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E3710, Long-Acting PPI as New Approach for the Treatment of Unmet Medical Needs for GERD

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1. Introduction

Gastroesophageal reflux disease (GERD) is a spectrum of multifunctional disorder caused by the failure of the normal antireflux mechanism with frequent acid reflux. Patients with GERD experience primary symptoms of heartburn and/or acid regurgitation. The patients with GERD have erosive esophagitis, peptic strictures, Barrett esophagus or evidence of extraesophageal diseases such as chest pain, pulmonary symptoms or symptoms in ear, nose and throat symptoms, while others have no apparent mucosal injury by endoscopic diagnosis (non-erosive GERD) [Armstrong, 2005]. GERD is a chronic, relapsing disorder requiring long term management. The pathophysiological mechanism of GERD is complicated. The decreased lower esophageal sphincter pressure, night time reflux, impaired mucosal defense factors, bile reflex, delayed gastric emptying, visceral hypersensitivity, hiatal hernia, insufficient esophageal clearance, physiological comorbidity and concomitant functional bowl diseases are implicated in the refractory mechanism of GERD [Castell et al., 2004; Fass and Sifrim, 2009].

GERD impairs both the quality of life (QOL) and work productivity of patients, so that they need to receive adequate remedy [Wahlqvist et al., 2008]. The goals of treatment for GERD are three folds; control of symptoms, healing of erosion and the maintenance of remission of esophagitis for prevention from complications such as stricture, Barrett esophagus and esophageal malignancy. Although presently available proton pump inhibitors (PPIs) made a large contribution to the treatment for GERD, their clinical efficacy still has some limitations. Further, the degree of acid control is inadequate for some patients as follows. First, about 30 % of patients still remain unhealed or unsatisfied symptom relief, even when the dose or dosing frequency of current PPIs is increased [Fass et al., 2005]. Second, healing rates with current PPIs at 8 weeks are relatively sufficient, whereas those at 4 weeks are not satisfactory and still need to be improved [Castell et al., 2002]. Third, there are still GERD patients whose esophagitis remain unhealed even after 8 weeks treatment with currently available PPIs, especially among patients in Los Angeles grades C and D, having high-grade

esophagitis with transverse mucosal breaks, and with inadequate symptom resolutions [Castell et al., 2002]. Fourth, the long-term maintenance study showed that 10-20% of GERD patients administered once-daily PPI relapsed within 6 months [Katz et al., 2006]. Fifth, symptom relief with once-daily PPIs administration was achieved in only 60-70% of GERD patients at 8 weeks [Katz et al., 2006].

GERD is evoked by the reflux of gastric contents including acid and pepsin; therefore, intragastric pH have extremely impact on GERD severities. The healing rate of GERD at 8 weeks is closely correlated with the maintenance of the intragastric pH over 4-holding time [Armstrong, 2004]. The comparison study in respect of intragastric pH with current PPIs in GERD patient was performed. As the result, esomeprazole given once daily was superior to other PPIs regarding intragastric pH over 4-holding time at day 5 [Minder et al., 2003]. However, since its effect lasted only 14 h per day, the intragastric pH fell below 4 in the remaining of the day. In achieving appropriate intragastric pH control, neither double-dose nor twice a day administration with current PPIs were fully effective for the patients with refractory GERD [Fass and Shfirm, 2009; Saches et al., 2010; Hershcovici and Fass, 2011]. An extended release formulation or a pro-drug approach has been recently addressed, while unstable pharmacokinetics and pharmacodynamics would be induced due to different individual absorption and metabolic capacities.

We expected that long-acting PPI, even given once daily, may control appropriate intragastric pH and that it would be promising for the treatment of these unmet medical needs of GERD. We evaluated about 500 compounds newly synthetized, finding one promising compound, a mixture of two optical isomers. Thus, we confirmed that R-isomer was a feasible candidate with the results of the comparative studies of both isomers on pharmacology, pharmacokinetics, CYP inhibition and metabolism by dog and human liver microsomes.

We finally determined that E3710, sodium(*R*)-2-[4-(2,2-dimethyl-1,3-dioxan-5-yl) methoxy-3, 5- dimethylpyridin-2-yl] methylsulfinyl-1 *H*-benzimidazole (Fig. 1), would be useful with once-daily administration for the treatment of GERD as new PPI with potent and long-acting acid neutralization [Kodama et al., 2010]. We compared the effects of E3710 on 24-h intragastric pH with that of esomeprazole to predict clinical superiority and usefulness by using newly established measurement system in gastric fistula dogs. In a clinical study, a cross-over design including placebo is performed to assess the efficacy of PPIs with accuracy. We investigated a cross over study design in gastric fistula dogs to confirm the long-acting effect of E3710 in comparison with esomeprazole.

2. Methods

2.1 Materials

E3710 was synthesized at Eisai (Ibaraki, Japan). Esomeprazole magnesium trihydrate was purchased from Kemprotec Ltd. (Middlesbrough, UK). Male 11-week old New Zealand White rabbits (Kitayama Labes, Nagano, Japan) and male 1-3 year old mongrel dogs (Kitayama Labes, Gifu, Japan) were maintained at a temperature of 23°C (20-26°C) and a humidity of 55% (40-70%) and on a 12-h light/dark cycle. All experiments were approved by the Animal Care and Use Committee at the Eisai Tsukuba Research Laboratories.

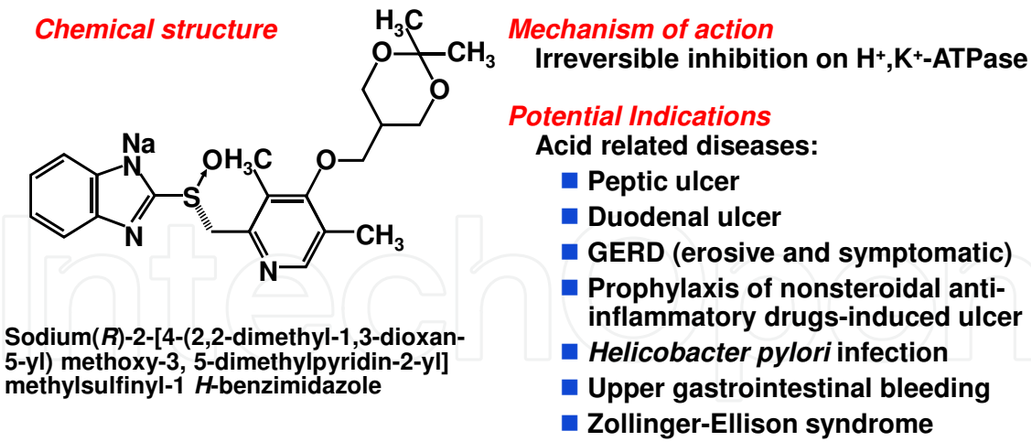

Fig. 1. Features of E3710

2.2 *In vitro* experiments

Inhibitory effects of E3710 on H^+,K^+-ATPase activity under several pH conditions were estimated and compared with the effects on Na^+,K^+-ATPase activities. The inhibitory mechanism of E3710 on H^+,K^+-ATPase is compared with that of esomeprazole (PPI), SCH28080 (P-CAB: potassium-competitive acid blocker) and famotidine (Histamine H_2 receptor antagonist). E3710, esomeprazole, SCH28080 and famotidine were dissolved in methanol and ouabain was dissolved in distilled water. The concentration of reagent is expressed as a final concentration.

2.2.1 Measurement of H^+,K^+-ATPase and Na^+,K^+-ATPase activities

H^+,K^+-ATPase prepared from pig gastric mucosa was incubated with E3710 (0.3-30 μmol/L at pH 6.1 or 1-30 μmol/L at pH 7.4), esomeprazole (0.3-30 μmol/L at pH 6.1 or 1-30 μmol/L at pH 7.4) or vehicle for 30 min at 37°C. KCl (or distilled water) and gramicidin were added, followed by incubation for 10 min. Then, Mg–ATP (pH 7.4) was added, followed by incubation for 10 min. After stopping the enzyme reaction, the amount of inorganic phosphorus released from ATP was determined.

To measure the inhibitory effects under acidic conditions, gastric microsomal membranes enriched in H^+,K^+-ATPase were isolated in a vesicular form, and accumulation of H^+ in the presence of ATP, Mg^{2+}, K^+ and valinomycin (K^+ ionophore) was established. The inhibitory effects of PPIs under this acidic condition can mimic the inhibition in the luminal canalicular acidic space. H^+,K^+-ATPase was mixed with E3710 (0.01-3 μmol/L), esomeprazole (0.01-3 μmol/L) or vehicle in a solution containing KCl (or NaCl) and valinomycin. The reaction was started by adding of Mg–ATP, and H^+,K^+-ATPase activity was measured for 30 min. H^+,K^+-ATPase activity was assayed by the coupled-enzyme method for last 10 min.

