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Pharmacodynamic comparison of pantoprazole enantiomers: inhibition of acid-related lesions and acid secretion in rats and guinea-pigs

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Abstract

Pantoprazole is an irreversible proton pump inhibitor that is administered as a racemic mixture clinically. The effects of pantoprazole sodium (PAN·Na) enantiomers on acid-related lesions were compared using models of pylorus ligation induced ulcer, histamine induced ulcer and reflux oesophagitis in rats and guinea-pigs. Compared with (+)-PAN·Na and (±)-PAN·Na, (–)-PAN·Na showed much stronger inhibitory effects on pylorus ligation induced and histamine induced ulcers, but similar effects on reflux oesophagitis. The doses of (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na required for 50% inhibition (ID50) of acid-related lesions were 1.28, 5.03 and 3.40 mg kg^{-1} against pylorus ligation induced ulcer, 1.20, 4.28 and 3.15 mg kg^{-1} against histamine induced ulcer, and 2.92, 3.56 and 3.70 mg kg^{-1} against reflux oesophagitis, respectively. The inhibitory effects of PAN·Na enantiomers on basal gastric acid output were compared in rats with acute fistula. In contrast to inhibitory rates of 89.3% and 83.6% on gastric acid output by (–)-PAN·Na and (±)-PAN·Na at 1.5 mg kg^{-1}, (+)-PAN·Na had an inhibitory rate of only 24.7% at the same dose. The above results indicate that (–)-PAN·Na is more potent than (+)-PAN·Na at inhibiting acid-related lesions owing to its stronger inhibition of acid secretion.

Introduction

The introduction of proton pump inhibitors has markedly improved the treatment of acid-related lesions, including peptic ulceration, gastroesophageal reflux disease and Zollinger-Ellison syndrome (Richardson et al 1998). Among the proton pump inhibitors, (±)-pantoprazole ((±)-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)-methyl] sulfinyl]-1H-benzimidazole) has been confirmed to be as effective as omeprazole, the first proton pump inhibitor (Brunner & Harke 1994; Fitton & Wiseman 1996; Cheer et al 2003; Pilotto et al 2003). In addition, the advantage of pantoprazole over omeprazole is the minimal risk of interaction when it is co-administered with other drugs (Simon et al 1991; Steinijans et al 1994). Pantoprazole exerts an inhibitory effect only under strongly acidic conditions and this is the basis for its selective action against gastric H^+K^+-ATPase (Beil et al 1992; Huber et al 1995). Pantoprazole in combination with antibacterial agents also shows some synergistic activity in the eradication of *Helicobacter pylori* infection (Bochenek et al 2003; Malfertheiner et al 2003).

The pharmacokinetic and pharmacodynamic differences between enantiomers have been reported, and such differences are important for new drug development (Drayer 1986; Nerurkar et al 1992; Katsuki et al 1996). For example, esomeprazole, the *S*-isomer of omeprazole, has proved to be more effective than omeprazole (Hassan-Alin et al 2000; Lind et al 2000; Andersson et al 2001a, b). There are some reports about the pharmacokinetic differences between pantoprazole enantiomers (Tanaka & Yamazaki 1996; Tanaka et al 1997, 2001), however little information is available about the pharmacodynamics of pantoprazole enantiomers.

We recently reported the varying ability of pantoprazole sodium (PAN·Na) enantiomers to prevent gastric mucosal lesions induced by water-immersion stress, aspirin,

ethanol and reserpine in rats; 50% inhibitory dose (ID50) values of (–)-PAN·Na were 1.5- to 1.9-times lower than the ID50 values of (+)-PAN·Na and (±)-PAN·Na (Cao et al 2004). The varying ability of pantoprazole enantiomers to suppress acid secretion might be responsible for their varying ability to prevent gastric mucosal lesions. In the present study, we provide evidence that (–)-PAN·Na is more potent than (+)-PAN·Na at inhibiting acid-related lesions owing to its greater inhibition of acid secretion in rats and guinea-pigs.

