The Effects of Orally Administered Y-25130, a Selective Serotonin3-Receptor Antagonist, on Chemotherapeutic Agent-Induced Emesis

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ABSTRACT—The antiemetic effects of orally administered Y-25130, a potent and selective 5-HT3-receptor antagonist, were compared with those of ondansetron, granisetron, metoclopramide and domperidone. Y-25130 (0.1–1.0 mg/kg) dose-dependently prolonged the latency to the first vomiting and decreased the number of vomitings induced by cisplatin in dogs. The antiemetic effect of Y-25130 against cisplatin-induced vomiting was more potent than that of metoclopramide and ondansetron, but it showed little difference from that of granisetron. The emesis induced by the combined treatment of doxorubicin and cyclophosphamide was also inhibited by Y-25130 (0.1–1 mg/kg) in ferrets. The antiemetic effect of Y-25130 was more potent than that of metoclopramide, almost the same as that of granisetron and less potent than that of ondansetron. Because of a notable difference of potency ranking between Y-25130 and ondansetron in these two tests, a third test was performed to evaluate the inhibitory effect of Y-25130 in ferrets on cisplatin-induced emesis in comparison with that of ondansetron. The antiemetic effect of Y-25130 on cisplatin-induced emesis in ferrets was very similar to that of ondansetron. Domperidone did not inhibit these cytotoxic agents-induced emeses. These results suggest that Y-25130 is an orally active antiemetic compound against cisplatin and doxorubicin/cyclophosphamide-induced emeses; and its the antiemetic potency is similar to those of granisetron and ondansetron, but superior to those of metoclopramide and domperidone.

Keywords: Y-25130, 5-HT3 receptor, Cisplatin, Doxorubicin/cyclophosphamide, Antiemesis

Cancer chemotherapeutic agents, for instance, cisplatin, doxorubicin and cyclophosphamide, used in the treatment of malignancies produce severe gastrointestinal side-effects such as nausea, vomiting and the accompanying gastrointestinal symptoms (1, 2). The dopamine-D2-receptor antagonist domperidone used in conventional antiemetic therapy has no effect against chemotherapeutic agents-induced emesis (3). A high dose of metoclopramide was reported to antagonize the serotonin (5-HT) M receptor (4) which was subsequently redesignated as the 5-HT3 receptor (5). Metoclopramide has antiemetic effects against chemotherapeutic agent-induced emesis; however, it can produce extrapyramidal side-effects which have been attributed to its dopamine receptor blocking activity (6). It is well known that the selective 5-HT3-receptor antagonists which do not have affinity for dopamine D2-receptor effectively inhibits chemotherapeutic agent-induced emesis in animals (7, 8) and humans (9, 10). A good correlation has been obtained between 5-HT3 antagonistic potency and antiemetic efficacy against chemotherapeutic agent-induced emesis (11).

(±)-N-(1-Azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine 8-carboxamide monohydrochloride (Y-25130) has a potent and selective 5-HT3-receptor antagonistic activity in vitro (12) and in vivo (13). Fukuda et al. reported that Y-25130 administered intravenously inhibited the chemotherapeutic agent-induced emesis more potently than metoclopramide in dogs and ferrets (14). In the present study, the antiemetic effect of Y-25130 administered orally against chemotherapeutic agent-induced emesis was examined in comparison with those of ondansetron, granisetron, metoclopramide and domperidone.

MATERIALS AND METHODS

Animals

Beagle dogs (Hazleton Research Products, Inc., Kalamazoo, MI, USA) of both sexes weighing 7.0–17.5 kg and male ferrets (Marshall Research Animals, Inc.,
North Rose, NY, USA) weighing 0.8–1.4 kg were used. Animals were housed in individual cages, and the animal quarters were maintained at 23±2°C, 55±5% humidity, and a 12-hr light/12-hr dark photocycle.

Drugs

Y-25130, ondansetron hydrochloride (ondansetron) and granisetron hydrochloride (granisetron) were prepared by the Yoshitomi Research Laboratories. Metoclopramide hydrochloride (metoclopramide) and cisplatin were purchased from Sigma (St. Louis, MO, USA). Domperidone and doxorubicin were obtained from Kyowa Hakko (Tokyo). Cyclophosphamide was obtained from Shionogi (Osaka). These drugs were dissolved in saline for intravenous injection and dissolved or suspended in saline for oral administration.