Na^+,K^+-ATPase prepared from porcine cerebral cortex was mixed with E3710 (0.3-100 μmol/L), esomeprazole (0.3-100 μmol/L), ouabain (0.01-10 μmol/L) or vehicle in a solution containing KCl, NaCl and 1 mmol/L ouabain (or distilled water). The reaction was started by the addition of Mg–ATP, and Na^+,K^+-ATPase activity was measured for 30 min. Na^+,K^+-ATPase activity was assayed by the coupled-enzyme method for last 10 min.

2.2.2 Investigation of the inhibitory mechanism on H^+,K^+-ATPase

The irreversibility of the inhibitory effects on H^+,K^+-ATPase activity was studied using the inhibitor dilution method. H^+,K^+-ATPase was preincubated with 100 μmol/L E3710, 100 μmol/L esomeprazole, 10 μmol/L SCH28080 or vehicle for 30 min at 37°C in buffer (pH 6.1). Then, H^+,K^+-ATPase activity was measured under two conditions: with or without dilution of the preincubated reaction mixture. KCl (or distilled water), gramicidin and Mg–ATP (pH 7.4) were added, followed by incubation for 10 min under the undiluted condition or 20 min under the diluted condition. After stopping the enzyme reaction, the amount of inorganic phosphorus released from ATP was determined.

The interaction of PPI with cysteine groups of H^+,K^+-ATPase was investigated using DTT (a sulfhydryl reducing agent). H^+,K^+-ATPase was incubated with 30 μmol/L E3710, 10 μmol/L esomeprazole, 10 μmol/L SCH28080 or vehicle, in coexistence with DTT (0.1-3 μmol/L) or distilled water, for 30 min at 37°C in buffer (pH 6.1). KCl (or distilled water) and gramicidin were added, followed by incubation for 10 min at 37°C. Then, Mg–ATP (pH 7.4) was added, followed by incubation for 10 min at 37°C. After stopping the enzyme reaction, the amount of inorganic phosphorus released from ATP was determined.

The inhibitory effects on acid secretion were investigated in isolated rabbit gastric glands. The gastric glands were incubated with E3710 (0.03-10 μmol/L), esomeprazole (0.03-10 μmol/L) or famotidine (0.3-100 μmol/L for db-cAMP stimulation and 0.03-10 μmol/L for histamine stimulation) in a solution containing [^{14}C]aminopyrine (0.1 μCi/mL) at 37°C for 30 min. Then, secretagogue (1 mmol/L db-cAMP or 0.1 mmol/L histamine) was added, followed by incubation for 30 min. Then the levels of radioactive [^{14}C]aminopyrine present in the supernatant and the pellet were measured using a liquid-scintillation counter. The ratio of the weak base [^{14}C]aminopyrine in the supernatant and pellet was used as a measure of the acid-secretory activity in the gastric glands.

2.3 *In vivo* experiments

Effects of E3710 on histamine-induced gastric acid secretion and 24-h intragastric pH in gastric fistula dogs underwent surgery to create gastric fistulae were studied to confirm its long-acting inhibitory effects. E3710 and esomeprazole were suspended in 0.5% methyl cellulose (MC) and intraduodenally administered.

2.3.1 Measurement of histamine-stimulated gastric acid secretion

Twelve dogs under surgery to create gastric fistula and divided into two groups: one received 0.1, 0.2, 0.4 or 0.8 mg/kg E3710 or the 0.5% MC vehicle alone (n=6) and the other received 0.2, 0.4, 0.8 or 1.6 mg/kg esomeprazole or the 0.5% MC vehicle alone (n=6). Each experiment used a 6 x 5 cross-over study design for both drugs including the vehicle and each experiment was carried out over two consecutive days. On day 1, gastric acid secretion was stimulated by intravenously infusing 50 or 75 μg/kg/min histamine over 180 min and gastric juice were collected every 20 min. Sixty minutes after the start of histamine infusion, 0.5% MC, E3710 or esomeprazole was administered intraduodenally. On day 2, 24 h after 0.5% MC, E3710 or esomeprazole administration, histamine was infused intravenously over 120 min and gastric juice were collected every 20 min (Fig. 2).

The volume of gastric juice was determined, and then the concentration of acid was measured by titrating 0.5 mL of gastric juice with 0.04 mol/L NaOH solution to pH 7.0 using a Titration Workstation. The gastric acid output was calculated using the following formula: gastric acid secretion (mEq/20 min) = volume of gastric juice (ml/20 min) × acid concentration (mEq/ml). The inhibitory effects of the drugs were measured for the 0-2 h time period after administration on day 1 and the 24-26 h time period after administration on day 2. In another study, blood sampling was made 0.25, 0.5, 1, 2 and 6 h after intraduodenal administration of E3710 or esomeprazole under the same condition in Fig. 2 for pharmacokinetic (PK) data.

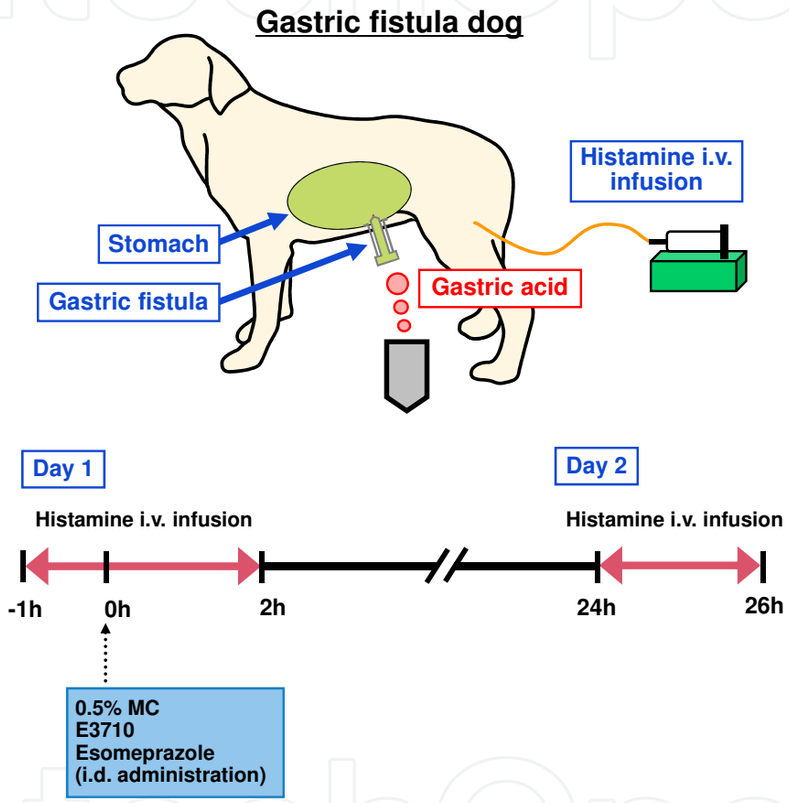

Fig. 2. The measurement system and experimental protocol for histamine-stimulated gastric acid secretion in gastric fistula dogs. i.d.: intraduodenal

2.3.2 Measurement of intragastric pH over 24 h

Glass pH electrode was inserted through gastric fistula to be immobilized in position to measure the intragastric pH changes. Intragastric pH was recorded by pH data recorder under the condition where dogs can move around and drink water freely during the experiment (Fig. 3).

We basically carried out three separate intragastric stimulations according to 3-times food intake schedule in the standard clinical trial for the evaluation of efficacy of PPI. We thus used histamine stimulation at a time appropriate for “breakfast” followed by two feeds at times appropriate for “lunch” and “dinner”.

