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ORIGINAL PAPER

Theoretical evaluation of antiemetic effects of 5-HT_3 receptor antagonists for prevention of vomiting induced by cisplatin

Hironori Nakamura · Haruko Yokoyama · Risa Takayanagi · Koichi Yoshimoto · Akihiro Nakajima · Kiyoshi Okuyama · Osamu Iwase · Yasuhiko Yamada

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Abstract 5-HT_3 receptor antagonists are widely used as antiemetic agents in clinical setting, of which palonosetron, with a long elimination half life ($t_{1/2}$), has recently become available. It is important to evaluate the concentration of serotonin when investigating the antiemetic effects of 5-HT_3 receptor antagonists, as those effects are not based solely on the $t_{1/2}$ value. We theoretically evaluated the antiemetic effects of three 5-HT_3 receptor antagonists (granisetron, azasetron, palonosetron) on cisplatin-induced nausea and vomiting by estimating the time course of the 5-HT_3 receptor occupancy of serotonin. We estimated the 5-HT_3 receptor occupancy of serotonin in the small intestine, based on the time course of plasma concentration of each 5-HT_3 receptor antagonist and the time course of concentration of serotonin near the 5-HT_3 receptor in the small intestine after administration of cisplatin. The antiemetic effect of each 5-HT_3 receptor antagonist was evaluated based on the normal level of 5-HT_3 receptor occupancy of serotonin. Our results suggest that an adequate antiemetic effect will be provided when a dose of 75 mg/m^2 of cisplatin is given to patients along with any single administration of granisetron, azasetron, or palonosetron at a usual dose. On the other hand, the 5-HT_3 receptor occupancy of serotonin was found to be significantly lower than normal for several days after administration of palonosetron, as compared to granisetron and azasetron, indicating that constipation may be induced. Our results show that granisetron, azasetron, and palonosetron each have an adequate antiemetic effect after administration of 75 mg/m^2 of cisplatin.

Keywords 5-HT_3 receptor antagonist · Antiemetic effect · Constipation · Cisplatin · 5-HT_3 receptor occupancy of serotonin

H. Nakamura · H. Yokoyama · R. Takayanagi · Y. Yamada (✉)
Department of Clinical Evaluation of Drug Efficacy, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1, Horinouchi, Hachioji, Tokyo 192-0392, Japan
e-mail: yamada@ps.toyaku.ac.jp

K. Yoshimoto · K. Okuyama
Department of Pharmacy, Tokyo Medical University Hachioji Medical Center, 1163, Tate-machi, Hachioji, Tokyo 193-0998, Japan

A. Nakajima · O. Iwase
Department of Hematology, Tokyo Medical University Hachioji Medical Center, 1163, Tate-machi, Hachioji, Tokyo 193-0998, Japan

1 Introduction

Chemotherapy-induced nausea and vomiting (CINV) can lead to discontinuation of treatment, decrease the quality of life of patients, and is an important complication in clinical settings. One of the main mechanisms of acute CINV is the activation of 5-HT_3 receptors by serotonin, which exists on vagus nerve afferent fibers in the small intestine mucous membrane. Following administration of an antineoplastic agent, serotonin is released from enterochromaffin cells, which bind to and stimulate 5-HT_3 receptors on adjacent vagal afferent nerves. Depolarization of the vagal afferent nerves stimulates the vomiting center in the brainstem and eventually induces a vomiting reflex (Andrews et al. 1988). Therefore, 5-HT_3 receptor antagonists are widely used as antiemetic agents in clinical settings. Recently, palonosetron, which has a long elimination half life ($t_{1/2}$), became available for prevention of CINV. Thus, its antiemetic effects are expected to persist for a long period. Cisplatin is

ranked in highly emetogenic antineoplastic agent and must be used concomitant with antiemetic drugs. It is recommended in all guidelines that the 5-HT_3 receptor antagonist should be administered for the patient receiving a single injection of cisplatin on day 1 only (Basch et al. 2011), since the vomiting induced by cisplatin is high in day 1 only. Therefore, it is important to evaluate the antiemetic effects of the various 5-HT_3 receptor antagonists, which have different $t_{1/2}$, on the nausea and vomiting induced by a single injection of cisplatin.