Cisplatin-induced emesis in dogs

The procedure used was a modification of the method described by Smith et al. (15). Dogs were starved for 22 hr and then fed for a 2-hr period before treatment with cisplatin (3 mg/kg, i.v.). The test drugs were administered orally 1 hr before the cisplatin injection, and then the number of vomitings were observed during the entire 24-hr period following the cisplatin injection. Animals were provided water ad libitum during the observation period and given commercial dog chow 21 hr after the cisplatin injection.

Doxorubicin/cyclophosphamide and cisplatin-induced emesis in ferrets

The procedure used was a modification of the method described by Bermudez et al. (8). The catheter was implanted into the jugular vein of a ferret about 24 hr before the experiment. Then the ferrets were starved and fed for a 2-hr period before the treatment with emetic agents. Doxorubicin (6 mg/kg) followed by cyclophosphamide (80 mg/kg) or cisplatin (8 mg/kg) was administered intravenously via the catheter. The test drugs were administered orally 1 hr before the injection of these cytotoxic drugs, and then the ferrets were observed for vomitings and retchings for 24 hr (doxorubicin/cyclophosphamide) or 5 hr (cisplatin). They were provided water ad libitum during the observation period and given commercial ferret chow about 19 hr after doxorubicin/cyclophosphamide injection.

Statistical analyses

Results are expressed as the mean±S.E.M. and analyzed by a one-way analysis of variance followed by the Least-Significant-Difference (LSD) method.

RESULTS

Cisplatin-induced emesis in dogs (Table 1)

Cisplatin (3 mg/kg, i.v.)-induced vomiting in all dogs treated with saline. Y-25130 (0.1–1 mg/kg) dose-dependently inhibited the vomiting and completely prevented the vomiting for 24 hr after cisplatin injection in five out of nine dogs at 0.3 mg/kg. Six of nine dogs at 1 mg/kg did not vomit for 24 hr, and the other dogs vomited only 1–3 times 18–22 hr after the cisplatin injection. Granisetron (0.3–3 mg/kg) dose-dependently prevented the vomiting. Ondansetron at 0.3 mg/kg did not decrease the number of vomitings, although it prolonged the latency to the first vomiting. At 1 and 3 mg/kg, ondansetron in-

Table 1. The effect of drugs on cisplatin-induced emesis in dogs

| Drugs          | Dose (mg/kg, p.o.) | Number of dogs (vomiting/tested) | Latency to first vomiting (hr) | Number of vomitings |
|---------------|-------------------|---------------------------------|-------------------------------|---------------------|
| Control       |                   | 9/9                             | 2.2±0.1                       | 9.3±1.4             |
| Y-25130       | 0.1               | 6/9                             | 13.3±3.4**                    | 2.8±1.3**           |
|               | 0.3               | 4/9                             | 17.9±3.1**                    | 2.1±1.0**           |
|               | 1.0               | 3/9                             | 22.9±0.6**                    | 0.7±0.4**           |
| Granisetron   | 0.3               | 7/9                             | 9.1±3.2*                      | 5.7±1.5*            |
|               | 1.0               | 6/9                             | 19.3±2.3**                    | 1.7±0.7**           |
|               | 3.0               | 4/9                             | 21.3±1.9**                    | 1.0±0.4**           |
| Ondansetron   | 0.3               | 9/9                             | 4.0±1.4                       | 9.6±1.8             |
|               | 1.0               | 5/9                             | 20.7±2.2**                    | 1.6±0.6**           |
|               | 3.0               | 6/9                             | 15.6±3.3**                    | 2.3±1.0**           |
| Metoclopramide| 10.0              | 7/9                             | 9.5±3.4*                      | 4.0±1.4**           |
| Domperidone   | 10.0              | 6/6                             | 1.7±0.1                       | 14.3±3.0*           |

