

Full Paper

Antiemetic Activity of FK1052, a 5-HT₃- and 5-HT₄-Receptor Antagonist, in *Suncus murinus* and Ferrets

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Abstract. We investigated the effect of FK1052 [(+)-8,9-dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one hydrochloride], a 5-HT₃- and 5-HT₄-receptor antagonist, on the emesis induced by motion stimuli, copper sulfate, or cisplatin in either *Suncus murinus* or ferrets and also clarified the role of the 5-HT₃ and 5-HT₄ receptors in these models. In *Suncus murinus*, oral administration of FK1052 (100 µg/kg) completely prevented emesis induced by cisplatin (18 mg/kg, i.p.). Intraperitoneal injection of scopolamine (10 mg/kg) and promethazine (32 mg/kg), but not FK1052 (1 mg/kg), significantly reduced the emetic responses by motion stimuli. In ferrets, copper sulfate (40 mg/kg, p.o.)-induced emesis was moderately prevented by FK1052 (3.2 mg/kg), but not by granisetron (3.2 mg/kg). Cisplatin-induced acute (10 mg/kg, i.v.) and delayed (5 mg/kg, i.p.) emesis were significantly reduced by single and multiple intravenous injection of both FK1052 (3.2 mg/kg) and granisetron (3.2 mg/kg), respectively. The present study suggests that FK1052 may be useful against both acute and delayed emesis induced by cancer chemotherapy. Moreover, it is suggested that blockades of 5-HT₃ and 5-HT₄ receptors are not relevant to the control of motion sickness; and furthermore, it suggested that blocking 5-HT₄ receptors in addition to 5-HT₃ receptors does not have an additional effect on the control of cisplatin-induced emesis, but that 5-HT₄ receptors are at least partly involved in the mechanism of emesis induced by copper sulfate.

Keywords: motion sickness, cisplatin, acute emesis, delayed emesis, copper sulfate

Introduction

Nausea and vomiting are distressing symptoms associated with a variety of conditions such as chemotherapy for cancer, ingestion of irritants, and motion sickness. To understand and potentially treat emesis induced by such diverse stimuli, various animal models are used to mimic the human emetic response to a particular stimulus (1). Although common laboratory animals such as the rat and guinea pig lack the emetic reflex, *Suncus murinus* (the house musk shrew) is a unique small animal in which vomiting can be induced by several emetogens

(2). A majority of studies have used dogs and ferrets and the cisplatin-induced acute emesis as a chemotherapy-induced emesis model, with emesis occurring within the first 24 h of chemotherapy. Both species have been extensively used to identify the antiemetic potential of novel drugs such as 5-HT₃-receptor antagonists (3). On the other hand, delayed emesis, which occurs 24 h or later after chemotherapy, remains less well controlled than acute emesis (4). Three animal models for chemotherapy-induced delayed emesis have been developed. Cisplatin induced delayed emesis in ferrets and piglets (5, 6) and both models were significantly, but not completely, prevented by selective 5-HT₃-receptor antagonists such as ondansetron and granisetron (7, 8). Methotrexate produced delayed emesis in dogs and emesis in this model was in part inhibited by ondansetron (9). All three models also revealed a 5-HT₃-

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receptor antagonist resistant component during the delayed phase (7–9).

FK1052 [(+)-8,9-dihydro-10-methyl-7-[(5-methyl-1*H*-imidazol-4-yl)methyl]pyrido[1,2-*a*]indol-6(7*H*)-one hydrochloride] has been reported to be an antagonist for the 5-HT₄ receptor, in addition to the 5-HT₃ receptor, both in vitro and in vivo (10, 11). FK1052 exhibited a potent antiemetic action against cisplatin-induced acute emesis in dogs (12). Both tropisetron, another dual antagonist for 5-HT₃ and 5-HT₄ receptors, and FK1052 significantly reduced methotrexate-induced delayed emesis in dogs, suggesting that the 5-HT₄ receptor might be in part involved in the production of delayed emesis induced by chemotherapy (13).