Materials and Methods

Reagents

(–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na were provided by Drs Mao-Sheng Cheng and Qing-He Wang, Department of Pharmaceutical Engineering, Shenyang Pharmaceutical University (Shenyang, China). The optical purity of (–)-PAN·Na and (+)-PAN·Na was 91.9% ($[\alpha]_D^{20} = -122°$ (c = 0.5, acetonitrile/methanol, 1:1)) and 91.3% ($[\alpha]_D^{20} = -120°$ (c = 0.5, acetonitrile/methanol, 1:1)), respectively. Histamine was purchased from Shanghai Biochemistry Institute (Shanghai, China). (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na were dissolved in 0.9% saline solution before use.

Animals

Male rats (Sprague-Dawley, 180–220 g) and guinea-pigs (400–500 g) were purchased from the Center of Animal Experiments, Shenyang Pharmaceutical University (Shenyang, China). The animals were fasted for 24 h with free access to water before the experiments. The Animal Research Ethics Board of Shenyang Pharmaceutical University approved the experiments.

Pylorus ligation induced ulcer in rats

The model of pylorus ligation induced ulcer in rats was established as described by Shay et al (1945). At 1 h after oral administration of pantoprazole, under ether anaesthesia, the pylorus was ligated and the abdomen was closed. After 17 h, the rats were killed with an overdose of ether. The stomachs were removed and fixed with 1% formalin for 15 min. The stomachs were opened along the greater curvature. The gastric mucosa was flushed with saline and then pinned on a cork plate. The lesion area (mm^2) was measured under a dissecting microscope and used as the ulcer index.

Histamine induced ulcer in guinea-pigs

The model of histamine induced ulcer in guinea-pigs was established as described by Eagleton & Watt (1965). Histamine ($7.5\,mg\,kg^{-1}$) was injected intraperitioneally 30 min after oral administration of pantoprazole. The animals were killed after 4 h. The lesion area (cm^2) in the stomachs was measured under a dissecting microscope and used as the ulcer index.

Reflux oesophagitis in rats

The pylorus and the junction between the forestomach and corpus were ligated under ether anaesthesia as described by Goto & Kishi (1989). After ligation, pantoprazole was immediately injected intraduodenally. The rats were killed after 6 h. The gastroesophageal portion was removed and fixed with 2% formalin for 20 min. From the lesion area in the thoracic oesophagus, the oesophagitis index was macroscopically scored as follows: no lesion = 0; lesion area 1–25% = 1; lesion area 26–50% = 2; lesion area 51–75% = 3; and lesion area > 75% or with a perforation = 4.

Detection of gastric acid output in rats with acute fistula

As described by Kromer et al (1990), pantoprazole was administered orally 1 h before anaesthesia with urethane ($1\,g\,kg^{-1}$ i.p.). A midline incision was made and a PVC catheter was inserted from the duodenum into the stomach. The gastric lumen was flushed with saline at a rate of $0.2\,mL\,min^{-1}$ for 2 h, and 1 mL of the collected fluid was titrated to pH 7 with 0.1 M NaOH. The gastric acid output was calculated by multiplying the titrated volume of NaOH with the volume of collected gastric liquid per hour. The inhibitory rate of the proton pump inhibitor on acid output was calculated as follows:

$$\text{Inhibitory rate} = (1 - \text{acid output with pantoprazole/acid output without pantoprazole}) \times 100\%$$

Statistical analysis

The ID50 values (–)-PAN·Na, (+)-PAN·Na, and (±)-PAN·Na for ulcers and reflux oesophagitis were compared. Each experimental group comprised at least 10 rats or guinea-pigs. Data are expressed as means ± s.e.m. The data were assessed by one-way analysis of variance using SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). If significant, a post-hoc analysis using Dunnett's test was then performed for multiple comparisons. P values less than 0.05 were considered statistically significant.

Results

Pylorus ligation resulted in various types of lesions, including punctate, elongated and band-like lesions mainly distributed in the glandular stomachs of the rats. The mean lesion area in the control group was $33.3 \pm 4.55\,mm^2$ and PAN·Na enantiomers prevented lesion formation in a dose-dependent manner (Table 1). Compared with (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na at lower doses did not show significant effects.