The test drug was administered p.o. at 1 hr before the cisplatin injection. *P<0.05, **P<0.01: significantly different from the vehicle control. If a dog did not vomit, the latency was taken as equal to the observation time (24 hr after the cisplatin injection). Each value indicates the mean±S.E.
hibited the number of vomitings. The weak antiemetic effect was observed by metoclopramide at 10 mg/kg, while domperidone at 10 mg/kg increased the number of vomitings. Each vomiting time course for 24 hr after administration of Y-25130 (0.3, 1 mg/kg), granisetron (0.3, 1), ondansetron (0.3, 1), metoclopramide (10) and domperidone (10) is illustrated in Fig. 1.

| Drugs    | Doses (mg/kg, p.o.) | No. | 8 | 16 | 24hr | Total vomits |
|----------|---------------------|-----|---|----|------|-------------|
| Control  |                     |     |   |    |      |             |
|          | 1                   |     |   |    |      |             |
|          | 2                   |     |   |    |      |             |
|          | 3                   |     |   | 1  | 1    | (5)         |
|          | 4                   |     |   | 1  | 1    | (7)         |
|          | 5                   |     |   |    |      | (13)        |
|          | 6                   |     |   |    |      | (15)        |
|          | 7                   |     |   |    |      | (6)         |
|          | 8                   |     |   |    |      | (7)         |
|          | 9                   |     |   |    |      | (10)        |
|          |                     |     |   |    |      | (3)         |
| Y-25130  |                     |     |   |    |      |             |
|          | 1                   |     |   | 1  | 1    | (4)         |
|          | 2                   |     |   | 1  | 1    | (2)         |
|          | 3                   |     |   |    |      | (3)         |
|          | 4                   |     |   |    |      | (6)         |
|          | 5                   |     |   |    |      | (8)         |
|          | 6                   |     |   |    |      | (10)        |
|          | 7                   |     |   |    |      | (9)         |
|          | 8                   |     |   |    |      | (19)        |
|          | 9                   |     |   |    |      | (3)         |
| Granisetron |                   |     |   |    |      |             |
|          | 1                   |     |   | 1  | 1    | (9)         |
|          | 2                   |     |   | 1  | 1    | (10)        |
|          | 3                   |     |   |    |      | (10)        |
|          | 4                   |     |   |    |      | (10)        |
|          | 5                   |     |   |    |      | (10)        |
|          | 6                   |     |   |    |      | (10)        |
|          | 7                   |     |   |    |      | (10)        |
|          | 8                   |     |   |    |      | (10)        |
|          | 9                   |     |   |    |      | (10)        |
| Ondansetron |                  |     |   |    |      |             |
|          | 1                   |     |   | 1  | 1    | (3)         |
|          | 2                   |     |   | 1  | 1    | (17)        |
|          | 3                   |     |   |    |      | (10)        |
|          | 4                   |     |   |    |      | (10)        |
|          | 5                   |     |   |    |      | (10)        |
|          | 6                   |     |   |    |      | (10)        |
|          | 7                   |     |   |    |      | (10)        |
|          | 8                   |     |   |    |      | (10)        |
|          | 9                   |     |   |    |      | (10)        |
| Metoclopramide |               |     |   |    |      |             |
|          | 1                   |     |   | 1  | 1    | (1)         |
|          | 2                   |     |   | 1  | 1    | (11)        |
|          | 3                   |     |   |    |      | (5)         |
|          | 4                   |     |   |    |      | (3)         |
|          | 10                  |     |   |    |      | (10)        |
|          | 5                   |     |   |    |      | (10)        |
|          | 6                   |     |   |    |      | (10)        |
|          | 7                   |     |   |    |      | (10)        |
|          | 8                   |     |   |    |      | (10)        |
|          | 9                   |     |   |    |      | (10)        |
| Domperidone |               |     |   |    |      |             |
|          | 1                   |     |   | 1  | 1    | (29)        |
|          | 2                   |     |   | 1  | 1    | (12)        |
|          | 3                   |     |   |    |      | (12)        |
|          | 4                   |     |   |    |      | (9)         |
|          | 5                   |     |   |    |      | (10)        |
|          | 6                   |     |   |    |      | (14)        |

