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Long-Lasting Anti-emetic Effect of T-2328, a Novel NK_1 Antagonist

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Abstract. The effect of T-2328 {2-fluoro-4'-methoxy-3'-[[[(2*S*,3*S*)-2-phenyl-3-piperidinyl] amino]methyl]-[1,1'-biphenyl]-4-carbonitrile dihydrochloride}, a novel tachykinin NK_1–receptor antagonist, was examined on cisplatin-induced emesis in ferrets. Cisplatin induced acute emesis in 24 h and delayed emesis during 24 and 72 h, respectively. Ondansetron, a 5-HT_3 antagonist, almost completely blocked the acute emesis and transiently reduced the delayed emesis. In contrast, T-2328 elicited long-lasting anti-emetic effects on both acute and delayed phases by a single intravenous administration. Suppression of delayed emesis was not due to elimination of the acute phase because the delayed emesis was also suppressed by administration after the onset of delayed emesis. Persistent blockade of NK_1 receptors in the brain was demonstrated by inhibition of the NK_1 agonist–induced foot tapping response for over 24 h. An appreciable amount of T-2328 was present in the brain 32 and 72 h after the injection. The NK_1 agonist–induced contractions of isolated ileum in guinea pigs was antagonized with IC_{50} values of 1.4 nM in an insurmountable manner. It is likely that T-2328 exerts the long-lasting anti-emetic effect by not only long-term presence in the brain but also its insurmountable inhibition of NK_1 receptors.

Keywords: emesis, NK_1, long-acting, cisplatin

Introduction

Nausea and vomiting continue to be critical problems in cancer chemotherapy. Uncontrolled emesis can adversely affect the quality of life and impair compliance with treatment in patients (1). Chemotherapeutic agents including cisplatin elicit an immediate emetic response on the day of therapy, that is, acute emesis, and also protracted nausea and vomiting lasting up to 5 days thereafter, that is, delayed emesis. Cisplatin damages the gastrointestinal epithelium and triggers acute emesis through stimulation of 5-HT_3 receptors in abdominal afferent fibers (2), whereas the precise mechanism of delayed emesis has not been fully revealed. In the prevention of acute emesis, 5-HT_3–receptor antagonists are effective in both animals and humans. In contrast, the incidence of delayed emesis is not sufficiently reduced by 5-HT_3–receptor antagonists (3).

Recent studies have suggested the involvement of substance P and NK_1 receptors in the generation of delayed emesis following the treatment with chemotherapeutic agents (4). Substance P-containing fibers and tackykinin NK_1 receptors are present in the solitary nucleus, a part of the emetic center (4, 5). Administration of substance P produced emesis in ferrets (6). Injection of an NK_1-receptor antagonist into the vicinity of the solitary nucleus inhibited cisplatin-induced emesis (7). Substance P–induced discharge of action potentials of single nucleus tractus solitaries neurons recorded in slices of ferret brain stem is inhibited by NK_1 antagonist

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(8). Recently, NK_1-receptor antagonists have been demonstrated to prevent not only acute emesis but also delayed emesis induced by ciaplatin in ferrets and humans (9 – 11). Previously, a brain-penetrant NK_1 antagonist, T-2328 {2-fluoro-4'-methoxy-3'-[[[(2*S*,3*S*)-2-phenyl-3-piperidinyl]amino]methyl]-[1,1'-biphenyl]-4-carbonitrile dihydrochloride} was synthesized (12). T-2328 inhibits the specific binding of [^{3}H][Sar^9,Met(O$_2$)^{11}]substance P to tachykinin NK_1 receptors with a K_i of 0.08 nM, while the affinities to NK_2 and NK_3 receptors were about 44,000 and 3,800 times lower than that for NK_1 receptors. Intravenous injection of T-2328 suppressed the foot-tapping response of gerbils induced by i.c.v. injection of GR73632. We performed the present study to investigate the anti-emetic efficacy of T-2328 against both acute and delayed emesis induced by cisplatin in ferrets.

Materials and Methods

Animals

Adult male ferrets (1.1 – 1.6 kg, n = 66; Marshall Farms, North Rose, NY, USA) were housed individually. Male gerbils (51 – 67 g, n = 12; Nippon SLC, Shizuoka) and male Hartley guinea pigs (275 – 450 g, n = 8; Nippon SLC) were housed as a group. All animals were maintained in a breeding room (lights on from 7:00 to 19:00) in which the room temperature was maintained at 23 ± 2°C for guinea pigs and gerbils or 25 ± 1°C for ferrets, and they had free access to drinking water. Gerbils and guinea pigs were allowed free access to standard laboratory chow and ferrets were fed a dry pellet diet (cat food: CS; Oriental Yeast, Tokyo). All animal experiments procedures were performed under the Guiding Principles for the Care and Use of Laboratory Animals by The Japanese Pharmacological Society and approved by the Animal Ethics Committee of Tanabe Seiyaku Co., Ltd.