The present study was aimed to investigate whether FK1052 could prevent emesis induced by motion stimuli, copper sulfate, and cisplatin (acute and delayed phase) in *Suncus murinus* and ferrets, thus clarifying the role of 5-HT₃ and 5-HT₄ receptors in these emesis models.

Materials and Methods

Animals

Suncus murinus of either sex (>10-week-old; 30–70 g body weight; Clea Japan, Inc., Tokyo) and adult male ferrets (1.0–2.3 kg body weight; Marshall Farms, North Rose, NY, USA) were housed respectively as a group and individually at 23 ± 1°C with lights on between 07:00 and 19:00, and free access to water. *Suncus murinus* were allowed free access to pellet chow (CIEA305, Clea Japan, Inc.) and ferrets were fed dry pellets (Ferret Diet; PMI Feeds, St. Louis, MO, USA). In all experiments, animals were removed from their home cages and transferred to observation cages in a quiet room. The emesis was characterized by rhythmic abdominal contractions associated with (vomiting) or without (retching) the oral expulsion of materials from the gastrointestinal tract. All animal experimental procedures were performed under the guidelines of the Animal Experiment Committee of Fujisawa Pharmaceutical Co., Ltd.

Dosage of FK1052

Systemic administration of FK1052 has not previously been studied in *Suncus murinus* and the ferret, and therefore the dose to be used was selected on the basis of a previous study in dogs (13).

Cisplatin-induced emesis in *Suncus murinus*

After the intraperitoneal injection of cisplatin (18 mg/kg), animals were observed continuously for 2 h, and the incidences of emesis were counted, as pre-

viously described (14). FK1052 (1, 10, and 100 µg/kg), granisetron (100 µg/kg), or vehicle (20 ml/kg) was orally administered 30 min before the injection of cisplatin.

Motion-induced emesis in *Suncus murinus*

Experimental conditions were similar to those reported previously by Okada et al. (14). Briefly, animals were placed individually in a transparent cage (10 × 15 × 12 cm) on a reciprocal shaker (TAITEC Double Shaker NR-3; Taiyo Scientific Industrial Co., Ltd., Saitama). After a 3-min acclimation, motion sickness was elicited by reciprocal shaking (amplitude of 40 mm, frequency of 1 Hz, duration 5 min). Vehicle was intraperitoneally administered 5 min before the start of motion stimuli. The number of vomiting episodes and the latency to the first vomit were recorded for 5 min. Animals were re-tested 7 days later with motion stimuli, 5 min after the intraperitoneal injection of scopolamine (10 mg/kg), promethazine (32 mg/kg), or FK1052 (1 mg/kg).

Copper sulfate-induced emesis in ferrets

Ferrets were deprived of food overnight. Copper sulfate solution (40 mg/kg) was rapidly flushed into the stomach via an orogastric tube, as previously described (15). Animals were observed continuously for 30 min for emetic responses, the time of onset to retching or vomiting, and the number of both retches and vomits. FK1052 (3.2 mg/kg), granisetron (3.2 mg/kg), or vehicle (1 ml/kg) was intravenously administered through a forelimb (cephalic) vein 5 min before the administration of copper sulfate.

Cisplatin-induced acute emesis in ferrets

In preliminary experiments, the intravenous injection of cisplatin (10 mg/kg) induced emesis reliably in this species, similar to the case of the intraperitoneal injection. Following administration of cisplatin (10 mg/kg, i.v.), animals were observed continuously for 4 h and the incidences of emetic responses, consisting of retches and vomits was counted. FK1052 (3.2 mg/kg) or vehicle (1 ml/kg) was intravenously administered at 8 h, and granisetron (3.2 mg/kg) or vehicle was intravenously administered at 4 h before the injection of cisplatin.

Cisplatin-induced delayed emesis in ferrets

Ferrets were intraperitoneally injected with cisplatin (5 mg/kg) at 08:30. Animal behavior was recorded using a video camera with an automatic night photograph system for up to 72 h and analyzed at the end of the experiment. FK1052 (3.2 mg/kg) or vehicle (1 ml/kg) was intravenously administered at 36, 48, and 60 h,

and granisetron (3.2 mg/kg) or vehicle was administered at 32, 40, 48, 56, and 64 h after cisplatin-treatment. A 12-h artificial light cycle (lights on between 07:00 to 19:00) was used throughout the study. Ferrets were given food (Ferret Diet, 70 g/day) and water ad libitum for 3 days.