Fig. 1. The effect of test drugs on cisplatin-induced vomiting in dogs. Test drugs were administered 1 hr before injection of cisplatin, and vomitings were observed for 24 hr. Each point (■) represents one vomiting, and the total vomitings are indicated on the right side.
Table 2. The effect of drugs on doxorubicin/cyclophosphamide-induced emesis in ferrets

| Drugs       | Dose (mg/kg, p.o.) | Number of ferrets (vomiting/tested) | Latency to first vomiting (hr) | Number of vomitings | Number of retchings |
|-------------|--------------------|-------------------------------------|-------------------------------|---------------------|---------------------|
| Control     |                    | 6/6                                 | 0.7±0.1                       | 19.0±3.8            | 91.0±13.3           |
| Y-25130     | 0.1                | 6/6                                 | 1.1±0.2                       | 11.7±2.8*           | 42.5±14.1*          |
|             | 0.3                | 3/6                                 | 15.4±4.5**                    | 2.3±1.5**           | 9.2±4.7**           |
|             | 1.0                | 0/6                                 | >24**                         | 0**                | 0**                |
| Granisetron | 0.1                | 4/6                                 | 9.6±4.6*                      | 3.2±1.3**           | 18.3±7.7**          |
|             | 0.3                | 3/6                                 | 12.9±5.0**                    | 4.0±2.6**           | 24.0±19.0**         |
|             | 1.0                | 1/6                                 | 20.8±3.2**                    | 0.3±0.3**           | 1.0±0.8**           |
| Ondasetron  | 0.1                | 5/6                                 | 5.4±3.7                       | 8.8±3.1*            | 52.5±21.3*          |
|             | 0.3                | 0/6                                 | >24**                         | 0**                | 0**                |
| Metoclopramide | 10.0             | 6/6                                 | 2.1±0.2                       | 8.3±3.5**           | 47.3±22.2*          |
| Domperidone | 10.0               | 4/4                                 | 0.6±0.1                       | 12.5±3.4            | 80.3±27.6           |

The test drug was administered p.o. at 1 hr before the doxorubicin/cyclophosphamide injection. *P<0.05, **P<0.01: significantly different from the vehicle control. If a ferret did not vomit, the latency was taken as equal to the observation time (24 hr after the doxorubicin/cyclophosphamide injection). Each value indicates the mean±S.E.

Table: The effect of drugs on doxorubicin/cyclophosphamide-induced emesis in ferrets

| Drugs       | Dose (mg/kg, p.o.) | No. | 0     | 8     | 16    | 24 hr | Total vomiting-retches |
|-------------|--------------------|-----|-------|-------|-------|-------|-------------------------|
| Control     |                    |     |       |       |       |       |                         |
|             | 1                  |     |       |       |       |       | (17–48)                |
|             | 2                  |     |       |       |       |       | (16–10)                |
|             | 3                  |     |       |       |       |       | (30–122)               |
|             | 4                  |     |       |       |       |       | (12–10)                |
|             | 5                  |     |       |       |       |       | (30–110)               |
|             | 6                  |     |       |       |       |       | (7–104)                |
| Y-25130     | 0.3                |     |       |       |       |       |                         |
|             | 1                  |     |       |       |       |       |                         |
|             | 2                  |     |       |       |       |       |                         |
|             | 3                  |     |       |       |       |       |                         |
|             | 4                  |     |       |       |       |       |                         |
|             | 5                  |     |       |       |       |       |                         |
|             | 6                  |     |       |       |       |       |                         |
|             | 1.0                |     |       |       |       |       |                         |
|             | 2                  |     |       |       |       |       |                         |
|             | 3                  |     |       |       |       |       |                         |
|             | 4                  |     |       |       |       |       |                         |
|             | 5                  |     |       |       |       |       |                         |
|             | 6                  |     |       |       |       |       |                         |
| Granisetron | 0.3                |     |       |       |       |       |                         |
|             | 1                  |     |       |       |       |       |                         |
|             | 2                  |     |       |       |       |       |                         |
|             | 3                  |     |       |       |       |       |                         |
|             | 4                  |     |       |       |       |       |                         |
|             | 5                  |     |       |       |       |       |                         |
|             | 6                  |     |       |       |       |       |                         |
| Ondasetron  | 0.1                |     |       |       |       |       |                         |
|             | 1                  |     |       |       |       |       |                         |
|             | 2                  |     |       |       |       |       |                         |
|             | 3                  |     |       |       |       |       |                         |
|             | 4                  |     |       |       |       |       |                         |
|             | 5                  |     |       |       |       |       |                         |
|             | 6                  |     |       |       |       |       |                         |
| Metoclopramide | 10.0            |     |       |       |       |       |                         |
|             | 1                  |     |       |       |       |       |                         |
|             | 2                  |     |       |       |       |       |                         |
|             | 3                  |     |       |       |       |       |                         |
|             | 4                  |     |       |       |       |       |                         |
| Domperidone | 10.0               |     |       |       |       |       |                         |
|             | 1                  |     |       |       |       |       |                         |
|             | 2                  |     |       |       |       |       |                         |
|             | 3                  |     |       |       |       |       |                         |
|             | 4                  |     |       |       |       |       |                         |