Cisplatin-induced emesis in ferrets

Two hours before cisplatin treatment, ferrets were transferred to observation cages. Cisplatin was intraperitoneally (i.p.) injected under halothane anesthesia at doses of 5 and 10 mg/kg for experiments of delayed and acute emesis, respectively. Animal behavior was remotely recorded by a video camera (TK-N1100; Victor Company of Japan, Yokohama) and a recording system (HM-DR10000, Victor Company of Japan) for 72 and 24 h in delayed and acute emesis experiments, respectively. Emesis was characterized by rhythmic abdominal contractions that were either associated with oral expulsion of solid or liquid material from the gastrointestinal tract, that is. vomiting, or not associated with the passage of material, that is. retching movements (13). Each emetic episode was considered separate when the animal changed its location in the observation cage or when the interval between retches and/or vomits exceeded 5 s. Total number of emetic episodes was counted in each 1-h period during the experiment. In the delayed emesis experiments, T-2328 (0.03 – 1 mg/kg) and ondansetron dihydrochloride (0.3 – 3 mg/kg) were intravenously (i.v.) administered via a tail vein immediately or 40 h after cisplatin treatment. In the acute emesis experiments, T-2328 (0.03 mg/kg) and ondansetron dihydrochloride (0.1 – 1 mg/kg) were i.v. administered via a tail vein immediately after or 30 min before cisplatin treatment, respectively.

GR73632-induced foot tapping in gerbils

Male gerbils were briefly anesthetized by inhalation of halothane. An incision was made in the middle of scalp to expose the skull. GR73632 (5 pmol in 5 μl), an NK_1 agonist, was intra-cerebroventricularly (i.c.v.) administered by vertical insertion of a cuffed 25-gauge needle to 1-mm lateral and 4.5-mm below the bregma. Immediately following the recovery of the righting reflex, the duration of repetitive hind foot tapping was recorded for 5 min in a clear observation box (15.5 cm × 22 cm × 12 cm). For antagonist studies, T-2328 (1 mg/kg) was i.v. administered via a vein of the penis 4 or 24 h before the injection of GR73632 under halothane anesthesia. After the measurement, gerbils were sacrificed by an overdose of diethyl ether.

Contraction of guinea-pig ileum induced by [Sar^9,Met(O$_2$)^{11}]substance P

Male Hartley guinea pigs were killed by exsanguination. Segments (1.5 – 2.0 cm length) of longitudinal ileum smooth muscles were rapidly excised and suspended in organ baths containing 10 ml Tyrode buffer bubbled with a mixture of 95% O_2 and 5% CO_2 at 37°C. The composition of the Tyrode buffer is as follows: 137.9 mM NaCl, 2.7 mM KCl, 1.8 mM $CaCl_2$, 0.5 mM $MgCl_2$, 11.9 mM $NaHCO_3$, 0.5 mM NaH_2PO_4, and 5.6 mM glucose. The contraction of the tissues was monitored using an isometric transducer (AP-621G; Nihon Kohden, Tokyo) and recorded on a chart recorder (WR3701; Graphtec, Yokohama). After 40-min equilibration under initial tension of 1 g, the tissues were contracted with 10 nM [Sar^9,Met(O$_2$)^{11}]substance P with 20-min intervals. After the contraction of the tissue attained the maximum tension, the tissue was washed with fresh Tyrode solution for 3 times each. The tissues were treated with T-2328 at various concentrations 20 min before the third treatment with [Sar^9,Met(O$_2$)^{11}] substance P. Responses to the NK_1 agonist were