Drugs

Cisplatin (Sigma-Aldrich, Inc., St. Louis, MO, USA) was prepared in saline at 70°C followed by gradual cooling to 40°C and administered immediately in a volume of 10 and 5 ml/kg for *Suncus murinus* and ferrets, respectively. Copper sulfate pentahydrate (Wako Pure Chemicals, Osaka) was dissolved in distilled water (20 mg/mL). FK1052 and granisetron were synthesized in the Medicinal Chemistry Laboratories of Fujisawa Pharmaceutical Co., Ltd. (Osaka), and scopolamine hydrochloride and promethazine hydrochloride were purchased from Sigma-Aldrich, Inc. They were freshly dissolved in 5% glucose solution for systemic injection or distilled water for oral administration.

Statistical analyses

Group results are expressed as the mean \pm S.E.M. Dunnett's test or a paired Student's *t*-test was used as a measure of significance. Values of $P < 0.05$ were regarded as statistically significant.

Results

Cisplatin-induced emesis in *Suncus murinus*

As shown in Table 1, FK1052 inhibited cisplatin-induced emesis in a dose-dependent manner, and no emesis was observed in three animals given FK1052 at 100 μ g/kg. Granisetron at 100 μ g/kg significantly

inhibited the emesis and completely prevented emesis in 1 of 3 animals.

Motion-induced emesis in *Suncus murinus*

Antiemetic effects of test drugs against motion sickness in *Suncus murinus* are summarized in Table 2. In the first control experiment, as the control, all of the animals vomited when they were exposed to the reciprocal shaking. After a rest period of 7 days, scopolamine (10 mg/kg) and promethazine (32 mg/kg) significantly inhibited the vomiting induced by motion, and the former and the latter completely prevented emesis in three of six and four of seven animals, respectively. FK1052 (1 mg/kg) completely prevented motion-induced emesis in one of six animals; In addition, FK1052 increased the latency of the emetic response with no statistical significance.

Copper sulfate-induced emesis in ferrets

As shown in Table 3, vomiting episodes evoked by copper sulfate were significantly reduced by 39.4% by FK1052 (3.2 mg/kg), but not granisetron (3.2 mg/kg).

Cisplatin-induced acute emesis in ferrets

As shown in Table 4, intravenous 8-h preadministration of FK1052 (3.2 mg/kg) completely prevented the subsequent cisplatin-induced acute emesis in all ferrets; 4-h pretreatment of granisetron (3.2 mg/kg) prevented the cisplatin-induced acute emesis in three of four ferrets.

Cisplatin-induced delayed emesis in ferrets

Because FK1052 or granisetron at 3.2 mg/kg significantly prevented cisplatin-induced acute emesis in ferrets, we examined whether FK1052 and granisetron

Table 1. Inhibitory effects of granisetron and FK1052 on cisplatin-induced emesis in *Suncus murinus*

Treatment ^a	Dose (μ g/kg)	Animals (vomits/total)	Latency ^b (min)	No. of vomits	Inhibition (%)
Control		3/3	55 \pm 7	5.0 \pm 2.1	—
FK1052	1	3/3	53 \pm 9	5.0 \pm 0.0	0
Control		3/3	48 \pm 6	5.3 \pm 0.3	—
FK1052	10	3/3	74 \pm 19	3.0 \pm 1.2	43.4
Control		3/3	47 \pm 5	6.0 \pm 1.5	—
FK1052	100	0/3	120 \pm 0*	0.0 \pm 0.0*	100
Control		3/3	47 \pm 5	6.0 \pm 1.5	—
Granisetron	100	2/3	68 \pm 27*	1.7 \pm 0.9*	71.7

^aGranisetron, FK1052, or vehicle was orally administered 30 min before the intraperitoneal injection of cisplatin.