Fig. 2. The effect of test drugs on doxorubicin/cyclophosphamide-induced emesis in ferrets. Test drugs were administered 1 hr before injection of doxorubicin/cyclophosphamide, and vomitings and retchings were observed for 24 hr. Each point (■) represents one vomiting or retching, and total vomitings and retchings are indicated on the right side.
Doxorubicin and cyclophosphamide-induced emesis in ferrets (Table 2)

The combined treatment of doxorubicin (6 mg/kg, i.v.) and cyclophosphamide (80 mg/kg, i.v.) induced consistent vomiting and retchings in all ferrets treated with saline. Y-25130 at 0.1 mg/kg significantly prevented the emetic episodes, and complete prevention was observed at 1 mg/kg. Similar complete prevention was obtained by ondansetron at 0.3 mg/kg. Granisetron at 0.1 mg/kg significantly inhibited the number of emetic episodes; however, complete prevention was not observed even at 1 mg/kg. Metoclopramide at the high dose (10 mg/kg) exhibited the weak antiemetic effect, while domperidone failed to prevent the emetic episode. Each vomiting time course for 24 hr after administration of Y-25130 (0.3, 1 mg/kg), granisetron (0.3, 1), ondansetron (0.1, 0.3), metoclopramide (10) and domperidone (10) is illustrated in Fig. 2.

Cisplatin-induced emesis in ferrets (Table 3)

In the preliminary test, by 24 hr after the injection of cisplatin (8 mg/kg), some animals had died. Therefore, we chose a 5-hr observation period in this experiment. Cisplatin induced vomiting and retching in all ferrets treated with saline. Y-25130 (0.1–1 mg/kg) dose-dependently inhibited the vomiting and retching, and it completely prevented the vomiting in five out of six ferrets at 1 mg/kg. Ondansetron at 0.3 and 1 mg/kg inhibited cisplatin-induced emesis to almost the same extent as Y-25130 at 0.3 and 1 mg/kg, respectively.

DISCUSSION

The present findings clearly demonstrate that Y-25130 is an orally active antiemetic agent that works against cisplatin-induced emesis as well as doxorubicin and cyclophosphamide-induced emeses. In blocking cisplatin-induced emesis in dogs, Y-25130 is more potent than ondansetron, metoclopramide and domperidone, and is not much different from granisetron. Doxorubicin and cyclophosphamide were used as the other chemotherapeutic agents in addition to cisplatin in ferrets. In blocking doxorubicin/cyclophosphamide-induced emesis in ferrets, Y-25130 is more potent than metoclopramide, almost the same as granisetron and less potent than ondansetron.

Some differences in the antiemetic potency ranking of Y-25130 and ondansetron between cisplatin-induced emesis in dogs and doxorubicin/cyclophosphamide-induced emesis in ferrets were observed. Therefore, to clearly define the reason for these differences, the inhibitory effect of Y-25130 in ferrets on cisplatin-induced emesis was compared with that of ondansetron. In ferrets, the antiemetic effect of ondansetron against cisplatin-induced emesis was almost the same as that of Y-25130. It has been reported that ondansetron was easily metabolized in dogs (16), but not in ferrets (17) and humans (16). The elimination half-lives of ondansetron were about 0.5 hr in dogs, 2.5 hr in ferrets and 3.2 hr in humans. In the case of Y-25130, the half-lives were about 2.0 hr in dogs and 5.4 hr in humans (M. Isobe et al., personal communication). Although the antiemetic activities of the drug metabolites are unknown, this may be one reason why the antiemetic activity of ondansetron was comparatively weaker in dogs than in ferrets. When the antiemetic activity of a 5-HT3-receptor antagonist is examined in dogs, we need to pay close attention to its pharmacokinetic properties. At this time, further study is needed to determine if ondansetron shows stronger antiemetic activity against doxorubicin/cyclophosphamide than against cisplatin.