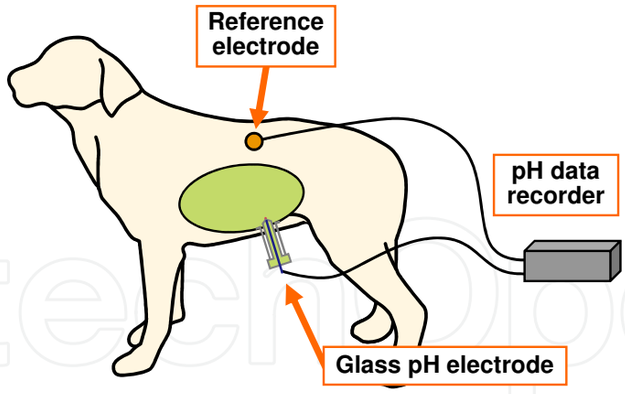

Fig. 3. The measurement system of 24-h intragastric pH in gastric fistula dogs

First, we evaluated the effect of histamine stimulation (as breakfast) on 24-h intragastric pH intraduodenally administered by E3710 to confirm the effect of breakfast intake. Experimental protocol was summarized in Fig. 4. After with or without intravenous histamine infusion for 40 min, E3710 both at 0.4 and at 0.8 mg/kg were intraduodenally administered. The measurement of intragastric pH over 24 h commenced at around 10:00 AM, and values were recorded every 10 s using ambulatory pH monitoring system (PH-101ZG; Chemical Instruments Co., Ltd, Tokyo, Japan) carried in a canine jacket, and the data were downloaded to a computer and analyzed using the W-IPC pH analysis program (Chemical Instruments Co. Ltd.). Two meals, each of ~225 g DS-A pellet diet (Oriental Yeast Co., Ltd., Tokyo), were offered to each animal separately at about 13:00 (as lunch) and 18:00 (as dinner).

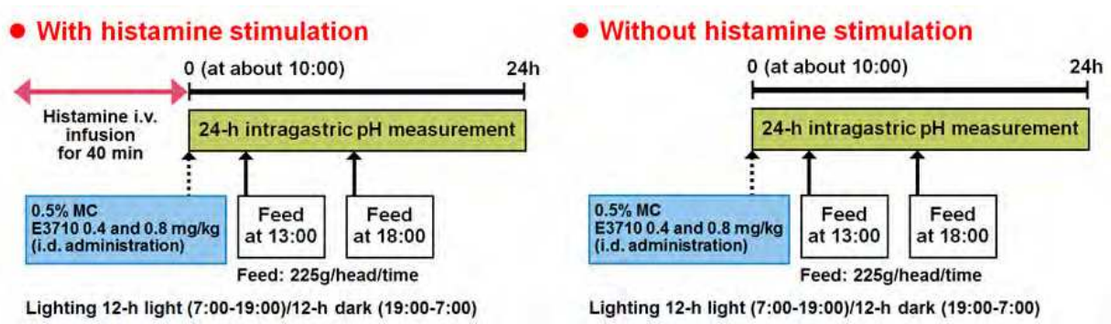

Fig. 4. Experimental protocol for measurement of effect of breakfast on 24-h intragastric pH by E3710 in gastric fistula dogs

Second, we obtained the dose dependent effects of E3710 and esomeprazole. Experimental protocol of comparative studies of E3710 with esomeprazole on 24-h intragastric pH was presented in Fig. 5. After infusion of histamine intravenously for 40 min (as breakfast) 0.5% MC, E3710 (0.2, 0.4 and 0.8 mg/kg) or esomeprazole (0.8 and 1.6 mg/kg) was administered intraduodenally. Third, in a clinical study a cross-over design including placebo is performed to assess the efficacies of PPIs with accuracy. A 6 x 3 cross-over design studies, using 0.5% MC, 0.4 mg/kg E3710 and 1.6 mg/kg esomeprazole (n=6), were carried out to confirm the long-acting inhibitory effects of E3710 compared to esomeprazole.

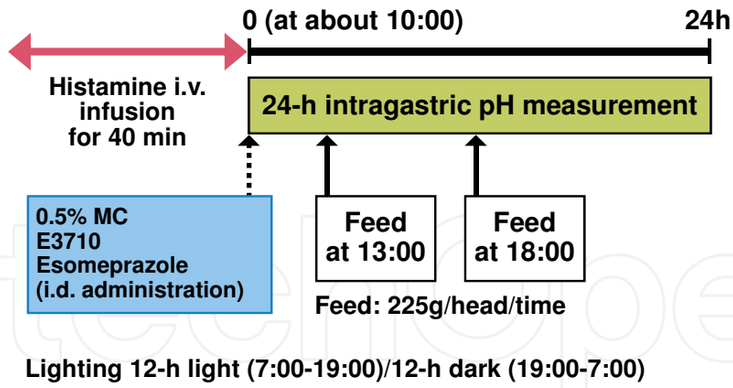

Fig. 5. Experimental protocol of comparative studies of E3710 with esomeprazole on 24-h intragastric pH in gastric fistula dogs

2.4 Statistical analysis

All data were expressed as means ± SEM. In *in vitro* experiments, the mean IC_{50} and 95% confidence intervals (CI) were calculated based on the IC_{50} values generated from separated sigmoid curves. In *in vivo* experiments, ED_{50} values were calculated by linear regression and the potency ratio with 95% CIs were calculated using two-by-three assay. Difference in the intragastric pH between with histamine stimulation and without histamine stimulation was analyzed using t-test. Differences in the intragastric pH between E3710 and 0.5% MC or esomeprazole and 0.5% MC were analyzed using Dunnett's multiple range test in a dose escalation study. Intragastric pH was evaluated using one-way analysis of variance followed by Tukey's multiple comparison test in a cross over study. Two-sided probability (p) values < 0.05 were considered statistically significant. Statistical analyses were performed using the SAS software package version 8.1 (SAS Institute Japan Ltd., Tokyo, Japan).

3. Results

3.1 Summary of *in vitro* studies

The inhibitory effects of E3710 and esomeprazole on H^+,K^+-ATPase activity were dependent on pH condition (Table 1). Ouabain inhibited Na^+,K^+-ATPase activity with an IC_{50} value of 0.43 µmol/L (95% CI 0.41–0.45). In contrast, both E3710 and esomeprazole were very poor inhibitors of Na^+,K^+-ATPase with IC_{50} values greater than 100 µmol/L.

	IC_{50} (µM)		
	Acidic condition	pH 6.1	pH 7.4
E3710	0.28 (0.17-0.44)	4.2 (3.8-4.7)	>30
Esomeprazole	0.53 (0.47-0.59)	2.3 (2.1-2.5)	>30

Table 1. Inhibitory effects of E3710 and esomeprazole on pig gastric H^+,K^+-ATPase activity. Each data represents mean from 3 independent experiments in performed in duplicate. Vesicles accumulated H^+ under the acidic condition, and did not accumulate H^+ under the conditions of medium pH 6.1 and 7.4. The 95% CIs are expressed in the parenthesis.

E3710 and esomeprazole inhibited acid secretion of isolated rabbit gastric glands stimulated by db-cAMP or histamine. By contrast, famotidine inhibited only acid secretion stimulated by histamine (Table 2).

	IC_{50} (μM)	
	db-cAMP	Histamine
E3710	0.40 (0.28-0.59)	0.27 (0.12-0.58)
Esomeprazole	0.53 (0.29-0.99)	0.41 (0.22-0.74)
Famotidine	>100	0.35 (0.25-0.48)

Table 2. Inhibitory effects of E3710 and esomeprazole on acid secretion of isolated gastric glands. Each data represents mean from 4 independent experiments in performed in duplicate. The 95% CIs are expressed in the parenthesis.

In dilution studies, 100 μmol/L E3710 inhibited H^+,K^+-ATPase activity by 55.4% and by 58.5% when the reaction mixture was diluted. Similarly, 100 μmol/L esomeprazole inhibited H^+,K^+-ATPase activity by 91.1% when undiluted and by 93.0% after dilution. In contrast, 10 μmol/L SCH28080 inhibited H^+,K^+-ATPase activity by 80.5% but by 7.0% after dilution. Accordingly, the inhibitory effects of E3710 and esomeprazole on H^+,K^+-ATPase activity were not reversed by diluting the drug concentration in the medium, whereas that of SCH28080 was reversed. DTT antagonized the inhibitory effects of E3710 and esomeprazole on H^+,K^+-ATPase, however not that of SCH28080 (Fig. 6).