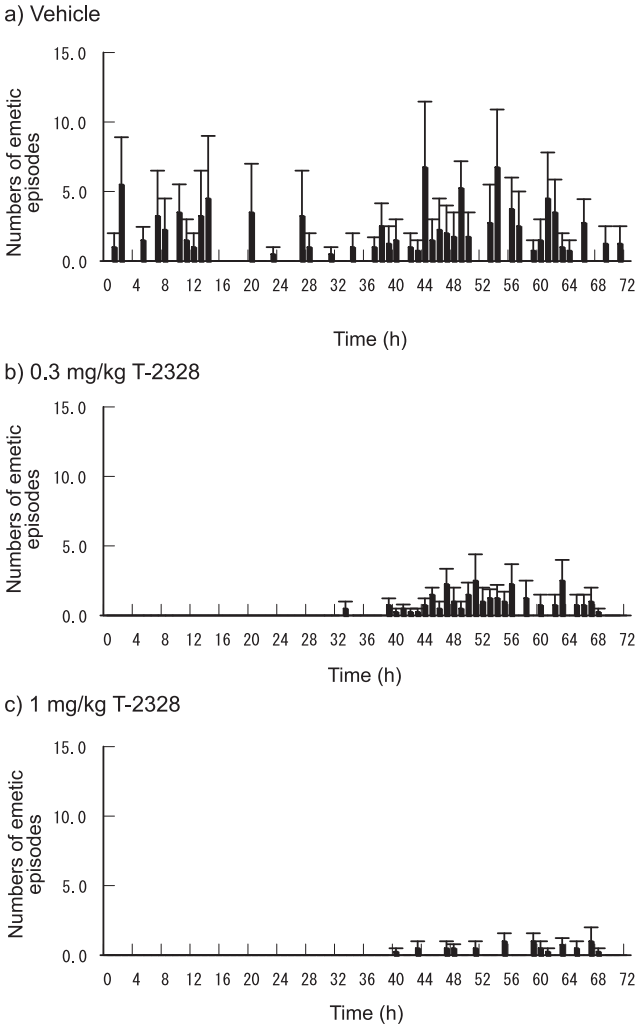

Fig. 1. Effect of T-2328 on the cisplatin (5 mg/kg, i.p.)–induced acute and delayed emesis in ferrets. Ferrets were intravenously treated with vehicle (a) or T-2328 (b, c) immediately after cisplatin administration. Results are shown as the means ± S.E.M. of emetic episodes in 1 h during a 72-h observation period from 4 animals per group.

expressed as the percentage of the second response. In the preliminary experiment, consistent contractions were elicited in at least 5 challenges with the NK_1 agonist. To examine the persistence of the effect, after washing out of T-2328, contractions to [Sar^9,$Met(O_2)^{11}$]substance P were examined twice with 20-min intervals between each. The IC_{50} value was calculated by non-linear regression analysis with GraphPad Prism software (GraphPad, San Diego, CA, USA).

Determination of plasma and brain concentration of T-2328

After the observation period in the cisplatin-induced emesis study in ferrets, blood samples were collected from the abdominal aorta using a heparinized syringe under halothane anesthesia and the brains were dissected out. Plasma and brain samples were stored at −80°C. Whole brains were homogenized with distilled water using a teflon homogenizer to prepare 20% brain homogenate. Following the extraction with cyclohexane /diethyl ether (1:1), the content of T-2328 was determined by HPLC (Shimadzu SPD-10A; Shimadzu, Kyoto).

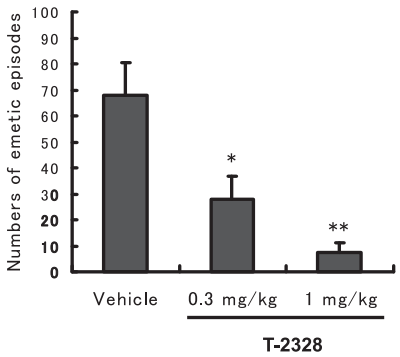

Fig. 2. Long-lasting effect of T-2328 on the emetic response induced by cisplatin (5 mg/kg, i.p.) in ferrets. Ferrets were intravenously treated with T-2328 or vehicle immediately after the cisplatin administration. Results are shown as the means ± S.E.M. of emetic episodes in a 24 – 72 h observation period from 4 animals per group. **P*<0.05, ***P*<0.01, compared with the vehicle.

Chemicals

T-2328 was synthesized at Tanabe Seiyaku Co., Ltd. (Osaka). [Sar^9,$Met(O_2)^{11}$]substance P (Tocris Bioscience, Ellisville, MO, USA), GR73632 (Research Biochemicals International, Natick, MA, USA), cisplatin [*cis*-platinum (II) diammine dichloride; Sigma-Aldrich, Inc., St. Louis, MO, USA], and ondansetron dihydrochloride (ZOFRAN INJECTION; Sankyo, Tokyo) were purchased from commercial sources.

Cisplatin was dissolved in saline at 70°C – 75°C followed by gradual cooling to 40°C – 50°C and i.p. administered in a volume of 5 ml/kg. Ondansetron dihydrochloride was diluted with saline and i.v. administered in a volume of 2 ml/kg. T-2328 was dissolved in DMSO and diluted with saline for in vivo studies (final concentration of DMSO: 1%) and with the Tyrode buffer in the isolated organ bath study. T-2328 was i.v. administered to gerbils and ferrets in the volume of 5 and 2 ml/kg, respectively.

Statistical analyses

Each value in the table and figures is a mean ± S.E.M. Statistical analysis was performed by means of Student's *t*-test or ANOVA followed by Dunnett's multiple comparison test. *P* values less than 0.05 were considered as statistically significant.