Table 1 Effect of pantoprazole sodium (PAN·Na) enantiomers on gastric lesions in pylorus-ligated rats

Drug	Dose (mg kg^{-1})	Ulcer index (mm^2)	Inhibition (%)
Control	–	33.3 ± 4.55	–
(–)-PAN·Na	1.5	15.5 ± 3.05[a]	53.4
	3	4.80 ± 1.41[a]	85.6
	6	2.04 ± 1.16[a]	93.9
(+)-PAN·Na	1.5	26.3 ± 3.98[b]	21
	3	20.5 ± 3.68[a,b]	38.4
	6	15.2 ± 2.48[a,b]	54.4
(±)-PAN·Na	1.5	28.9 ± 4.93[b]	13.2
	3	16.2 ± 2.94[a,b]	51.4
	6	9.1 ± 2.21[a]	72.7

Data are mean ± s.e.m., n = 10. [a]$P < 0.05$, compared with the control value. [b]$P < 0.05$, compared with the corresponding value for (–)-PAN at the same dose.

Table 2 Effect of pantoprazole sodium (PAN·Na) enantiomers on histamine induced ulcer in guinea-pigs

Drug	Dose (mg kg^{-1})	Ulcer index (cm^2)	Inhibition (%)
Control	–	3.79 ± 0.83	–
(–)-PAN·Na	0.67	2.70 ± 0.63	28.8
	2	1.01 ± 0.26[a]	73.4
	6	0.57 ± 0.14[a]	85.0
(+)-PAN·Na	0.67	3.26 ± 0.46	14.0
	2	3.00 ± 0.91[b]	20.8
	6	1.51 ± 0.32[a]	60.1
(±)-PAN·Na	0.67	2.96 ± 0.66	22.0
	2	2.81 ± 0.84	25.8
	6	1.07 ± 0.33[a]	71.7

Data are mean ± s.e.m., n = 10. [a]$P < 0.05$, compared with the control value. [b]$P < 0.05$, compared with the corresponding value for (–)-PAN at the same dose.

ID50 values of (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na were 1.28, 5.03 and 3.40 mg kg^{-1}, respectively.

Histamine induced severe ulcers and even penetration in the stomachs of guinea-pigs, and the mean lesion area in the control group was 3.79 ± 0.83 cm^2. As shown in Table 2, (–)-PAN·Na was much more potent than (+)-PAN·Na and (±)-PAN·Na at inhibiting the formation of histamine induced ulcers. The ID50 values of (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na were 1.20, 4.28 and 3.15 mg kg^{-1}, respectively.

Erosion was observed in most areas of the thoracic oesophagus in the double-ligated rats, and the rate of perforation was 10%. The oesophagitis index in the control group was 3.6 ± 0.22. (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na inhibited the formation of oesophagitis to a similar degree (Table 3). The ID50 values were 2.92, 3.56 and 3.70 mg kg^{-1}, respectively.

The inhibitory effects of PAN·Na enantiomers on basal gastric acid output were compared in rats with acute fistula. The basal acid output was 35.9 ± 3.32 μmol H$^+$ h^{-1}. In contrast to inhibitory rates of 89.3% and 83.6% on gastric acid output by (–)-PAN·Na and (±)-PAN·Na at 1.5 mg kg^{-1}, (+)-PAN·Na showed an inhibitory rate of 24.7% at the same dose. At a higher dose (6 mg kg^{-1}), all the enantiomers had similar inhibitory rates of greater than 90% (Figure 1).

Table 3 Effect of pantoprazole sodium (PAN·Na) enantiomers on reflux oesophagitis in rats

Drug	Dose (mg kg^{-1})	Oesophagitis index	Inhibition (%)
Control	–	3.60 ± 0.22	–
(–)-PAN·Na	1.5	2.32 ± 0.37[a]	35.6
	3	2.20 ± 0.40[a]	38.9
	6	0.89 ± 0.10[a]	75.3
(+)-PAN·Na	1.5	2.16 ± 0.43[a]	40.0
	3	2.35 ± 0.30[a]	34.7
	6	1.27 ± 0.34[a]	64.7
(±)-PAN·Na	1.5	2.07 ± 0.45[a]	42.5
	3	2.02 ± 0.28[a]	43.9
	6	1.27 ± 0.34[a]	71.3

Data are mean ± s.e.m., n = 10. [a]$P < 0.01$ compared with the control value.