^bIf a *Suncus murinus* did not vomit, the latency period was taken to be equal to the observation time (120 min).

*Compared with the control, $P < 0.05$.

Table 2. Inhibitory effects of scopolamine, promethazine and FK1052 on motion sickness in *Suncus murinus*: no statistical significant effect of FK1052

Treatment ^a	Dose (mg/kg)	Animals (vomits/total)	Latency ^b (s)	No. of vomits	Inhibition (%)
Control		6/6	121 ± 43	5.7 ± 1.6	—
Scopolamine	10	3/6	233 ± 43*	1.0 ± 0.5*	71.7
Control		7/7	136 ± 27	5.1 ± 1.2	—
Promethazine	32	3/7	197 ± 49	0.4 ± 0.2*	92.2
Control		6/6	102 ± 34	6.2 ± 1.2	—
FK1052	1	5/6	161 ± 45	4.5 ± 1.3	27.4

^aTest drug or vehicle was intraperitoneally administered 5 min before motion stimuli. ^bIf a *Suncus murinus* did not vomit, the latency period was taken to be equal to the observation time (300 s). *Compared with the control, $P < 0.05$ (paired *t*-test).

Table 3. Inhibitory effect of FK1052 on copper sulfate-induced emesis in ferrets: no effect of granisetron

Treatment ^a	Animals (vomits/total)	Latency (min)	Retches + vomits	Inhibition (%)
Control	3/3	2.9 ± 0.3	68 ± 9	—
Granisetron	3/3	3.4 ± 0.2	82 ± 6	−20.6
Control	4/4	1.5 ± 0.3	99 ± 8	—
FK1052	4/4	4.8 ± 1.2	60 ± 2*	39.4

^aGranisetron (3.2 mg/kg) or FK1052 (3.2 mg/kg) was intravenously administered 5 min before the intragastric administration of copper sulfate, respectively. *Compared with the control, $P < 0.05$.

Table 4. Inhibitory effects of granisetron and FK1052 on cisplatin-induced acute emesis in ferrets

Treatment ^a	Animals (vomits/total)	Latency ^b (min)	Retches + vomits	Inhibition (%)
Control	4/4	78 ± 11	121 ± 50	—
Granisetron	1/4	232 ± 8**	4 ± 4**	96.9
Control	3/3	82 ± 3	183 ± 58	—
FK1052	0/3	240 ± 0**	0 ± 0**	100

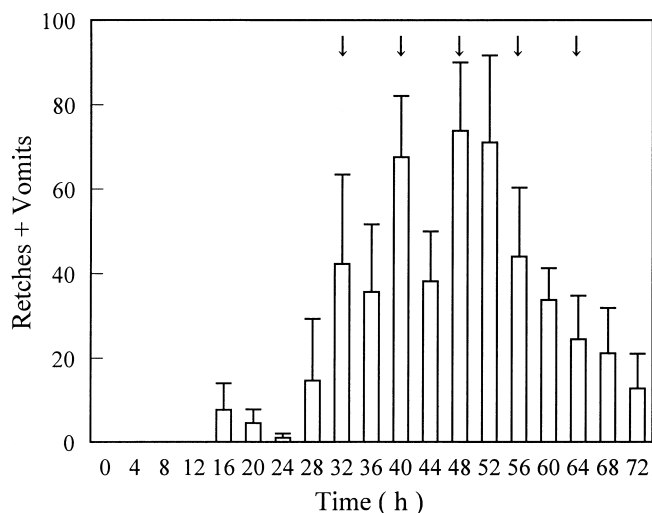
^aGranisetron (3.2 mg/kg) or FK1052 (3.2 mg/kg) was intravenously administered 4 or 8 h before the intravenous injection of cisplatin, respectively. ^bIf a ferret did not vomit, the latency period was taken to be equal to the observation time (240 min). **Compared with the control, $P < 0.01$.

could inhibit delayed emesis caused by cisplatin in ferrets. The episodes of acute (0–24 h) and delayed (>24 h) emesis are shown in Figs. 1 and 2. As shown in Fig. 1 and Table 5, granisetron (3.2 mg/kg, i.v.) at 32, 40, 48, 56, and 64 h significantly reduced delayed emesis (32–72 h) by 76%, compared with the vehicle-treated control. In addition, FK1052 (3.2 mg/kg, i.v.) at 36, 48, and 60 h significantly inhibited delayed emesis by 81%, compared with the control during 36–72 h (Fig. 2 and Table 5).