We consider that the concentration of serotonin near the 5-HT_3 receptor in the small intestine is an indicator of the degree of emetic action induced by antineoplastic agent. Therefore, it is important to determine concentration of both serotonin and the 5-HT_3 receptor antagonist for evaluation of the antiemetic effect associated with the 5-HT_3 receptor antagonist. In addition, we already reported that the 5-HT_3 receptor occupancy of serotonin after concomitant administration of antineoplastic agent and the 5-HT_3 receptor antagonist became a useful index for prediction of the antiemetic effect of the 5-HT_3 receptor antagonist (Nakamura et al. 2013; Yamada et al. 2004).

In the present study, we evaluated the antiemetic effects of granisetron, azasetron, and palonosetron after administration of cisplatin by estimating the time course of 5-HT_3 receptor occupancy of serotonin based on the time courses of urinary 5-HIAA/Creatinine (Cre) ratio and plasma concentration of each of those 5-HT_3 receptor antagonists.

2 Methods

We estimated the time course of 5-HT_3 receptor occupancy of serotonin in the small intestine with or without administration of three different 5-HT_3 receptor antagonists, based on the time courses of plasma concentration of each antagonist and concentration of serotonin near the 5-HT_3 receptor in the small intestine after administration of cisplatin. We hypothesized that emesis will be induced when the estimated 5-HT_3 receptor occupancy of serotonin in the small intestine is higher than normal. Thus, the antiemetic effect of each 5-HT_3 receptor antagonist was evaluated based on the normal level of 5-HT_3 receptor occupancy of serotonin.

2.1 Analysis of time courses of plasma concentration of 5-HT_3 receptor antagonists

The data of plasma concentration after an intravenous infusion for 30 min of granisetron were used. To estimate the pharmacokinetic parameters of α, V_1, k_{10}, k_{21}, and β, the time courses of the plasma concentration of granisetron (40 μg/kg) (Kumakura et al. 1990) during and after intravenous infusion were simultaneously fitted to Eqs. 1 and 2 using the nonlinear least-squares methods. Equations 1 and 2 show the time course of plasma concentration during and after administration, respectively, using the following 2-compartment pharmacokinetic model.

$$C_p(t) = \frac{k_0}{W \cdot V_1 \cdot k_{10}} \left\{ 1 + \frac{(\beta - k_{10})}{(\alpha - \beta)} \cdot \cdot \exp(-\alpha \cdot t) + \frac{(k_{10} - \alpha)}{(\alpha - \beta)} \cdot \exp(-\beta \cdot t) \right\} \quad (1)$$

$$C_p(t) = \frac{k_0 \cdot (k_{21} - \alpha) \cdot \{\exp(-\alpha \cdot T) - 1\}}{W \cdot V_1 \cdot \alpha \cdot (\alpha - \beta)} \cdot \exp(-\alpha \cdot t') + \frac{k_0 \cdot (\beta - k_{21}) \cdot \{\exp(-\beta \cdot T) - 1\}}{W \cdot V_1 \cdot \beta \cdot (\alpha - \beta)} \cdot \exp(-\beta \cdot t') \quad (2)$$

where, α (h^{-1}), β (h^{-1}), C_p (ng/mL), V_1 (L/kg), k_{10} (h^{-1}), k_{12} (h^{-1}), k_{21} (h^{-1}), and t' (h, $t = t' + T$) represent the elimination rate constant of the distribution phase, elimination rate constant of the elimination phase, plasma concentration of granisetron, central distribution volume per weight, elimination rate constant of granisetron, rate constant to the peripheral compartment from the central compartment, rate constant to the central compartment from the peripheral compartment, and time after finishing administration, respectively. Here, the relationship among α, β, and k_{10}, k_{12}, k_{21} was expressed as $\alpha + \beta = k_{10} + k_{12} + k_{21}$, $\alpha \cdot \beta = k_{10} \cdot k_{21}$. Furthermore, the values used for infusion rate (k_0) (ng/h), weight (W) (kg), total infusion time (T) (h), and dosage of granisetron (D) (μg) were 4,780,000 ng/h, 59.75 kg, 0.5 h, and 2390 μg, respectively, in a phase I clinical trial (Kumakura et al. 1990). We used the usual dose (3 mg/body) to estimate the 5-HT_3 receptor occupancy of serotonin, since a linear relationship can be observed between the dose administered and plasma concentration of granisetron.