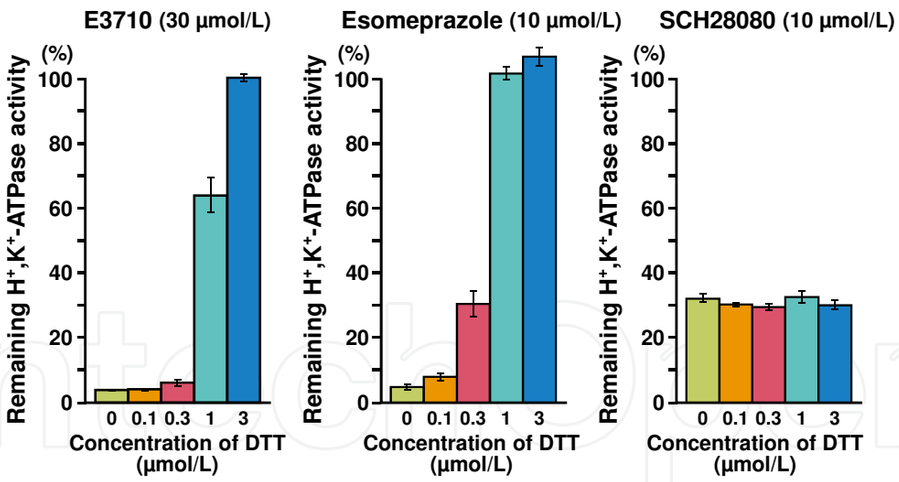

Fig. 6. Effects of the concomitant presence of DTT on the inhibition of H^+,K^+-ATPase activity with E3710, esomeprazole or SCH28080 at indicated concentrations. Each data point represents the mean ± SEM from three independent experiments performed in duplicate.

3.2 Summary of *in vivo* studies

3.2.1 Inhibitory effect of E3710 on histamine-stimulated gastric acid secretion

E3710 inhibited gastric acid secretion in a dose-dependent manner and at 0.4 and 0.8 mg/kg fully inhibited gastric acid secretion within 1 h of administration. Even 24 h after

administration, these sustained inhibitory effect was still observed after histamine stimulation (Fig. 7).

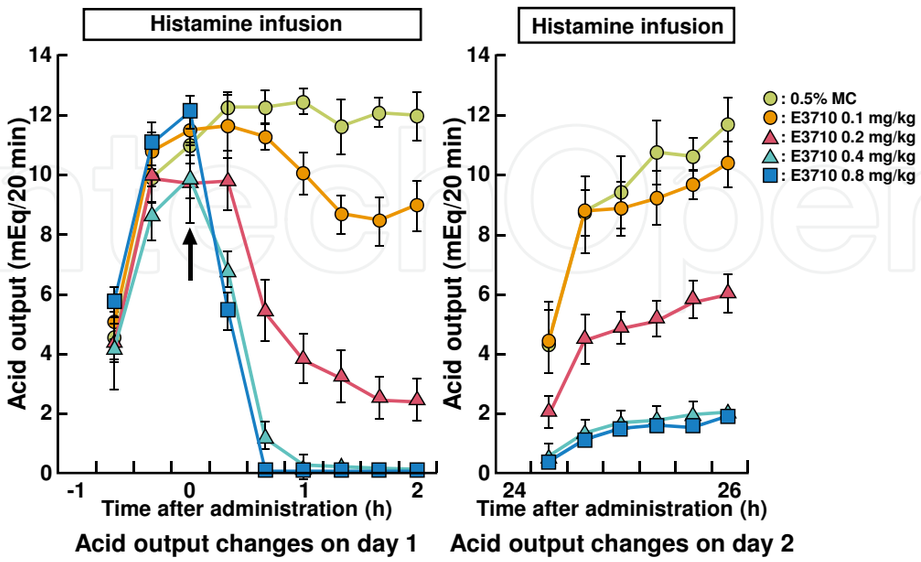

Fig. 7. Effect of E3710 on histamine-stimulated gastric acid secretion in gastric fistula dogs. E3710 was administrated at the arrow (time zero). Results are expressed as the mean ± SEM of 6 dogs (6 x 5 cross-over study).

Esomeprazole also inhibited histamine-stimulated gastric acid secretion 1 h after administration. However 24-26 h after administration these inhibitory effect was not sustained in the way seen with E3710 (Fig. 8).

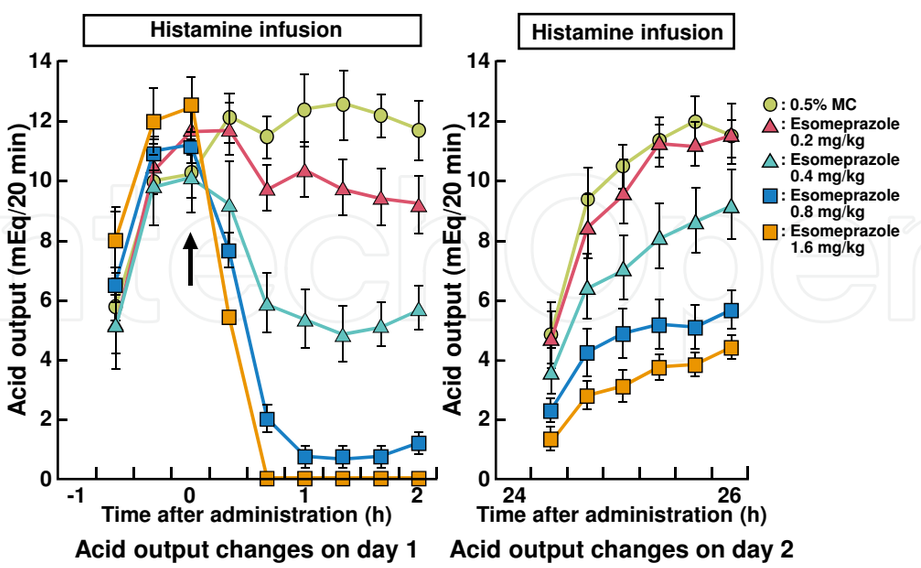

Fig. 8. Effect of esomeprazole on histamine-stimulated gastric acid secretion in gastric fistula dogs. Esomeprazole was administered at the arrow (time zero). Data are expressed as the mean ± SEM of 6 dogs (6 x 5 cross-over study).

The ED_{50} values for E3710 (liner regression range: 0.1, 0.2 and 0.4 mg/kg) and esomeprazole (liner regression range: 0.2, 0.4 and 0.8 mg/kg) during 0-2 h and 24-26 h after administration are shown in Table 3. The potency ratio for E3710 to esomeprazole during 0-2 h and 24-26 h after administration was 2.3 (95% CI: 1.9 - 2.6) and 2.8 (95% CI: 2.2 - 3.6), respectively.

	ED_{50} (mg/kg)	
	0-2 h	24-26 h
E3710	0.18 (0.15-0.20)	0.22 (0.19-0.27)
Esomeprazole	0.40 (0.37-0.43)	0.71 (0.58-0.99)

Table 3. The ED_{50} values of E3710 to esomeprazole on histamine-induced gastric acid secretion in gastric fistula dogs

E3710 (mg/kg)	N	T max (h)	Cmax (μg/mL)	AUC (μg•h/mL)	$T_{1/2}$ (h)
0.1	4	0.25	0.16	0.22	0.77
0.2	4	0.31	0.30	0.49	1.01
0.4	4	0.25	0.54	0.65	0.76
0.8	4	0.25	1.74	2.56	0.70

Table 4. PK data of E3710 in gastric fistula dogs.

Esomeprazole (mg/kg)	N	T max (h)	Cmax (μg/mL)	AUC (μg•h/mL)	$T_{1/2}$ (h)
0.2	4	0.25	0.27	0.24	0.59
0.4	4	0.25	0.40	0.36	0.47
0.8	4	0.25	0.81	0.72	0.52
1.6	4	0.25	1.73	1.64	0.58

Table 5. PK data of esomeprazole in gastric fistula dogs.

3.2.2 Effect of E3710 on 24-h intragastric pH with or without histamine stimulation

Effect of E3710 on intragastric 24-h pH profile was reduced in without histamine stimulation in comparison of that with histamine stimulation (Fig. 9, 10).

Mean pH at 0.4 mg/kg of E3710 and the % of time with pH≥4/24 h at 0.4 and 0.8 mg/kg of E3710 were significantly reduced without histamine stimulation (Fig. 10).

Time course changes of intragastric pH with E3710 (Fig. 11) and esomeprazole (Fig. 12) was summarized. E3710 and esomeprazole elevated the mean intragastric pH in a dose-dependent manner and increased %of time with pH≥4/24 h, compared to the 0.5% MC (Table 6).

In a cross over study, E3710 even at one fourth of esomeprazole dose rapidly elevated intragastric pH, and E3710 kept higher intragastric pH in comparison with esomeprazole almost during 24 h (Fig. 13). Thus mean intragastric pH of E3710 group was relatively higher, compared with that of esomeprazole. These potencies of E3710 were the same results observed in dose-dependent study (Fig. 11 and 12). In both E3710- and esomeprazole-treated groups the intragastric pH gradually dropped after the maximum pH-elevating effects had been reached. The intragastric pH in the esomeprazole-treated group dropped

below 4 just after midnight (between 1:00 to 3:00), while that in the E3710-treated group was substantially above pH4 during the same time period. In terms of intragastric pH profile during night-time (0:00-04:00), E3710 is superior to that of esomeprazole.