In the 5-HT3-receptor affinity to the synaptic membranes of the rat's cerebral cortex (12, 18), the 5-HT3-receptor antagonism of Y-25130 is at least the same as those of ondansetron and granisetron. A good correlation has been obtained between 5-HT3-receptor antagonis-

| Drugs     | Dose (mg/kg, p.o.) | Number of ferrets (vomiting/tested) | Latency to first vomiting (hr) | Number of vomitings | Number of retchings |
|-----------|--------------------|------------------------------------|--------------------------------|---------------------|---------------------|
| Control   |                    | 6/6                                | 1.5±0.1                        | 12.0±3.8            | 55.8±14.2          |
| Y-25130   | 0.1                | 4/6                                | 2.9±0.7*                       | 8.2±3.3             | 37.0±16.7          |
|           | 0.3                | 2/6                                | 3.9±0.7**                      | 3.5±2.3**           | 10.0±6.5**         |
|           | 1.0                | 1/6                                | 5.0±0.01**                     | 0.5±0.5**           | 2.0±1.3**          |
| Ondansetron| 0.3                | 4/6                                | 3.2±0.6*                       | 4.3±2.0*            | 11.5±6.5**         |
|           | 1.0                | 1/6                                | 4.9±0.1**                      | 1.2±1.2**           | 2.5±2.5**          |

The test drug was administered p.o. and 1 hr before the cisplatin injection. *P<0.05, **P<0.01: significantly different from the vehicle control. If a ferret did not vomit, the latency was taken as equal to the observation time (5 hr after the cisplatin injection). Each value indicates the mean±S.E.
tic potency and antiemetic efficacy against chemotherapeutic agents-induced emesis (11). These results imply that the efficacy of Y-25130 as an antiemetic agent against cisplatin- and doxorubicin/cyclophosphamide-induced emesis is not much different from those of ondansetron and granisetron.

Most studies on the antiemetic activities of 5-HT$_3$-receptor antagonists have been conducted with only a 3 to 5 hr observation period (11, 15, 19). To evaluate the antiemetic activity of the test drugs during a longer period, we have observed the vomiting for 24 hr after the treatment of dogs with cisplatin and ferrets with doxorubicin/cyclophosphamide. The antiemetic duration of the action of Y-25130 is not much different from that of ondansetron and granisetron. It was observed that the dogs treated with 5-HT$_3$-receptor antagonists tended to vomit about 20 hr after cisplatin injection. The remaining food in the stomach and intestine of acutely unvomitted dogs might have some relevance to the late vomittings, whereas further study is needed to determine this point.

It is well known that dopamine D$_2$-receptors do not have a major role in chemotherapeutic agents-induced emesis (3). Domperidone, a selective dopamine-D$_2$-receptor antagonist, which has been widely prescribed to treat nausea and vomiting resulting from gastrointestinal disorders, did not inhibit the cisplatin- or the doxorubicin/cyclophosphamide-induced emesis. The reason why domperidone increased the number of vomitings in cisplatin-induced emesis in dogs is not clear; however, there might be some relevance to the toxicity study in dogs where much higher doses of domperidone induced vomiting (20). High doses of metoclopramide showed weak antiemetic effects, but this can be explained by 5-HT$_3$-receptor antagonism of metoclopramide (4). Y-25130 is a selective 5-HT$_3$-receptor antagonist (12, 13, 18), and the lack of affinity of this compound for dopamine D$_2$-receptors indicated that Y-25130 is free of the extrapyramidal side-effects associated with metoclopramide and domperidone.

In conclusion, the present study suggests that the potent and selective 5-HT$_3$-receptor antagonist Y-25130 is expected to become an orally active antiemetic agent against cisplatin- and doxorubicin/cyclophosphamide-induced emesis, and its antiemetic potency is not much different from those of granisetron and ondansetron, but superior to those of metoclopramide and domperidone.

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