Discussion

Although the precise mechanisms or neuronal circuitry involved in the emetic reflex are not fully understood, there is evidence that the 5-HT receptors are involved in the pathway in several emesis models (3, 13, 14, 16–19). In the present study, FK1052, but not granisetron, showed a significant inhibition of emesis induced by copper sulfate in ferrets. Previous studies have demonstrated that copper sulfate-induced emesis in ferrets and dogs is abolished by tropisetron, a 5-HT₃- and 5-HT₄-receptor dual antagonist at high

a) Control



b) Granisetron

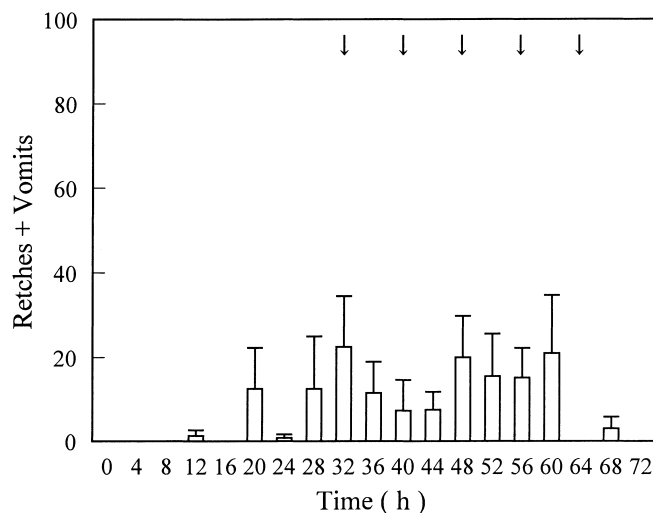
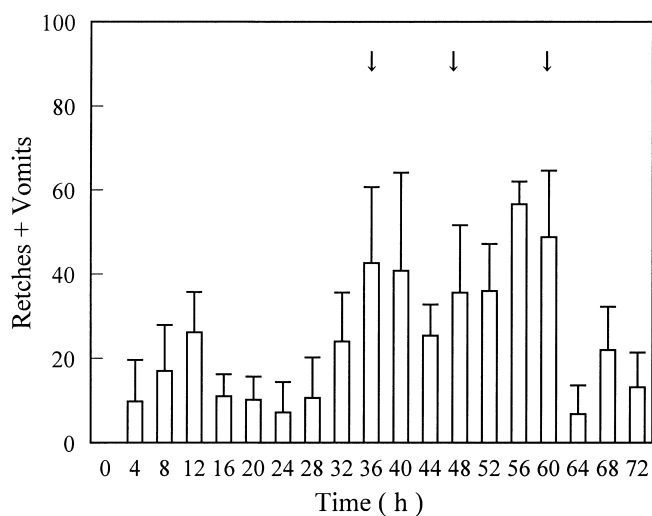


Fig. 1. Inhibitory effect of granisetron on cisplatin-induced delayed emesis in ferrets. Ferrets received cisplatin (5 mg/kg, i.p.), followed by the intravenous injection of a) 1 ml/kg vehicle (Control) or b) 3.2 mg/kg granisetron. Administration point of vehicle or drug is indicated by the arrow. Results represent the mean \pm S.E.M. of the total numbers of retches + vomits occurring at 4-h time intervals after cisplatin injection at 0 h.