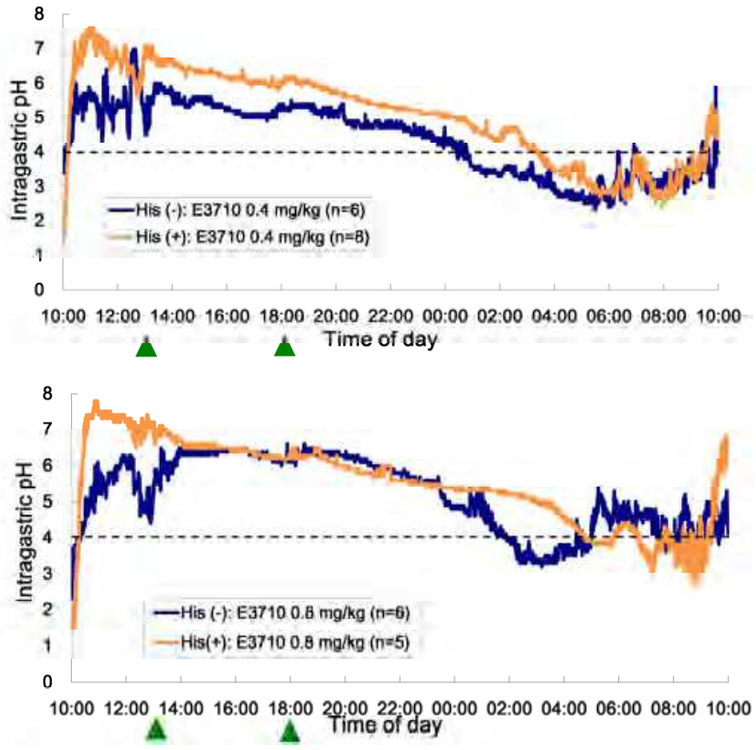

Fig. 9. Profiles of E3710-administered intragastric pH under with or without histamine stimulation in gastirc fistula dogs. His (+): Histamine infusion was performed approximately from 9:10 to 9:50. His (-): No treatement was performed approximately from 9:10 to 9:50. E3710 was intraduodenally administrated at about 10:00. Arrows indicate feeding time.

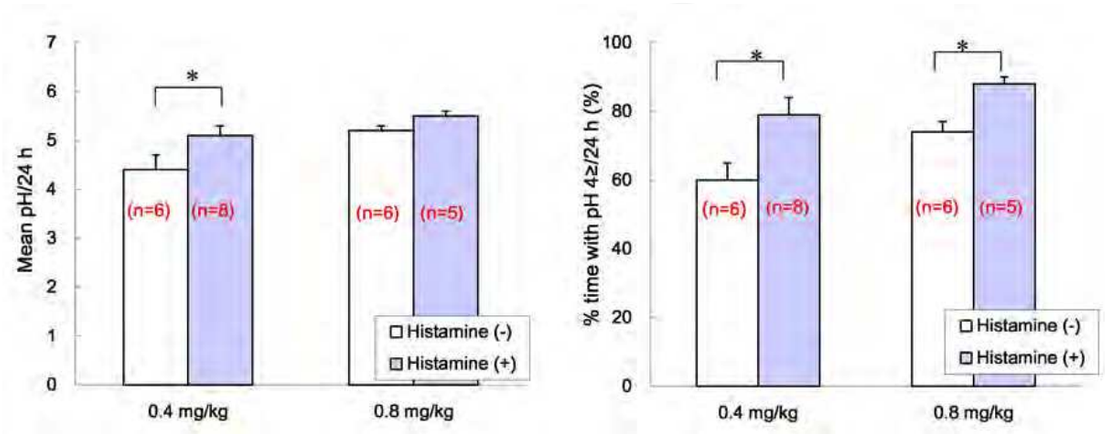

Fig. 10. Effect of histamine stimulation on E3710-administered intragastric pH profile in gastric fistula dogs. Data are expressed as the mean ± SEM. *p<0.01 versus Histamine (-).

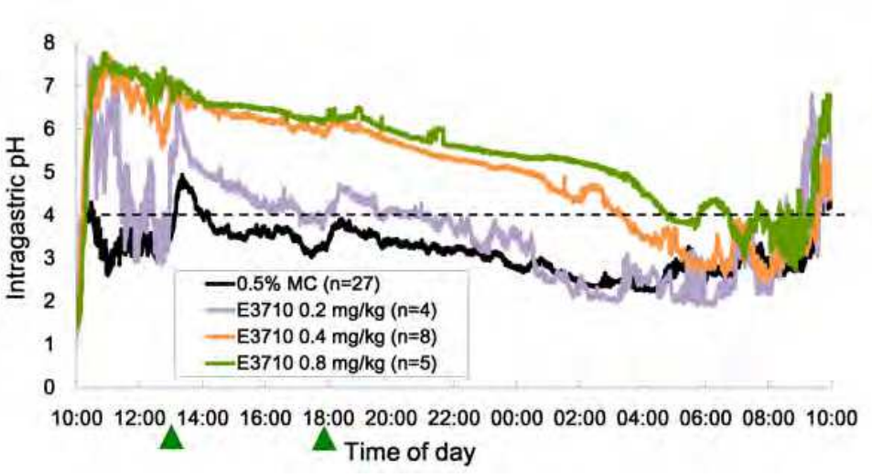

Fig. 11. Profiles of E3710 on intragastric pH in gastric fistula dogs. Histamine infusion was performed approximately from 9:10 to 9:50. E3710 was intraduodenally administrated at about 10:00. Arrows indicate feeding time.

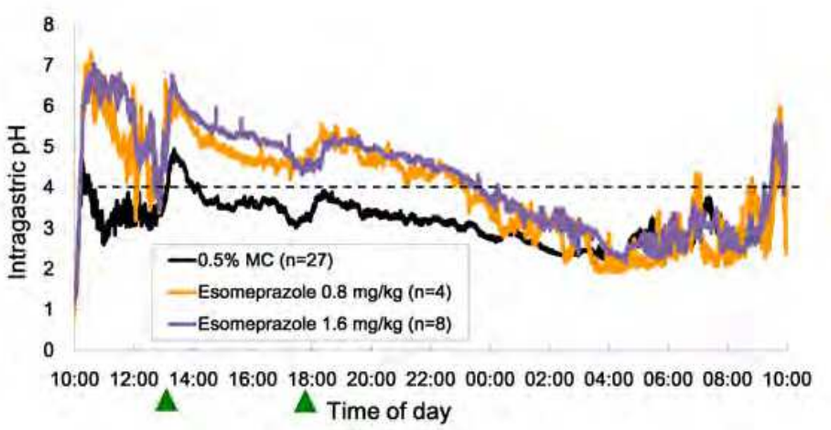

Fig. 12. Profiles of esomeprazole on intragastric pH in gastric fistula dogs. Histamine infusion was performed approximately from 9:10 to 9:50. Esomeprazole was intraduodenally administrated at about 10:00. Arrows indicate feeding time.

Treatment	Dose (mg/kg)	N	Mean pH/24 h	% Time with pH≥4/24 h
0.5% MC		27	3.2 ± 0.1	17 ± 3
E3710	0.2	4	3.7 ± 0.2	40 ± 6*
	0.4	8	5.1 ± 0.1**	79 ± 3**
	0.8	5	5.5 ± 0.1**	88 ± 2**
Esomeprazole	0.8	4	4.0 ± 0.2*	55 ± 3**
	1.6	8	4.3 ± 0.1**	59 ± 4**

Table 6. Effects of E3710 and esomeprazole on 24-h intragastric pH in gastric fistula dogs. Data is expressed as the mean ± SEM. *p<0.01, **p<0.001 versus the 0.5% MC

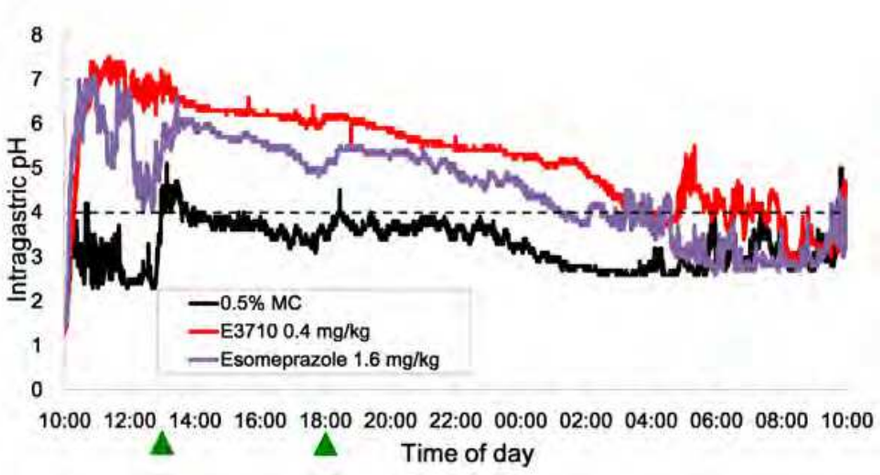

Fig. 13. Profiles of intragastric pH in gastric fistula dogs in cross over study. Histamine infusion was performed approximately from 9:10 to 9:50. E3710 or esomeprazole was intraduodenally administrated at about 10:00. Arrows indicate feeding time. (6 x 3 cross-over study).