The data of plasma concentration after an intravenous bolus administration of azasetron or palonosetron were used. To estimate the pharmacokinetic parameters of α, V_1, k_{21}, and β, the time course of the plasma concentrations (Igarashi et al. 1992; Shah et al. 2006) of azasetron (10 mg/body) and palonosetron (10 μg/kg) after intravenous administration, we used Eq. 3 with the nonlinear least-squares method.

$$C_p(t) = \frac{D \cdot (k_{21} - \alpha)}{W \cdot V_1 \cdot (\beta - \alpha)} \cdot \exp(-\alpha \cdot t) + \frac{D \cdot (k_{21} - \beta)}{W \cdot V_1 \cdot (\alpha - \beta)} \cdot \exp(-\beta \cdot t) \quad (3)$$

We used the usual dose values (azasetron 10 mg/body, palonosetron 0.75 mg/body) for estimating the 5-HT_3 receptor occupancy of serotonin, since a linear

relationship can be observed between the dose administered and their plasma concentrations.

2.2 Analysis of 5-HT$_3$ receptor occupancy of serotonin in small intestine

Serotonin is rapidly metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase and aldehyde dehydrogenase, and then subsequently excreted in urine. Moreover, it has been reported that there is a relationship between the cumulative frequency of vomiting and cumulative amount of urinary excretion of 5-HIAA after administration of cisplatin (50 mg/m^2) (Cubeddu et al. 1990). Therefore, the urinary concentration of 5-HIAA is considered to be suitable as an indicator of the degree of emetic action (Yamada et al. 2007), but not the plasma concentration of serotonin.

Accordingly, we searched other reports regarding 5-HIAA/Cre ratios in urine before and after administration of high-dose cisplatin (>75 mg/m^2), and used those values in our analysis.

To estimate the parameters of H, k_e, and k_r, the time course of the urinary 5-HIAA/Cre ratio after intravenous administration of cisplatin was fitted to Eq. 4 using the nonlinear least-squares method. The concentration of serotonin near the 5-HT$_3$ receptor in the small intestine was calculated using the estimated parameters and Eq. 5 (Yamada et al. 2007).

$$C_u(t) = H \cdot \{\exp(-k_e \cdot t) - \exp(-k_r \cdot t)\} + C_u^0 \quad (4)$$

$$C_s(t) = \frac{C_{is} \cdot f_s \cdot C_u(t)}{C_u^0} \quad (5)$$

where, $C_u(t)$ (μg/mg Cre), H (μg/mg Cre), k_e (h^{-1}), k_r (h^{-1}), C_u^0 (μg/mg Cre), and $C_s(t)$ (nM) represent the urinary 5-HIAA/Cre ratio, constant of proportion, elimination rate constant of serotonin, free rate constant of serotonin, normal urinary concentration of 5-HIAA/Cre, and concentration of serotonin near the 5-HT$_3$ receptor in the small intestine, respectively. Furthermore, the values used for normal concentration of serotonin in the small intestine (C_{is}) (nM) and ratio of normal concentration of free serotonin to all serotonin in the small intestine (f_s) were 850 nM (Resnick and Gray 1961) and 0.01 (Cubeddu et al. 1992), respectively.

To estimate the 5-HT$_3$ receptor occupancy of serotonin in the small intestine without administration of a 5-HT$_3$ receptor antagonist (Φ_s), the concentration of serotonin near the 5-HT$_3$ receptor in the small intestine was substituted in Eq. 6. Moreover, the plasma concentration of the 5-HT$_3$ receptor antagonist and concentration of serotonin near the 5-HT$_3$ receptor in the small intestine were substituted in Eq. 7, to estimate the 5-HT$_3$ receptor occupancy of serotonin in the small intestine with a 5-HT$_3$ receptor antagonist (Φ_s^D).

$$\Phi_s(t) = \frac{C_s(t)}{K_I^s + C_s(t)} \cdot 100 \quad (6)$$

$$\Phi_s^D(t) = \frac{C_s(t)}{K_I^s \cdot \left(1 + \frac{C_p(t) \cdot f_u}{K_I^A}\right) + C_s(t)} \cdot 100 \quad (7)$$

where, Φ_s (%), Φ_s^D (%), f_u, and K_I^A represent the 5-HT$_3$ receptor occupancy of serotonin in the small intestine without a 5-HT$_3$ receptor antagonist, that with a 5-HT$_3$ receptor antagonist, the value for the plasma unbound fraction for a 5-HT$_3$ receptor antagonist, and the 5-HT$_3$ receptor dissociation constant of a 5-HT$_3$ receptor antagonist, respectively. Furthermore, the value used for the 5-HT$_3$ receptor dissociation constant of serotonin (K_I^S) (nM) was 150 nM (Sakamori et al. 1992).