a) Control



b) FK1052

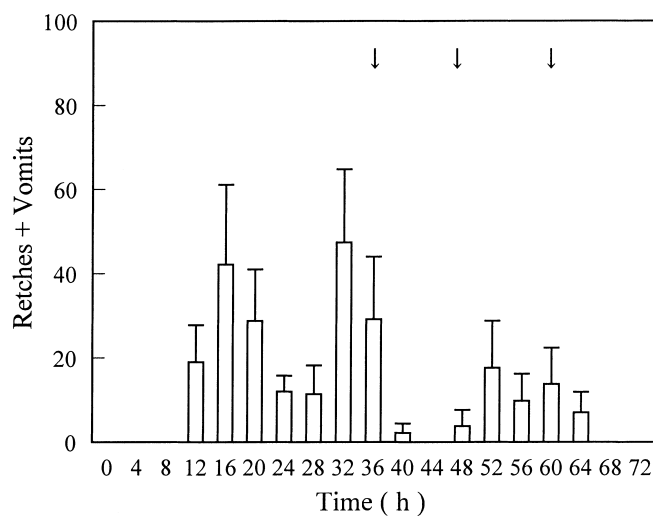


Fig. 2. Inhibitory effect of FK1052 on cisplatin-induced delayed emesis in ferrets. Ferrets received cisplatin (5 mg/kg, i.p.), followed by the intravenous injection of a) 1 ml/kg vehicle (Control) or b) 3.2 mg/kg FK1052. Administration point of vehicle or drug is indicated by the arrow. Results represent the mean \pm S.E.M. of the total numbers of retches + vomits occurring at 4-h time intervals after cisplatin injection at 0 h.

doses (20), but not by other 5-HT₃-receptor antagonists such as ondansetron, granisetron, and MDL 72222 (17, 18). However, other studies have provided evidence that 5-HT₄ receptors were not involved in copper sulfate-induced emesis in ferrets (21). Although the role of

5-HT₄ receptors in the induction of copper sulfate-induced emesis is controversial, our results support the hypothesis that 5-HT₄ receptors play an important role in copper sulfate-induced emesis.

Most studies have used cisplatin as the anticancer

Table 5. Inhibitory effects of FK1052 and granisetron on cisplatin-induced delayed emesis in ferrets

Treatment ^a	Animals (vomits/total)	Retches + vomits		
		Time after cisplatin (h)		
		0–24	24–36	36–72
Control	5/5	81 ± 23	77 ± 34	285 ± 39
FK1052	5/5	102 ± 23	88 ± 18	54 ± 17**
		0–24	24–32	32–72
Control	6/6	13 ± 10	57 ± 32	423 ± 67
Granisetron	6/6	15 ± 9	35 ± 16	101 ± 31**

^aFK1052 (3.2 mg/kg) was intravenously administered at 36, 48, and 60 h after the intraperitoneal injection of cisplatin. Granisetron (3.2 mg/kg) was intravenously administered at 32, 40, 48, 56, and 64 h after the intraperitoneal injection of cisplatin. **Compared with the control, $P < 0.01$.

agent of choice in their models for the induction of emesis. It is generally accepted that stimulation of the abdominal vagal afferent nerves via the 5-HT₃ receptor is important for triggering acute emesis induced by cisplatin and other antineoplastic agents (22). FK1052, administered both intravenously and orally, exhibited a potent antiemetic activity against cisplatin-induced emesis in dogs (12). The present study also demonstrated that oral administration of FK1052, as well as granisetron, was effective against cisplatin-induced acute emesis in *Suncus murinus*. Co-administration of GR125487, a 5-HT₄-receptor antagonist, and granisetron significantly reduced emetic episodes induced by the high dose (50 mg/kg, i.p.) of cisplatin in *Suncus murinus*, in which antiemetic activity was the same as tropisetron alone, suggesting that both the 5-HT₃ and 5-HT₄ receptors are involved in the emesis induced by high-dose cisplatin in *Suncus murinus* (23). The present study shows that there is no difference between the antiemetic activity of FK1052 and granisetron in *Suncus murinus* on emesis induced by almost the usual dose (18 mg/kg, i.p.) (24) of cisplatin in this species. These results suggest that the 5-HT₄ receptors were not involved in acute emesis induced by usual dose of cisplatin (18 mg/kg, i.p.) in *Suncus murinus*.