The mean intragastric pH in the E3710 group was higher than that in the esomeprazole group, although the difference was not statistically significant. The %of time with pH≥4/24 h was significantly longer in the E3710-treated group than in the esomeprazole-treated group (Table 7).

Treatment	Mean pH/24 h	% of time with pH≥4/24 h
0.5% MC	3.3 ± 0.2	20 ± 5
E3710 0.4 mg/kg	5.3 ± 0.3**	82 ± 5 **, #
Esomeprazole 1.6 mg/kg	4.6 ± 0.3*	61 ± 7**

Table 7. Effects of E3710 and esomeprazole on 24-h intragastric pH in gastric fistula dogs in a cross over study. Data are expressed as the mean ± SEM. *p<0.01, **p<0.001 versus the 0.5% MC; #p<0.05 versus the esomeprazole.

4. Discussion

4.1 Summary of preclinical experiments

E3710 irreversibly inhibited H^+,K^+-ATPase which is responsible for the final common pathway of hydrochloric acid secretion in gastric parietal cells *in vitro*, especially under acidic condition. The inhibitory effect of E3710 on H^+,K^+-ATPase activity was antagonized by DTT and not reversed by diluting the drug concentration in the medium, suggesting that the pharmacological active form (sulfenamide) inhibited the H^+,K^+-ATPase activity via formation of covalent disulfide bridges with cysteine groups on this enzyme [Sachs et al., 2006]. E3710 inhibited the acid secretion similar to the mode of action of esomeprazole, but unlike histamine H_2 receptor antagonist. In gastric fistula dogs, E3710 potently inhibited the histamine-stimulated gastric-acid secretion with potency 2.3 and 2.8 times higher than that of esomeprazole at 0-1 h and 24-26 h posttreatment, respectively. Moreover, E3710

immediately elevated intragastric pH above 4 and provided prolonged and better intragastric pH control compared with esomeprazole over a 24 h period.

4.2 Effects of E3710 on 24-h intragastric pH

It is well known that PPIs inhibit the activated proton pumps induced by food intake. Breakfast is commonly given after the oral PPIs administrations in many clinical trials. The study showed that better acid suppressions were observed when PPIs were taken before breakfast than without breakfast. When taking the PPIs, the median % of time with pH ≥ 4/8 h (from 8:00 until 16:00 with lunch at 12:00) was 83% with breakfast in comparison with that of 58% without breakfast (P=0.01) [Hatlebakk et. al., 2000]. In our experiment each dog did not necessary simultaneously finish breakfast when we fed in the morning, therefore we used intravenous histamine infusion instead of breakfast to evoke an assured H^+,K^+-ATPase activation. We also confirmed that the effects of E3710 on mean pH and % of time with pH ≥4/24 h were significantly reduced without histamine stimulation.

Although GERD affects patients during the day as well as the night, the symptoms of heartburn and regurgitation during the night time have a greater negative impact on QOL in such a way as to interrupt sleep patterns and to increase the risk of esophageal and respiratory complications [Shaker et al., 2004]. The pattern of reflux during the day is usually postprandial and promptly cleared. The occurrence of reflux during sleep is relatively less frequent but events are significantly longer and are associated with delayed acid clearance. This is partly caused by such factors as 1) reduced saliva production, which would otherwise protect the esophageal tissue and neutralize acidic reflux events, 2) decline in the frequency of swallowing, which contributes to the volume gastric acid cleared, 3) prone position during the night, which delays the clearance of acid compared with an upright position during the day. Furthermore, nocturnal acid breakthrough (NAB), defined as a period of intragastric pH below 4 for more than 1 h at night during PPI therapy [Peghini et al., 1998], has been suggested as a possible refractory causes for GERD. Even though currently available PPIs are administered twice a day before breakfast and before dinner, NAB cannot be sufficiently controlled [Hatlebakk et al., 1998]. Clinical significance of NAB for GERD has been uncertain, while it has been suggested as a possible refractory causes for GERD. The night-time esophageal acid exposures, including the mean number of acid reflux episodes, mean % time esophageal pH<4 in were significantly higher in the PPI failing group compared with PPI success group [Hershcovici et al., 2011].

In a cross-over study E3710 at 0.4 mg/kg didn't completely hold intragastric pH≥4 during night, although the intragastric pH remained substantially above pH4 during midnight (between 1:00 to 3:00). On the contrary, that of the esomeprazole-treated group dropped below 4 during the same period. Considering that NAB in midnight in comparison with that in early morning may be a high risk factor to cause heartburn which leads sleeping disturbance and reduction of QOL, E3710 would show better symptom relief during night than esomeprazole does. The doubling dose has been used to deal with heartburn not responding to current PPIs, while this approach hasn't fully succeeded [Fass and Shfirm, 2009; Saches et al., 2010]. Regarding the dose-dependent efficacy of the % of time with pH ≥4/24 h of esomeprazole in GERD patients, the slight elevation was observed from 61.4% at 40 mg (clinical standard dose) to 65.8% at 80 mg (clinical double dose) [Armstrong, 2004] with the similar elevation from 55% at 0.8 mg/kg to 59% at 1.6 mg/kg in gastric fistula dogs

(Table. 6). It seems the clinical efficacy of esomeprazole may reach its maximum even at double dose. On the contrary, the % of time with pH≥4/24 h with E3710 was increased from 79% at 0.4 mg/kg to 88% at 0.8 mg/kg in gastric fistula dogs (Fig. 12). These results revealed that a dose escalation of E3710 would be a promising way to control 24-h intragastric pH in an appropriate manner. Accordingly, E3710 would be more useful for the treatment of NAB in comparison with esomeprazole.

4.3 A hypothesis for the long-acting effect of E3710 based on the acid-induced split mechanism

The plasma half-life of E3710 (0.70-1.01 h: mean 0.81 h: Table 4) was relatively longer than that of esomeprazole (0.47-0.59 h: mean 0.54 h: Table 5) in gastric fistula dogs. Moreover, the AUC levels of E3710 were higher than those of esomeprazole under the same dose comparison. We assumed that these different PK parameters may account for a long-acting of E3710.

Besides plasma half-life, we speculated another long-acting mechanism of E3710 with respect of chemical features. We calculated the distribution coefficient (oil/water) of E3710 and esomeprazole at pH 7.4 (blood) and pH 1.0 (stomach) by PhysChem ver 12.01 (Advanced Chemistry Development, Canada) as an index of lipophilicity (Fig. 14). PPIs including E3710 are absorbed from intestine into blood and reach in the canalicular space of gastric parietal cells finally crossing the basolateral and apical membranes of the parietal cell owing to the highly lipophilic characteristics of PPIs. The distribution coefficient (oil/water) of E3710 is calculated to be 3.3-fold greater than that of omeprazole at neutral pH, indicating that E3710 more quickly reach in the canalicular space than omeprazole. PPIs are pro-drugs and their acid activated compound bind with Cys residues in H^+,K^+-ATPase from the canalicular side (not from the intracellular side). A recent study indicates that the transformation of PPI into its activated states requires very low pH (less than 1) [Shin et al., 2004]. This indicates that the activation of PPIs occurs only near the proton exit site of H^+, K^+-ATPase that is actively secreting acid. One particular feature of E3710 is the following. E3710 has 2, 2-dimethyl-1, 3-dioxane moiety. This dimethyl group is unstable in the strong acidic space and the isopropyl group including the dimethyl group is splitted leaving two OH groups in the remaining main body, which gives a higher hydrophilicity. The distribution ratio of the acid activated form of E3710 at pH 1 is calculated to be 1/6-fold that of omeprazole; that is, the acid activated form of E3710 is more hydrophilic than that of acid-activated omeprazole. A higher hydrophilic property of the acid-activated E3710 gives a higher accumulation power in the strongly acidic canalicular space because of its less membrane-permeability, which may contribute to the long-acting acid-inhibitory effect.