2.3 Analysis

We used the MLAB nonlinear least-squares program (Civilized Software Inc., Maryland, USA) for analysis. In addition, the dose of the 5-HT$_3$ receptor antagonist was changed to dose per body weight when body weight was 60 kg.

3 Results

3.1 Analysis of time courses of plasma concentration of 5-HT$_3$ receptor antagonists

The time course of the plasma concentration of granisetron (40 μg/kg) after administration in the phase I clinical trial is shown in Fig. 1a. The symbol shows the observed value and the line shows the fitted curve, and they were well matched. The estimated pharmacokinetic parameters of α, β, V_1, k_{21}, and k_{10} for granisetron were 4.26 ± 0.71 (h^{-1}), 0.22 ± 0.02 (h^{-1}), 63.28 ± 6.77 (L), 1.52 ± 0.25 (h^{-1}), and 0.96 ± 0.33 (h^{-1}), respectively.

The time course of the plasma concentration of azasetron (10 mg/body) after administration in the phase I clinical trial is shown in Fig. 1b. The symbol shows the observed value and the line shows the fitted curve, and they were well matched. The estimated pharmacokinetic parameters α, β, V_1, and k_{21} for azasetron were 10.62 ± 0.70 (h^{-1}), 0.21 ± 0.02 (h^{-1}), 33.77 ± 1.07 (L), and 1.61 ± 0.12 (h^{-1}), respectively.

The time course of the plasma concentration of palonosetron (10 μg/kg) after administration in the phase I clinical trial is shown in Fig. 1c. The symbol shows the observed value and the line shows the fitted curve, and they

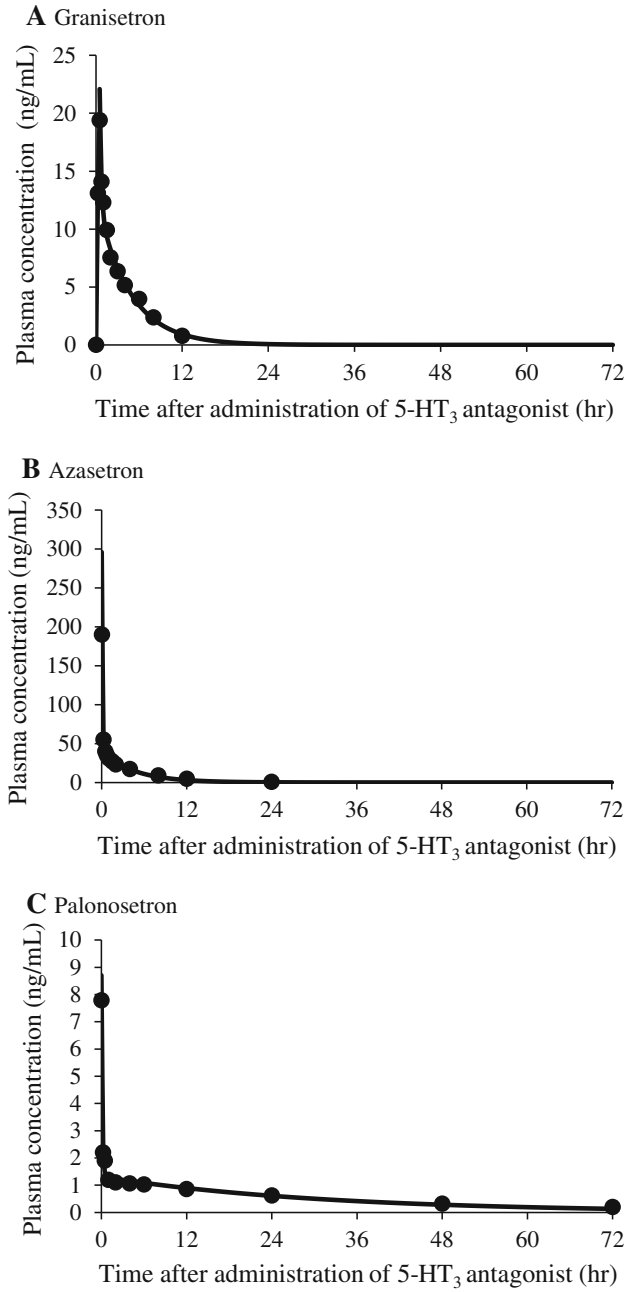

Fig. 1 Plasma concentration after intravenous administration of **a** granisetron (40 μg/kg), **b** azasetron (10 mg/body), **c** palonosetron (10 μg/kg)