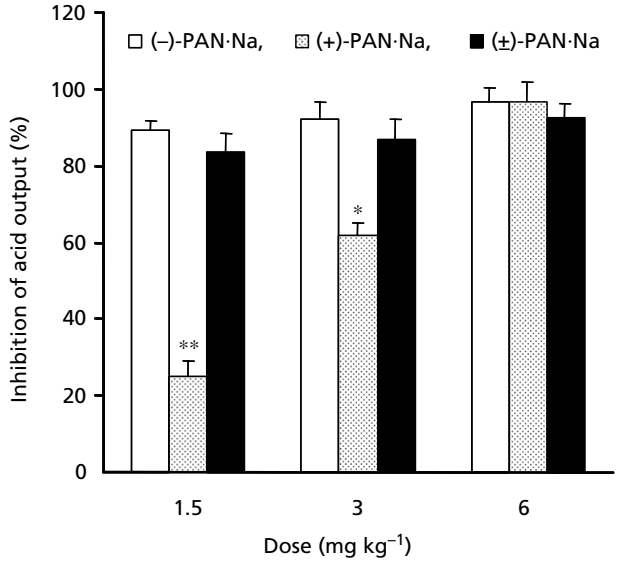

Figure 1 Ability of pantoprazole sodium (PAN·Na) enantiomers to suppress basal gastric acid output in models of acute fistula in rats. Results are expressed as the mean percent inhibition ± s.e.m. (n = 10) of the basal acid output by (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na. *$P < 0.05$, **$P < 0.01$, compared with the corresponding values for (–)-PAN·Na and (±)-PAN·Na at the same dose.

Discussion

Esomeprazole is the first proton pump inhibitor developed as an optical isomer of omeprazole. Esomeprazole shows an improved pharmacokinetic profile, less

inter-individual variability and stronger activity to suppress gastric acid secretion than racemic omeprazole (Hassan-Alin et al 2000; Lind et al 2000; Andersson et al 2001a, b). Another proton pump inhibitor, pantoprazole, also displays different stereoselective pharmacokinetics (Tanaka & Yamazaki 1996; Tanaka et al 1997, 2001). However, little is known about the pharmacodynamics of pantoprazole enantiomers. We recently evaluated the effects of pantoprazole enantiomers on gastric mucosal lesions in rats; the results indicated that (–)-PAN·Na was the most potent at inhibiting gastric mucosal lesions induced by water-immersion stress, aspirin, ethanol and reserpine (Cao et al 2004).

In the present study, we compared the inhibitory effects of PAN·Na enantiomers on acid-related lesions and acid output in rats and guinea-pigs. (–)-PAN·Na was more potent than (+)-PAN·Na at preventing ulcers induced by pylorus ligation and histamine stimulation. Furthermore, (–)-PAN·Na was more potent than (+)-PAN·Na at inhibiting acid secretion in acute fistula rats, indicating that the different abilities of the enantiomers to inhibit acid output is responsible for the different protective effects against acid-related lesions.

It has been reported that unidirectional chiral inversion from (+)-PAN·Na to (–)-PAN·Na occurred after intravenous and oral administration of (+)-PAN·Na at an inversion ratio of 36.3% and 28.1%, respectively (Masubuchi et al 1998). The chiral inversion may be responsible for the weak activity of (+)-PAN·Na. Therefore, a more potent effect can be expected by direct administration of (–)-PAN·Na instead of (±)-PAN·Na clinically.

(–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na inhibited the formation of reflux oesophagitis to a similar degree. The precise mechanism for this phenomenon remains unclear. The animal model for reflux oesophagitis may not be the most suitable model of 'reflux' in this experiment. The data from the animal model of reflux oesophagitis may not therefore accurately represent conditions in humans. In addition, it has been reported that the pathogenesis of reflux oesophagitis involves vagal pathway-dependent acid secretion, and there is a high prevalence of parasympathetic nerve dysfunction in gastro-oesophageal reflux disease (Ogilvie et al 1985; Cunningham et al 1991). Therefore, the possible effects of (–)-PAN·Na, (+)-PAN·Na and (±)-PAN·Na on the parasympathetic nerve may need to be investigated further.

Conclusion

(–)-PAN·Na was more potent than (+)-PAN·Na and (±)-PAN·Na at inhibiting pylorus ligation induced and histamine induced ulcers in rats and guinea-pigs owing to its stronger inhibition of acid secretion. Therefore, in the clinical setting, greater efficacy can be expected by direct administration of (–)-PAN·Na instead of (±)-PAN·Na.

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