4.4 Summary of pharmacokinetics, toxicology and clinical study of E3710

4.4.1 Pharmacokinetic features

E3710 shows weak or no inhibitory effects on CYPs in human liver microsomes and revealed weak or no induction of CYPs in primary culture of human hepatocytes, indicating that E3710 would show low potential of drug-drug interaction. Regarding CYP3A4, E3710 was also found to be a weak mechanism-based inhibitor of this isozyme. E3710 was shown to be a substrate and a weak inhibitor of multidrug resistance 1 glycoprotein.

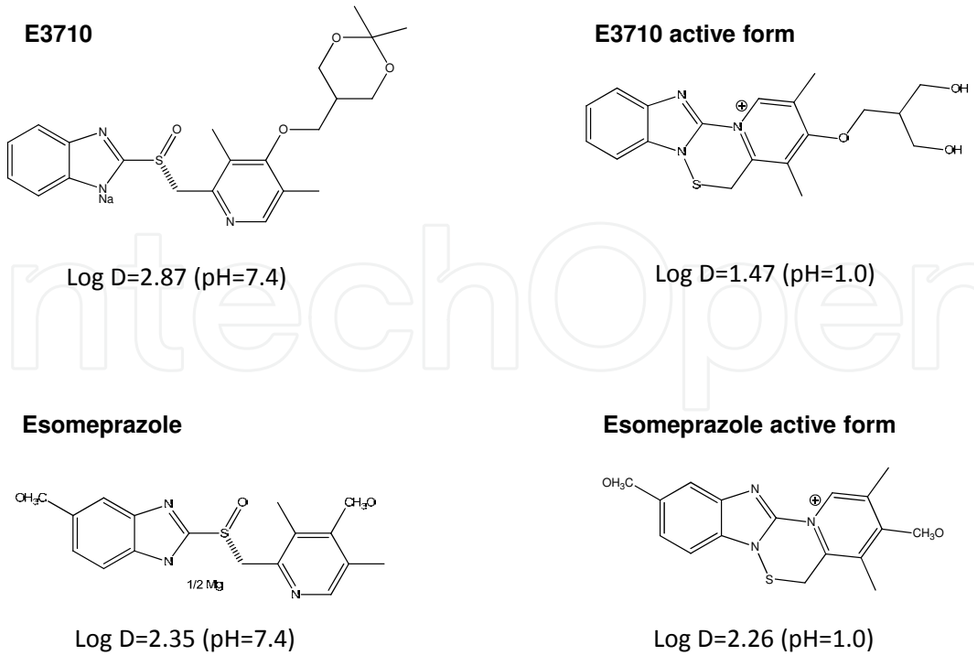

Fig. 14. Anticipated log D values of E3710, esomeprazole and their active forms.

The primary metabolic enzyme for E3710 in human microsomes was CYP3A4 and contributions of another CYP were negligible. The metabolism of E3710 and its efficacy may be less affected by CYP2C19 polymorphism, unlike other PPIs such as omeprazole, lansoprazole where CYP2CY19 pathway is a significant metabolic pathway. Besides for GERD, PPIs are widely used with clopidogrel, an antiplatelet drug, to reduce the risk of gastrointestinal bleeding. Clopidogrel is converted to its active form mainly through CYP2C19 and this active metabolite reduces the cardiovascular event based on its platelet inhibitory effect [Disney et al., 2011]. Antiplatelet efficacy of clopidogrel therefore may be reduced in patients with receiving medicine which is metabolized by CYP2C19. In these days, there is growing concern about concomitant use of omeprazole with clopidogrel may be associated with the risk to reduce platelet inhibition and to increase cardiovascular events. Although clinical relevant interactions of PPIs with clopidogrel was not clearly clarified so far [Disney et al., 2011], European Medical Agency released a statement and FDA issued the warning letter on the concomitant use of these drugs [Laine and Hennekens, 2010]. As the metabolism of E3710 was less involved with CYP2C19, we expect that possibility of E3710 to interfere with clopidogrel may be low.

4.4.2 Toxicological features

E3710 inhibited human ether-a-go-go related gene (hERG) tail current with the IC_{50} value of 88.2 μmol/L, but it showed no effect on action potential at concentrations of 5 and 50 μmol/L. Similarly, cardiovascular safety study *in vivo* using the telemetry in conscious dogs indicated that E3710 had no effects on heart rate, blood pressure or electrocardiogram parameters, including QT intervals up to 30 mg/kg. E3710 up to 1000 mg/kg did not induce any effects on the respiratory function parameters and it up to 100 mg/kg had no effects on any observation/measurement in the central nervous system toxicity study in rats. These

results suggested that E3710 is a low risk for adverse effects on the cardiovascular, respiratory and central nervous system.

The level for no observed adverse effect in 4-week repeated oral dose toxicity study was 10 mg/kg in rats and 3 mg/kg in dogs. The toxicological profile of E3710 is similar to those of other compounds in the same class. E3710 has been shown to have a tendency to exert its effect in more acidic state in comparison with esomeprazole (acidic condition in Table 1). Based on the results of several genotoxicity studies such as Ames test, mouse lymphoma thymidine kinase assay *in vitro*, rat micronucleus assay and rat liver unscheduled DNA synthesis *in vivo*, the genotoxic risk of E3710 is low. E3710 for 26 weeks administration showed no evidence of a carcinogenic potential in the strain of mice including $p53^{+/-}$ heterozygous knockout mice.

4.4.3 Study on the safety and tolerability in humans

The clinical ascending single and multiple dose studies of E3710 were carried out to examine its safety, tolerability and PKs in non-erosive GERD patients. For 14 days of continuous oral administration, the C_{max} and AUC increased in approximately proportion to doses and no accumulation upon multiple dosing. E3710 is well tolerated up to 180 mg designed as the maximum dose and no serious safety issues were observed at any doses. In summary, there were no clinically significant safety issues and the overall safety profile was similar to other PPIs in the clinical studies so far.

4.5 Competitive landscape with new concept in future acid related diseases

Besides of PPIs as gastric acid inhibitors, many pharmacological approaches such as P-CAB, transient lower esophageal sphincter relaxation (TLESR) inhibitors, transient receptor potential vanilloid (TRPV) 1 antagonist have been developing for the treatment of GERD (Fig. 15).

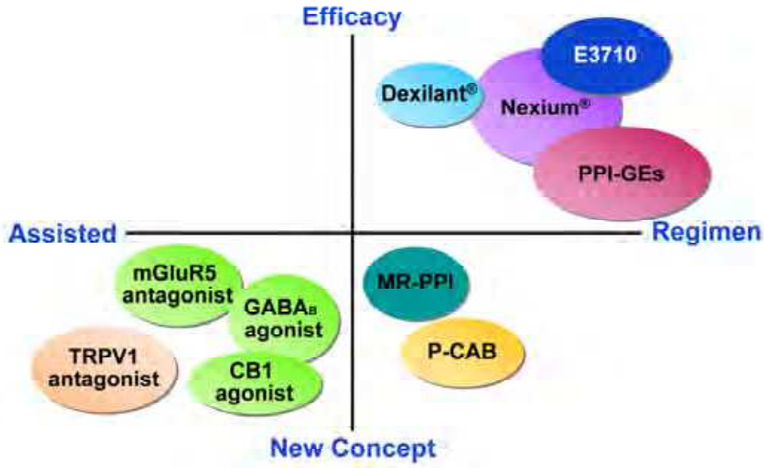

Fig. 15. Competitive landscape with new concept in future acid related diseases. Nexium®: esomeprazole, Dexilant®: dexlansoprazole modified-release, PPI-GEs: proton pump inhibitor generics, MR-PPI: modified-release proton pump inhibitor, P-CAP: potassium-competitive acid blocker, mGluR5: metabotropic glutamate receptor 5, GABAB: gamma-aminobutyric acid B, CB1: cannabinoid receptor 1, TRPV1: transient receptor potential vanilloid 1.