were well matched. The estimated pharmacokinetic parameters α, β, V_1, and k_{21} for palonosetron were 7.89 ± 0.93 (h^{-1}), 0.03 ± 0.01 (h^{-1}), 72.36 ± 2.21 (L), and 1.22 ± 0.20 (h^{-1}), respectively.

3.2 Analysis of 5-HT_3 receptor occupancy of serotonin in small intestine

We performed a literature search regarding the 5-HIAA/Cre ratio in urine before and after a single administration of high-dose cisplatin (>75 mg/m^2), and found results in three different studies, which reported cisplatin doses of 75 mg/m^2 (Cubeddu et al. 1992), 78 ± 7 mg/m^2 (du Bois et al. 1996), and 75 ± 5 mg/m^2 (Cubeddu 1996). The time courses of urinary 5-HIAA/Cre ratio after intravenous administration of cisplatin in each study and the fitted curve are shown in Fig. 2. The fitted curve was well matched to the observed data. The estimated parameters H, k_e, k_r and C_u^0 were 202.27 ± 387.25 (μg/mg Cre), 0.22 ± 0.04 (h^{-1}), 0.26 ± 0.05 (h^{-1}) and 4.77 ± 0.03 (μg/mg Cre).

The time course of the estimated 5-HT_3 receptor occupancy of serotonin in the small intestine without administration of a 5-HT_3 receptor antagonist (Φ_s) is shown in Fig. 3. Our findings indicated induction of emesis, since the 5-HT_3 receptor occupancy of serotonin without a 5-HT_3 receptor antagonist was higher than normal (gray area in Fig. 3).

The time courses of the estimated 5-HT_3 receptor occupancy of serotonin in the small intestine with each 5-HT_3 receptor antagonist (Φ_s^D) are shown in Fig. 4. Our findings suggest that an adequate antiemetic effect was provided by each, because the 5-HT_3 receptor occupancies of serotonin were lower than normal (gray area in Fig. 4) even when a 5-HT_3 receptor antagonist was administered. Moreover, the 5-HT_3 receptor occupancy of serotonin in the small intestine with granisetron or azasetron returned to a normal level for 30–40 h after administration, whereas that with palonosetron continued at below normal for several days after administration. The 5-HT_3 receptor occupancy of serotonin in the small intestine with palonosetron was lower than normal (28.5 % of normal) at 72 h after administration.

4 Discussion

In clinical settings, 5-HT_3 receptor antagonists are widely used as antiemetic agents. In the present study, we

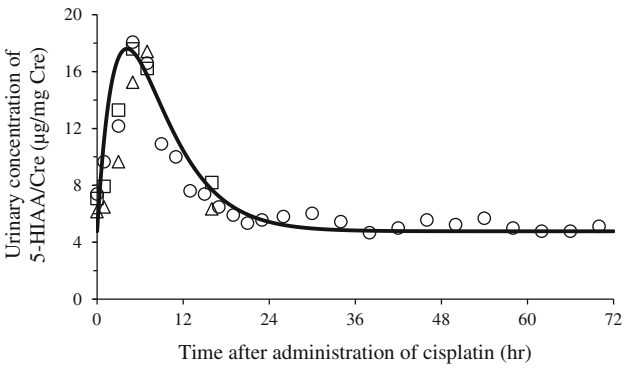

Fig. 2 Urinary concentration of 5-HIAA/Cre after administration of cisplatin. *Unfilled circle*; (Cubeddu et al. 1992), *unfilled triangle*; (du Bois et al. 1996), *unfilled square*; (Cubeddu 1996)