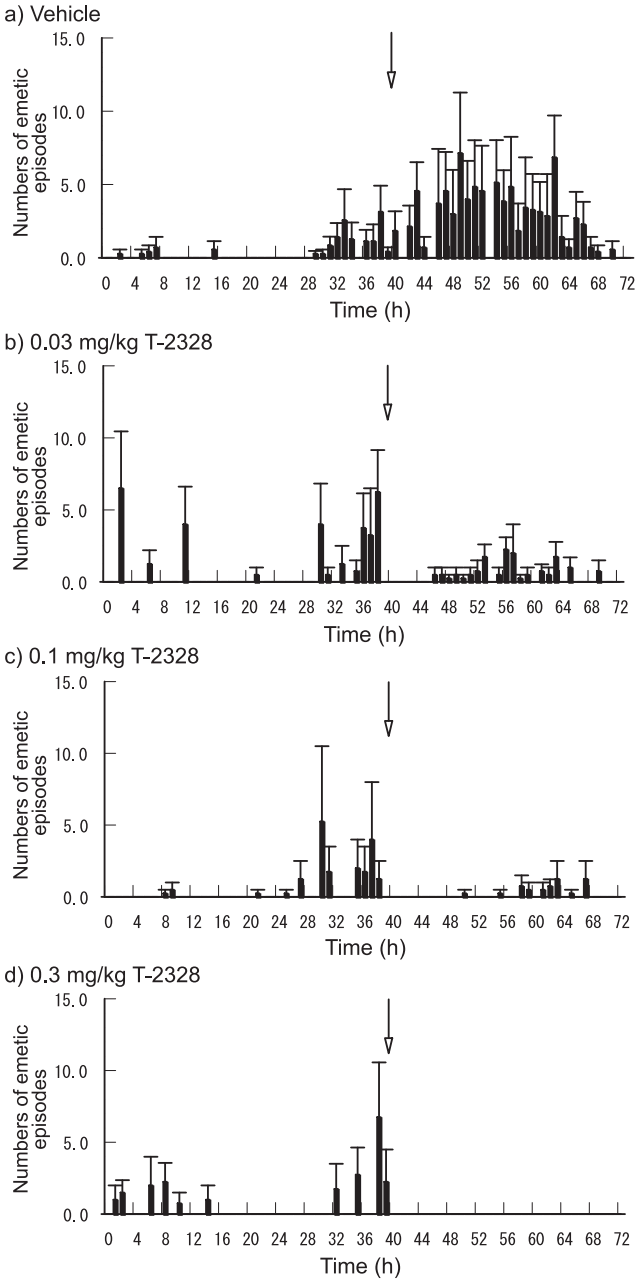

Fig. 3. Effect of T-2328 against the delayed emesis. Ferrets were intravenously treated with vehicle (a) or T-2328 (b – d) 40 h after the cisplatin administration. The arrows indicate the administration point of the vehicle or T-2328. Results are shown as the means ± S.E.M. of emetic episodes in 1 h during a 72-h observation period from 4 – 7 animals per group.

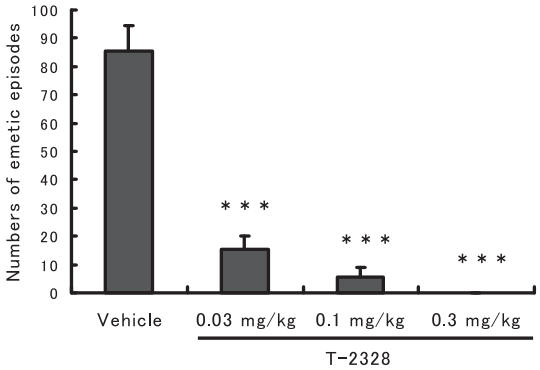

Fig. 4. Inhibitory effect of T-2328 on the cisplatin (5 mg/kg, i.p.)–induced delayed emesis in ferrets. Ferrets were intravenously treated with T2-2328 or vehicle 40 h after cisplatin administration. Results are shown as the means ± S.E.M. of emetic episodes in a 40 – 72 h period from 4 – 7 animals per group. ***P<0.001, compared with the vehicle.