4.5.1 P-CAB

P-CAB inhibits H^+,K^+-ATPase based on different mechanism from PPIs. In contrast to the covalent biding and irreversible mechanism of action of PPIs, P-CAB binds to the potassium binding site of H^+,K^+-ATPase and result in its enzyme inhibition in a potassium-competitive manner with reversible inhibition. P-CAB doesn't need to be transferred its active form unlike to PPI; therefore, P-CAB would rapidly inhibit gastric acid secretion. The onset of relief of GERD symptoms may be related to the rapidity to the intragastric pH elevation. P-CAB has been expected to show the fast onset of heartburn relief, whereas this favorable clinical benefit has not been delivered so far. Full effect of gastric acid inhibition was actually observed on the first day of AZD0865 administration in Ph I study [Sachs et al., 2010]; however no dose response was observed regarding the time to sustained absence of heart burn among AZD0865-treated groups (25, 50 and 75 mg) in both GERD and non-erosive GERD patients [Kaharilas et al., 2007; Dent et al., 2008]. Moreover, AZD0865-treated groups didn't achieve faster sustained heartburn relief in comparison with esomeprazole (40 mg). Despite the long research history similar to PPI, no P-CAB has been launched up to now. A new type P-CAB, TAK-438, is only under Ph II trials in Japan [Sachs et al., 2010].

4.5.2 TLESR inhibitor

The lower esophageal sphincter plays a critical role in regulating flow across the gastro-esophageal junction by generating a tonic pressure to prevent reflux of gastric contents into the esophagus. TLESR is an episode of lower esophageal relaxation that occurs unrelated to swallowing [Kessing et al., 2011], and it is considered to be the underlying refractory factors for GERD treatment with PPIs. Many receptors in central nervous system is involved in TLESR, hence several approaches for TLESR inhibitors mediated through $GABA_B$, metabolic glutamine (mGlu) and cannabinoid (CB) receptors have been developed to enhance the lower esophageal sphincter constriction for blocking the gastric acid and non-acid reflux. Although $GABA_B$ receptor agonist (baclofen, R-baclofen, AZD9343, lesogaberan: AZD3355), mGlu receptor 5 antagonist (ADX10059, AZD2066, AZD2516) and CB1 agonist (D9-THC) reduced the TLESR, central nerve side effects such as headache and drowsiness, and low compliance (need to be taken twice or three times a day) were observed in clinical studies [Blondeau, 2010; Kessing et al., 2011]. Lesogaberan which was administered twice daily as add-on treatment to PPI ameliorated heartburn and regurgitation symptoms in persistent GERD symptoms even daily PPI therapy [Boeckxstaens et al., 2011]; however these effects were not adequate. Potent TLSER inhibitor without side effects is likely to be favorable as an add-on treatment for patients of GERD with PPIs in the future.

4.5.3 TRPV1 antagonist

Many patients show hypersensitivities to heat and acid; therefore, transient receptor TRPV1 might be a potential target for the remedy of refractory GERD. In the clinical study of TRPV1 antagonist, AZD1386, healthy volunteers were subjected to painful heat, mechanical, electrical stimulation similar to acid-induced hyperalgesia in esophagus. The skin and deep pressure pain was used as somatic controls. AZD1386 elevated the heat pain threshold in the esophagus and skin. Favorable safety profile was observed, dose dependent increases in body temperature were observed [Krarup et al., 2011]. This pursuit is still in smoke.

4.6 E3710 in the future

In the light of these disappointing situations for approaches associated with other mechanism, PPIs provide the most effective pharmacotherapy for treating acid related diseases (ARDs) with respect of efficacy and safety at present. We expect that E3710 with long-acting suppressive effects on gastric acid secretion would keep longer intragastric pH over-4 holding time in comparison with current PPIs for the treatment of the unmet medical needs of GERD. GERD is known as a common gastroesophageal disorder with a high prevalence rate at 10-20% in the USA [Dent et al., 2005]. The prevalence of GERD in Asia was reported to be relatively lower, while the recent research presented that the prevalence of symptom-based GERD and endoscopic reflux esophagitis has increased [Jung, 2011]. The adoption of a Western lifestyle accompanied by diet with high fat and energy, smoking and alcohol consumption, and increases in body mass index, obesity and metabolic syndrome may account for the increased prevalence rate of GERD in these areas [Goh, 2011]. According to better diagnosis system such as endoscope and questionnaire, GERD would be perceived as major gastroesophageal diseases all over the world.

In addition to GERD, there are still unmet medical needs in the treatment of patients with ARDs including NSAID (nonsteroid anti-inflammatory drug) -related ulcers, gastrointestinal bleeding, and *Helicobacter pylori* eradication. The widespread use of NSAID and aspirin would involve the risk of drug-related ulcers especially for the patients including personal history of complicated ulcer diseases, concurrent use of NSAID or aspirin, use of high doses, concurrent use of anticoagulant, personal history of uncomplicated peptic ulcer disease, age>70 and concurrent use of steroid. For these patients, concomitant use of promising PPIs with NSAID and/or aspirin would be useful to protect ulcers [Katz et al., 2006; Scarpignato and Pelosini, 2006]. E3710 possesses the appropriate stability in the point view of physical and chemical characteristics, combinational formulation of E3710 with NSAID and/or aspirin therefore may be expected. The co-therapy of PPIs with aspirin reduced not only upper gastrointestinal bleeding, but also cardiovascular events due to the increased aspirin adherence. This concomitant use is likely to be cost-effective [Saini et al., 2005]. In order to induce platelet aggregation, clot formulation and stability, a sustained intragastric pH>6 is necessary. The current PPIs are not able to maintain intragastric pH>6 for prolonged periods. The potent and long-acting PPI would be feasible for the treatment of gastrointestinal bleeding [Katz et al., 2006; Scarpignato and Pelosini, 2006]. The success rate of *Helicobacter pylori* eradication therapy depends on intragastric pH, so a long-acting PPI would be acceptable [Katz et al., 2006; Scarpignato and Pelosini, 2006]. Optimizing the control of intragastric pH would also be beneficial in these ARDs, so that a potent and long-acting PPI such as E3710 would be expected to offer improved clinical outcomes for patients with these ARDs as well as GERD.

Concerns have been expressed about the increased risk with long-term PPIs administration such as bone fracture, community-acquired pneumonia and in hospital-acquired *Clostridium difficile* diarrhea and malabsorption of nutrients etc. [Kushner and Peura, 2011]. Given that the potent and long-acting intragastric acid neutralization would lead to faster resolution of symptoms, faster healing of lesions, better responses in severe lesions and less frequent relapses for GERD, patients administered with E3710 would lead to sufficiently healed for only 4- or 6-weeks treatment instead of a standard 8-weeks treatment and less incidence of recurrence. These shorted remedy periods with E3710 may result in the reduced these

warnings. As a consequence, E3710 would provide a cost-effective and a valid therapy, improving patients' QOL for GERD in clinic, especially for intractable with current PPIs.

In conclusion, E3710, a newly synthesized long-acting PPI, could achieve potent and a long-acting suppression of gastric acid production. E3710 provides cost-effective and improved therapy for the treatment of unmet medical needs of GERD as well as other ARDs.

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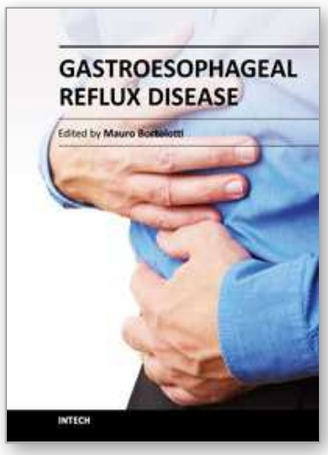

Gastroesophageal Reflux Disease
Edited by Prof. Mauro Bortolotti

ISBN 978-953-51-0314-1
Hard cover, 186 pages
Publisher InTech
Published online 16, March, 2012
Published in print edition March, 2012

Gastroesophageal reflux disease affects many patients. This disease not only lowers their quality of life, but it also threatens some of them with an underhand risk of cancer. Additionally, it becomes an economic burden for the patients and society. The aim of this book on gastroesophageal reflux disease is to provide advice and guidance to gastroenterologists to help them understand and manage some aspects of this proteiform disease.

How to reference
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Kotaro Kodama, Hideaki Fujisaki, Hideo Tonomura, Miwa Jindo, Misako Watanabe, Junichi Nagakawa and Noriaki Takeguchi (2012). E3710, Long-Acting PPI as New Approach for the Treatment of Unmet Medical Needs for GERD, Gastroesophageal Reflux Disease, Prof. Mauro Bortolotti (Ed.), ISBN: 978-953-51-0314-1, InTech, Available from: http://www.intechopen.com/books/gastroesophageal-reflux-disease/e3710-long-acting-ppi-as-new-approach-for-the-treatment-of-unmet-medical-needs-of-gerd

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