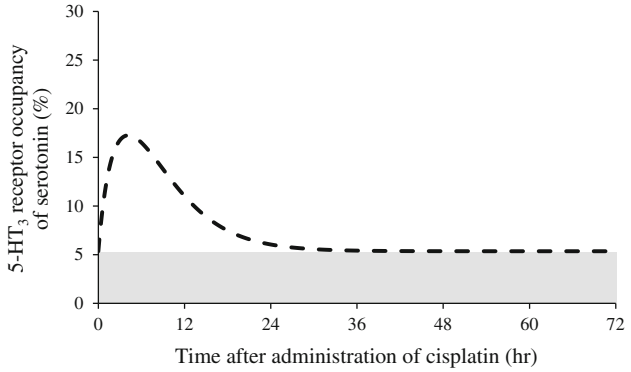

Fig. 3 5-HT_3 receptor occupancy of serotonin (Φ_s) after administration of cisplatin without 5-HT_3 receptor antagonist. *Gray area*; normal 5-HT_3 receptor occupancy of serotonin

evaluated the antiemetic effects of granisetron, azasetron, and palonosetron for cisplatin-induced nausea and vomiting based on the time course of the 5-HT_3 receptor occupancy of serotonin.

A literature search regarding the ratio of 5-HIAA/Cre in urine before and after a single administration of high-dose cisplatin (>75 mg/m^2) found three different studies that reported those values. The time courses of the urinary 5-HIAA/Cre ratio after intravenous administration of cisplatin showed similar profiles and the parameters for serotonin were estimated. Another report noted that the ratio of 5-HIAA/Cre in urine at 2–10 h after administration in patients given high-dose cisplatin was significantly higher than that in patients administered a low dose (Cubeddu et al. 1992). Thus, it was considered that the releasing behavior of serotonin differs based on the dosage of cisplatin and we concluded that it was appropriate to estimate the 5-HT_3 receptor occupancy of serotonin using these values of estimated parameters in those three studies, which presented similar doses.

The 5-HT_3 receptor occupancy of serotonin without administration of a 5-HT_3 receptor antagonist was estimated from the concentration of serotonin near the 5-HT_3 receptor after a single administration of cisplatin, which was higher than the normal level. Thus, emesis induction was suggested, even though the value at 24 h after administration had returned to the level before administration in every study. du Bois et al. reported that the urinary 5-HIAA/Cre ratio returned to a normal level within 24 h after administration of cisplatin, which did not increase from 24 to 72 h after administration (du Bois et al. 1996). Consequently, it was speculated that emesis was not induced by serotonin 24 h after administration. On the other hand, it has been reported that the risk of induced emesis was increased until 24 h and later after administration of cisplatin (Martin 1996). The early increasing risk of induced emesis (<24 h) is mainly by the action of