Results

Acute and delayed emesis

Cisplatin at 5 mg/kg induced emetic responses with 31.3 ± 16.2 and 68.0 ± 12.5 episodes within the first 24 h and in the next 24 – 72 h period, respectively (Fig. 1a). Because the delayed emesis but not the acute emesis was consistently induced, effects on delayed emesis were analyzed with this dosage of cisplatin. I.v. administration of T-2328, at 0.3 or 1 mg/kg, immediately after cisplatin treatment, significantly inhibited the delayed emesis (Fig. 1: b, c and Fig. 2). The anti-emetic activity was further evaluated by administration at 40 h after the cisplatin treatment when the delayed emesis had already started (Fig. 3). T-2328 (0.03 – 0.3 mg/kg) dose-dependently reduced the delayed emetic episodes and completely prevented it at the dose of 0.3 mg/kg (Fig. 4). On the other hand, ondansetron (0.3 – 3 mg/kg) only transiently reduced the delayed emetic responses at 40 h after the cisplatin treatment (Fig. 5). The total number of emetic episodes during 40 – 72 h was not significantly different between vehicle and ondansetron treatment (Fig. 6).

Acute emesis

Higher dose of cisplatin (10 mg/kg) induced severe emetic responses during 0 – 4 h after administration (Fig. 7 and Table 1). About 80% of the episode occurred during the first 4 h in the 24-h observation period. Both T-2328 (0.03 mg/kg) and ondansetron (0.3, 1 mg/kg) almost completely blocked the emetic episodes during the first 4-h period. Ondansetron (0.3, 1 mg/kg) increased the number of emetic episodes during the 4 – 24 h period. In contrast, T-2328 extensively inhibited the emetic response also in the next 4 – 24 h period.

GR73632-induced foot tapping in gerbils

I.c.v. administration of NK_1 agonist stimulates NK_1 receptors in the brain and induces the foot tapping response in gerbils (14). T-2328 completely inhibited the foot tapping response when administered 4 h before

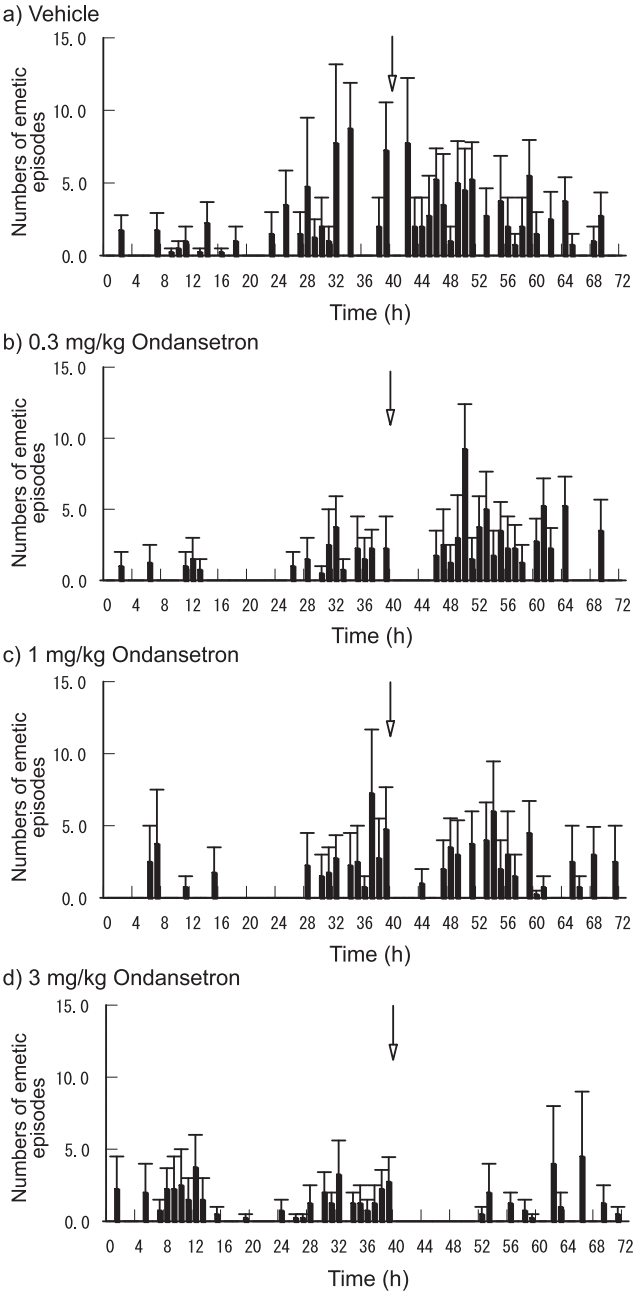

Fig. 5. Effect of ondansetron on the delayed emesis induced by cisplatin (5 mg/kg, i.p.) in ferrets. Ferrets were intravenously treated with vehicle (a) or ondansetron (b – d) 40 h after the cisplatin administration. The arrow indicates the administration point of vehicle or ondansetron. Results are shown as the means ± S.E.M. of emetic episodes in 1 h during a 72-h observation period from 4 animals per group.

the GR73632 injection (Table 2). The inhibition rate of T-2328 was 24.6% at 24 h after i.v. administration, although it was not statistically significant.

