and skeletal fetal abnormality during pregnancy up to 480 mg/kg in rat and 60 mg/kg in rabbit.

In Phase I single rising dose trial, the dose-dependent pharmacodynamics of YH1885 was confirmed in man. YH1885 showed rapid onset of action with less inter-individual variance of pharmacokinetic profiles than PPIs. YH1885 induced a dose-related increase in intragastric pH during 16hrs daytime (Figure 4). These facts suggest YH1885 can provide the potential of rapid relief of ulcer pain. In contrast of YH1885, PPIs were known to take 3-4 days to gain the peak activity. Only one metabolite of YH1885 was detected at the concentration of less than 100ng/ml in human plasma.

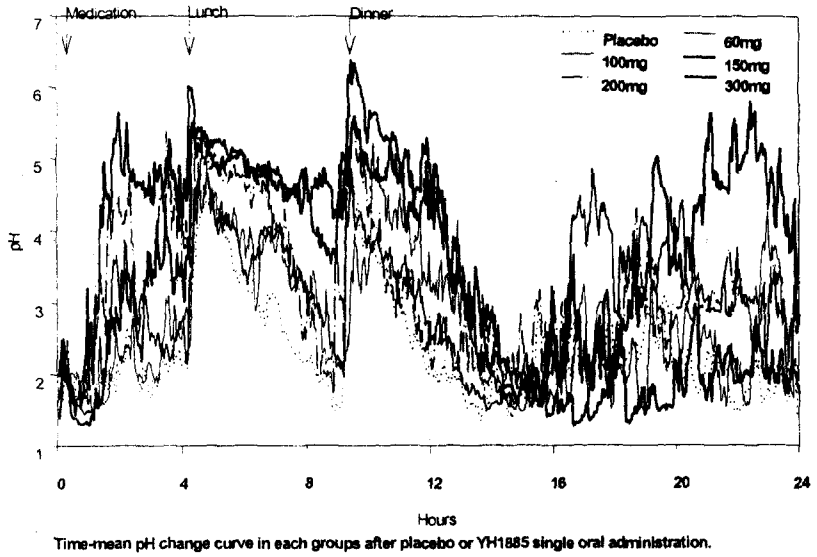

Figure 4. Time-mean pH change curve after placebo or YH1885 single oral administration.

There were no clinically relevant effects or adverse drug reactions up to 300mg in human. A positive relationship was found between AUC and mean daytime gastric pH for YH1885. In Phase I multiple rising dose trial, pharmacokinetic and pharmacodynamic profiles at day 7 was similar to those of day1.

In conclusion, YH1885 is a very potent and highly safe antisecretory agent having reversible mode of action on acid pump as well as showing rapid onset of action without adverse reactions in human.