In contrast to the case of chemotherapy-induced acute emesis, the involvement of the 5-HT₃ and 5-HT₄ receptors in delayed emesis, which occurs 24 h or later after the start of chemotherapy, is poorly understood. Cisplatin (5 mg/kg, i.p.)-induced delayed emesis in ferrets is often used because the profile of emesis is similar to that of the delayed phase of emesis observed in humans (5). A previous study showed that this delayed emesis in ferrets was significantly prevented by selective 5-HT₃-receptor antagonists (7). However, no reports are available concerning the role of the 5-HT₄ receptors

on the delayed emesis in ferrets. In the present study, we examined the effect of granisetron and FK1052 on cisplatin (10 mg/kg, i.v.)-induced acute emesis in ferrets in order to determine appropriate intervals of treatment for antiemetics in the experiments on delayed emesis by cisplatin (5 mg/kg, i.p.). Granisetron (3.2 mg/kg, i.v.) given 4 h prior to cisplatin showed almost complete prevention of acute emesis in ferrets, when continuously observed for 4 h after cisplatin administration. This result suggests that the duration of antiemetic action of granisetron in ferrets may be about 8 h. Since FK1052 (3.2 mg/kg, i.v.) administered 8 h prior to cisplatin completely inhibited acute emesis in ferrets, this also suggests that the duration of action for FK1052 is at least 12 h. Multiple injections of granisetron every 8 h from 32–72 h significantly inhibited subsequent emetic responses by 76%. In previous study, methotrexate-induced delayed emesis in dogs was significantly inhibited by FK1052 and tropisetron, but not ondansetron, suggesting that the 5-HT₄ receptor might in part be involved in the production of delayed emesis induced by methotrexate (13). However, multiple injections every 12 h of FK1052 during 36–72 h significantly inhibited cisplatin-induced delayed emesis in ferrets by 81%, an inhibitory effect that was similar to that of granisetron. In this study the numbers of retches and vomits were different between the control group of FK1052 and that of granisetron. A previous report indicated that the generally low level of retching or vomiting observed 20 to 30 or 40 h after cisplatin injection might reflect the initially intense and persistent retching observed over a 12-h period followed by exhaustive disruption and general debilitation (25). Therefore, the variability in the control groups might partly have a influence on the magnitude and the significance of the effect of the drugs in the present study. These results demonstrate that 5-

HT₃-receptor antagonists combined with 5-HT₄-receptor antagonistic action, compared with 5-HT₃-receptor antagonist alone, may produce little additive effect on the cisplatin-induced delayed emesis model in ferrets, and it suggests that the mechanisms for production of cisplatin-induced delayed emesis in ferrets may be different from that of methotrexate-induced delayed emesis in dogs. Further studies are required to clarify the exact role of 5-HT₄ receptors in the delayed emesis by using other models.

The currently used antihistaminergic and anticholinergic agents are the most effective drugs for alleviating the symptoms of motion sickness (26). It seems likely that *Suncus murinus* is a suitable animal for the study of motion sickness because the experimental apparatus in *Suncus murinus* is very compact compared with those in other animals such as cats (27, 28). The present study confirmed that *Suncus murinus* affords a model of motion sickness susceptible to inhibition by the reference antiemetic agent scopolamine and promethazine. The antiemetic effect of FK1052 on motion sickness was very weak, compared with those of scopolamine and promethazine. It has been shown that granisetron and GR125487 failed to reduce motion sickness in *Suncus murinus* (29). Thus, it seems unlikely that 5-HT₃ and 5-HT₄ receptors are involved in the motion sickness in *Suncus murinus*.

In conclusion, the present study suggests that FK1052 may be useful against both acute and delayed emesis induced by cancer chemotherapy. Moreover, it is suggested that blockade of 5-HT₃ and 5-HT₄ receptors is not relevant to the control of motion sickness. Furthermore, it is suggested that blocking 5-HT₄ receptors in addition to 5-HT₃ receptors does not influence the control of acute and delayed cisplatin-induced emesis, but that 5-HT₄ receptors are at least partly involved in the mechanism of emesis induced by copper sulfate.

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