Plasma and brain concentrations of T-2328

Plasma and brain concentrations of T-2328 increased

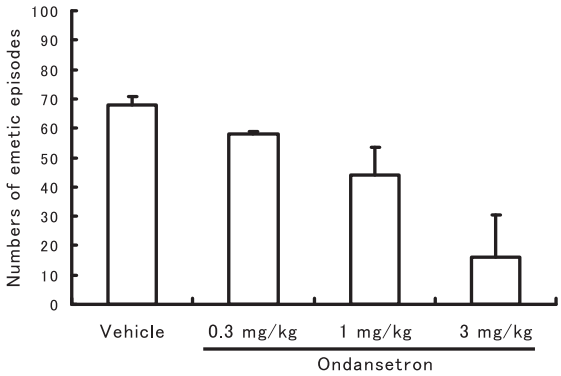

Fig. 6. Inhibitory effect of ondansetron on the cisplatin (5 mg/kg, i.p.)–induced delayed emesis in ferrets. Ferrets were intravenously treated with ondansetron or vehicle 40 h after cisplatin administration. Results are shown as the means ± S.E.M. of emetic episodes in a 40 – 72 h period from 4 animals per group.

in a dose-dependent manner in cisplatin-treated ferrets (Table 3). Since the molecular weight of T-2328 is 415.51, the brain levels with a 0.3 mg/kg dosage correspond to 41.6 and 19.0 nM at 32 and 72 h following the injection, respectively.

Contraction of guinea-pig ileum induced by [Sar^9,Met(O$_2$)^{11}]substance P

T-2328 concentration-dependently inhibited the contraction of guinea-pig ileum by [Sar^9,Met(O$_2$)^{11}]substance P (10 nM) (Fig. 8). The IC_{50} value of T-2328 was 1.4 nM. Repeated washing of the tissue with a fresh Tyrode buffer did not eliminate the inhibition.

Discussion

Induction of long-lasting emesis is a burden for patients with cancer chemotherapy (1). In ferrets, single administration of cisplatin at 5 mg/kg, i.p. induced emetic responses in acute (up to 24 h) and delayed (up to 72 h) phases. With a higher dose (10 mg/kg) of cisplatin, the emesis in the acute phase was more severe with the peak at the first 4 h in the 24-h observation period. Stimulation of the abdominal vagal afferent fibers via 5-HT$_3$ receptor triggers acute emesis (2), while the precise mechanism of delayed emesis is not fully revealed. Antagonists for the 5-HT$_3$ receptor have been shown to prevent the incidence of the acute emesis, but does not sufficiently decrease the incidence of delayed emesis in patients with chemotherapy (3). In this experiment, ondansetron only transiently reduced the incidence of delayed emesis at a dose of 3 mg/kg, although the acute emesis was almost completely suppressed at the dose of 0.3 mg/kg. Thus the cisplatin-induced acute and delayed emesis resembles the emetic