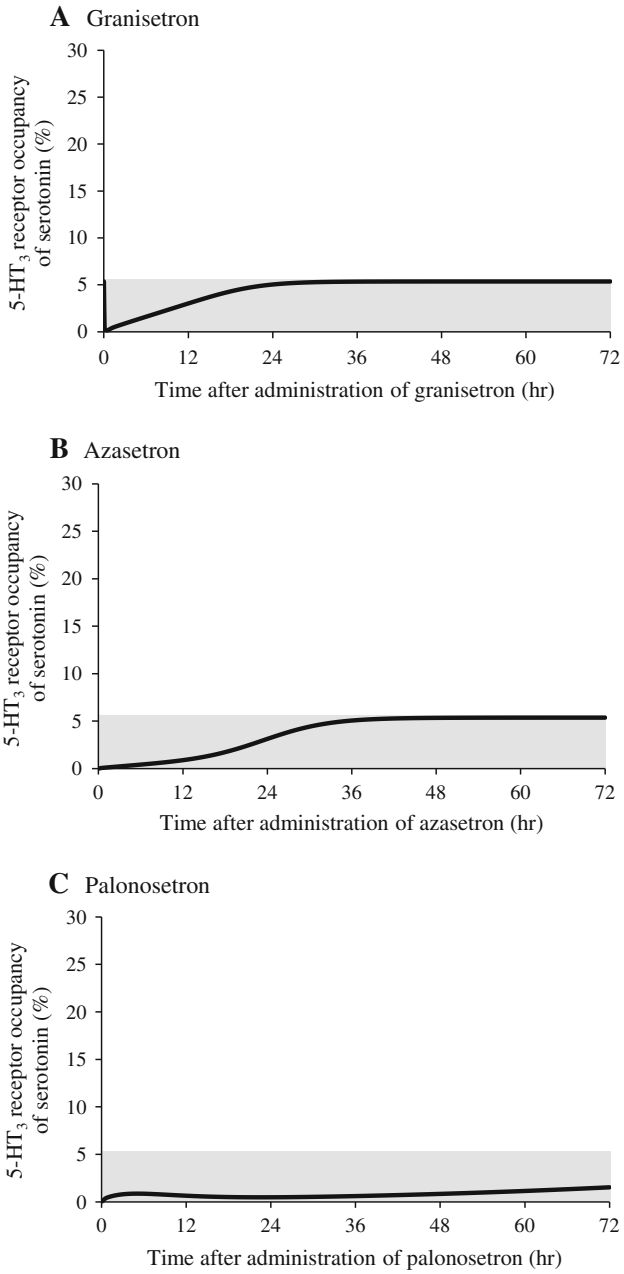

Fig. 4 5-HT_3 receptor occupancies of serotonin (Φ_s^D) after administration of cisplatin with granisetron (**a**), azasetron (**b**), or palonosetron (**c**). *Gray area*; normal 5-HT_3 receptor occupancy of serotonin

serotonin, because the urinary 5-HIAA/Cre ratio was increased until 24 h after administration of cisplatin. On the other hand, the later increasing risk of induced emesis (>24 h) is mainly the action of substance P, as its concentration was increased 24 h after administration of cisplatin.

The 5-HT_3 receptor occupancy of serotonin (Φ_s^D) in the small intestine with a 5-HT_3 receptor antagonist was estimated based on the time course of plasma concentration of each 5-HT_3 receptor antagonist and time course of

concentration of serotonin near the 5-HT_3 receptor in the small intestine after administration of cisplatin; that value was lower than normal, regardless of the 5-HT_3 receptor antagonist administered. Although the $t_{1/2}$ value for each 5-HT_3 receptor antagonist was different, an adequate antiemetic effect was obtained for emesis induced by cisplatin (75 mg/m^2) with a single administration of the 5-HT_3 receptor antagonist at a usual dose. In contrast, the releasing behavior of serotonin differs by type and dosage of the antineoplastic agents (Cubeddu et al. 1992; Cubeddu 1996). Thus, it is necessary to investigate each regimen used for chemotherapy. Our results indicate that an adequate antiemetic effect was provided when a dose of 75 mg/m^2 of cisplatin was administered, when granisetron, azasetron, or palonosetron was given at a usual dose.

The 5-HT_3 receptor occupancy of serotonin in the small intestine with granisetron or azasetron returned to normal for 30–40 h after administration, while that with palonosetron was lower than normal (28.5 % of normal) at 72 h after administration. Side effects caused by low 5-HT_3 receptor occupancy of serotonin should be considered, because serotonin is an endogenous and physiologically active substance. One of those side effects is constipation. The percentage of cases of constipation induced by granisetron, azasetron, and palonosetron in clinical trials is reported to be 0.17 % (1/584), 0.19 % (1/516), and 16.5 % (222/1343), respectively. Furthermore, Zhou et al. reported that constipation was increased in 39 % of patients treated with palonosetron (Likun et al. 2011). Also, the appearance of constipation in the palonosetron group was significantly higher than that in the first-generation 5-HT_3 receptor antagonist group (e.g., granisetron) (Likun et al. 2011). In the present study, the 5-HT_3 receptor occupancy of serotonin at 72 h after administration of cisplatin (75 mg/m^2) with palonosetron (0.75 mg/body) was only 28.5 % of normal. These results suggest that a continuous low level of 5-HT_3 receptor occupancy of serotonin is associated with incidence of constipation.

5 Conclusion

We found that an adequate antiemetic effect would be provided when a dose of 75 mg/m^2 of cisplatin was given and the patient received a single administration of granisetron, azasetron, or palonosetron at a normal dose. Furthermore, the 5-HT_3 receptor occupancy of serotonin was found to be significantly lower than the normal level for several days after administration of palonosetron, as compared to granisetron and azasetron, which may induce constipation. In the future, it will be important to examine the antiemetic effects of 5-HT_3 receptor antagonists with other antineoplastic agents.

Conflict of interest The authors declare no conflict of interest.

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