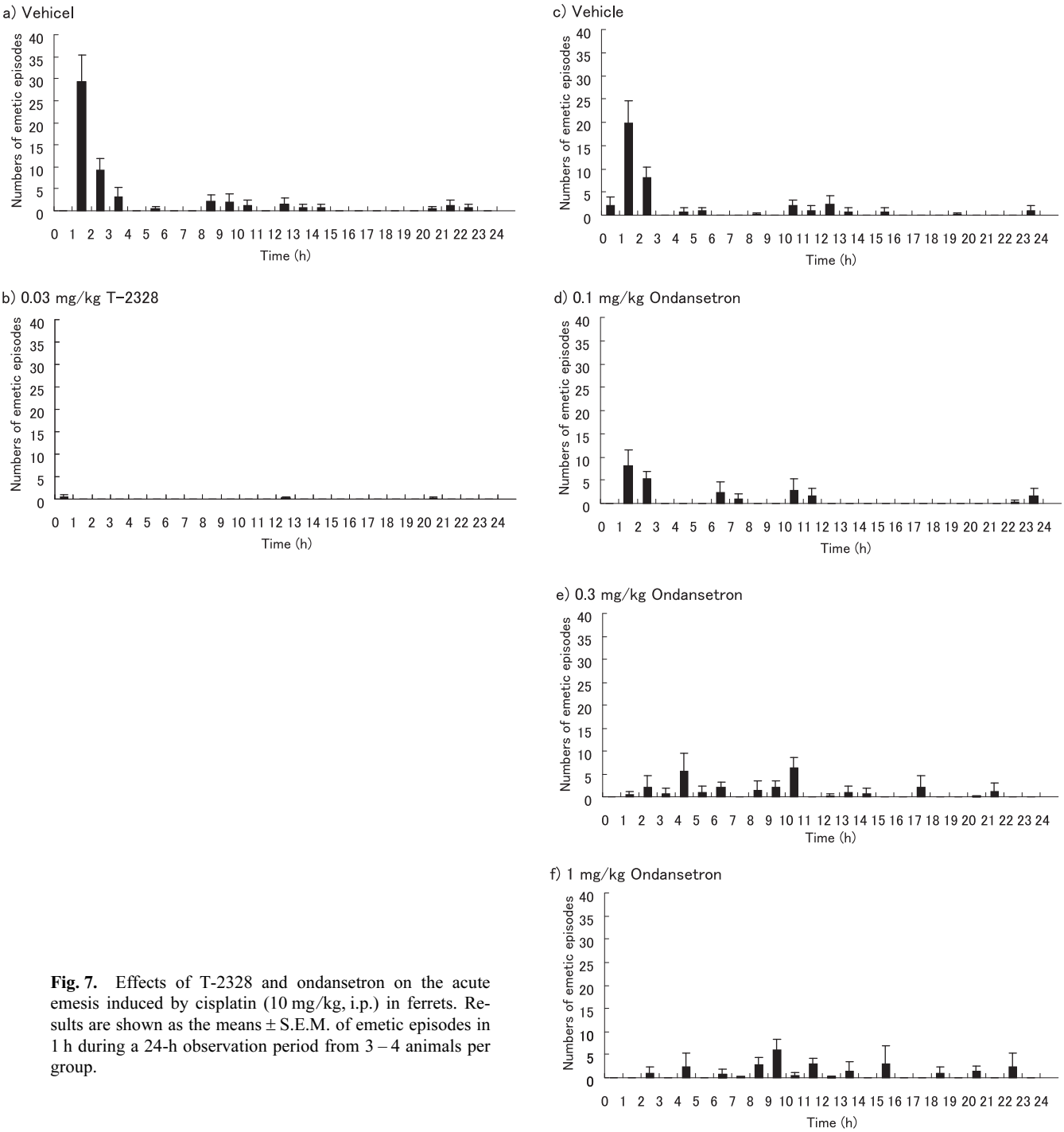

Fig. 7. Effects of T-2328 and ondansetron on the acute emesis induced by cisplatin (10 mg/kg, i.p.) in ferrets. Results are shown as the means ± S.E.M. of emetic episodes in 1 h during a 24-h observation period from 3 – 4 animals per group.

episodes in patients with cancer chemotherapy in terms of the time course and the response to a 5-HT_3 antagonist.

Involvement of substance P and its specific NK_1 receptors in vomiting has been documented by the presence of highly dense [^{3}H]substance P bindings in the solitary nucleus, a part of the vomiting center (4, 5). T-2328 is a potent and selective NK_1-receptor antagonist that penetrates into the central nervous system upon i.v. injection (12). The cisplatin (5 mg/kg, i.p.)–induced acute and delayed emetic episodes were greatly reduced by treatment with T-2328 (above 0.3 mg/kg). The acute emesis with a higher dose of cisplatin was also suppressed by T-2328 (0.03 mg/kg). When T-2328 (above 0.03 mg/kg) was administered at 40 h, that is, after the onset of delayed emesis, the incidence of emesis was blocked. In contrast, ondansetron suppressed the acute emesis (above 0.3 mg/kg) but did not suffi-

Table 1. Effects of T-2328 and ondansetron on the acute emesis induced by cisplatin (10 mg/kg, i.p.) in ferrets

Drugs		Numbers of emetic episodes	
		0–4 h	4–24 h
Vehicle		41.8 ± 7.0	11.5 ± 2.4
T-2328	0.03 mg/kg	0.5 ± 0.5**	0.5 ± 0.3**
Vehicle		29.8 ± 6.8	10.0 ± 3.7
Ondansetoron	0.1 mg/kg	13.3 ± 3.2	9.7 ± 2.9
	0.3 mg/kg	3.3 ± 2.0*	23.8 ± 13.9
	1 mg/kg	1.0 ± 1.0*	25.0 ± 11.4

Results represent the means ± S.E.M. of the emetic episodes in a 0 – 4 h period or a 4 – 24 h period during 24-h observation from 3 – 4 animals per group. *P<0.05, **P<0.01, compared with the vehicle.

Table 2. Inhibitory effect of T-2328 (1 mg/kg, i.v.) on GR73632 (i.c.v.)–induced foot tapping in gerbils

Time after administration	Tapping time (s)		Inhibiton (%)
	Vehicle	T-2328	
4 h	300.0 ± 0.0	0.0 ± 0.0	100
24 h	299.0 ± 0.4	226.3 ± 21.4	24.6

Gerbils were i.v. treated with T-2328 or vehicle at 4 or 24 h before GR73632 injection. Results represent the means ± S.E.M. of tapping time from 3 animals per group.

ciently decrease the delayed emesis (even at 3 mg/kg). Therefore suppression of the delayed emesis is unlikely due to elimination of the acute emesis. Also, the short plasma half-life of ondansetron might be concerned with the transient anti-emetic efficacy against the delayed emesis. However, the anti-emetic activity of 5-HT_3–receptor antagonists is poor by means of varying the dosing intervals, routes of administration, and combination therapy (15). Consequently, the results indicate that the NK_1 antagonist can control the incidence of emetic episodes in both acute and delayed phases in contrast to 5-HT_3 antagonists.

An i.c.v. administrated NK_1-receptor agonist induces a characteristic foot tapping response in gerbils. Since

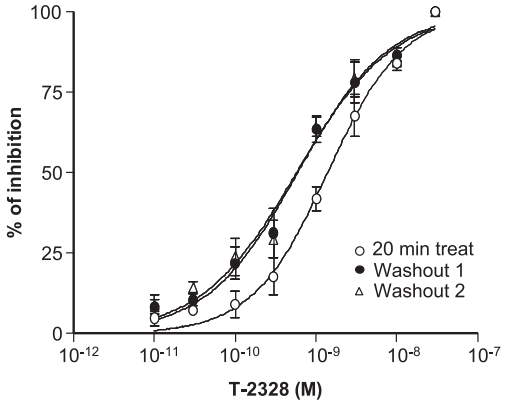

Fig. 8. Concentration-dependent effect of T-2328 on the [Sar^9,$Met(O_2)^{11}$]substance P–induced contraction in the guinea-pig ileum. The peak height of the NK_1 agonist–induced contractile response was expressed as percentage of the pre-drug treatment response. The contractile responses were assessed during the treatment with (open circle), after the first (closed circle), and second (open triangle) washout of T-2328. Each symbol and bar represents the mean ± S.E.M. of 4 preparations.

this readily quantifiable response is inhibited by brain-penetrating NK_1 antagonists, it is feasible to measure the brain NK_1-receptor activity with this model (14). Inhibition of central NK_1 receptors by T-2328 was thus assessed in NK_1 agonist–induced foot tapping of gerbils. T-2328 suppressed the foot tapping response for more than 24 h after i.v. injection, although there was no significant difference. Therefore, it is suggested that central NK_1 receptors were continuously inactive over 24 h after i.v. treatment with T-2328.

An appreciable amount of T-2328 was present in the brain at the end of the experiments on emesis. The brain levels of 19.0 to 41.6 nM were apparently over the IC_{50} of 1.4 nM to inhibit the NK_1 agonist–induced contraction of the ileum. However, since the plasma protein-binding ratio of T-2328 is over 99% (data not shown), it is uncertain whether the protein-unbound fraction is sufficient to antagonize the endogenous agonist throughout the experiment. Nevertheless, the presence in both plasma and brain may explain the long-lasting

Table 3. Concentrations in plasma and brain of T-2328 in cisplatin-treated ferrets

Dose (mg/kg)	Plasma and brain concentrations of T-2328			
	32 h after administration		72 h after administration	
	plasma (ng/ml)	brain (ng/g)	plasma (ng/ml)	brain (ng/g)
0.03	1.8 ± 1.1	6.0 ± 2.4		
0.1	4.0 ± 1.8	10.3 ± 1.3		
0.3	19.0 ± 11.2	17.3 ± 4.4	3.6 ± 1.9	7.9 ± 1.6
1			30.1 ± 22.7	27.6 ± 12.3

The values are each a mean ± S.E.M. (n = 4).

effect of T-2328.

The NK_1 agonist–induced contraction of the isolated guinea-pig ileum was inhibited by T-2328, and washing out of T-2328 did not restore the agonist-induced contractions. Thus T-2328 seems to inhibit the NK_1 receptor in an insurmountable manner. It has been documented that when the antagonist binds at the active site and is an insurmountable antagonist, the inhibition is apparently non-competitive. In accord with this, there was a non-competitive inhibition of human NK_1 receptor with T-2328 in the previous study (12). Thus it is likely that the brain NK_1 receptor is continuously suppressed even after the concentration of T-2328 is decreased. The long-lasting anti-emetic effect of T-2328 may be due to insurmountable inhibition of NK_1 receptors in addition to long-term maintenance of the level in the central nervous system.

In summary, T-2328 prevented the cisplatin-induced emesis in both acute and delayed phases. The long-lasting anti-emetic effect was not only due to the pharmacokinetic profile but also the pharmacodynatic profile of the compound. The treatment with an NK_1 antagonist like T-2328 may be a novel option for prevention of emesis, a major side effect associated with cancer chemotherapy.

Acknowledgments

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