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ORIGINAL ARTICLE

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Receptor occupancy theory-based analysis of antiemetic effects and standard doses of 5-HT_3 receptor antagonists in cancer patients

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Abstract *Purpose*: The aim of this study was to determine the usefulness of receptor occupancy theory-based analysis using pharmacokinetic and pharmacodynamic parameters for predicting the average receptor occupancy (Φ_B) in humans of each of five 5-HT_3 antagonists administered at standard doses. *Methods*: The relationship between the Φ_B value and the complete vomiting inhibition rate after a single intravenous administration of cisplatin (not less than 50 mg/m^2) was analyzed. *Results*: The predicted Φ_B values after intravenous administration and oral administration of 5-HT_3 antagonists were more than 65% and 50%, respectively, suggesting that relatively high receptor occupancy is required to elicit sufficient antiemetic effects of 5-HT_3 antagonists. Moreover, significant ($P < 0.05$) linear relationships were found between Φ_B values and complete vomiting inhibition rates of 5-HT_3 antagonists in preventive cisplatin therapy, with correlation coefficients higher than 0.9, suggesting that the 5-HT_3 receptor occupancy is an appropriate index of clinical efficacy of 5-HT_3 antagonists, with higher receptor occupancy indicating more extensive antiemetic action. *Conclusion*: The receptor occupancy theory-based analysis of the antiemetic effect of a 5-HT_3 receptor antagonist used in this study should be very useful for not only estimating a rational dosage regimen but also determining the standard dose of a new drug using experimental data obtained in a preclinical study.

Keywords 5-HT_3 receptor · Occupancy · 5-HT_3 antagonist · Antiemetic effect · Cisplatin

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Introduction

Nausea and vomiting are common and distressing side effects associated with chemotherapy for malignant disease and are the principal cause of discontinuation of cancer chemotherapy. Prevention of these side effects is important for ensuring continuation of chemotherapy and for improving patient quality of life [1–6]. One of the main mechanisms of nausea and vomiting induced by antineoplastic agents is activation of 5-HT_3 receptors, which exist on vagus nerve afferent fibers in the small intestine mucous membrane [7–10]. Antineoplastic drugs have been shown to elicit direct effects on the intestine and to induce the release of serotonin from enterochromaffin cells in the small intestinal mucosa, where more than 90% of the total body serotonin is contained. It is thought that released serotonin stimulates vagal afferent fibers through 5-HT_3 receptors located in the vagal afferent terminals in the gastrointestinal tract and initiates sensory signals to the area postrema and the emetic center, thereby initiating nausea and vomiting. 5-HT_3 antagonists competitively inhibit serotonin at its specific binding sites, 5-HT_3 receptors, and thereby elicit an antiemetic effect. Therefore, receptor occupancy may be a more appropriate indicator of the antiemetic activity of a 5-HT_3 antagonist than its dose or blood concentration.

In this study, we analyzed receptor occupancy (Φ_B) of 5-HT_3 antagonists by integrating pharmacokinetic and

receptor-binding kinetic parameters published in the literature based on receptor occupancy theory [11–13, 31–34] in order to quantitatively determine the relationship between Φ_B and antiemetic efficacy.

Materials and methods

Pharmacokinetic and pharmacodynamic parameters of 5-HT_3 antagonists

The area under the plasma concentration-time curve ($AUC_{0-\infty}$) [14–22] and value of the plasma unbound fraction (f_u) [23–27] of both parenteral preparations (granisetron hydrochloride, ondansetron hydrochloride, azasetron hydrochloride, and ramosetron hydrochloride) and oral preparations (granisetron hydrochloride, ondansetron hydrochloride, azasetron hydrochloride, ramosetron hydrochloride, and tropisetron hydrochloride) of 5-HT_3 antagonists were obtained from the reported data of a phase I clinical trial. The value of the pharmacodynamic parameter receptor dissociation constant (K_I) of each drug was obtained from reported results of in vitro binding inhibition experiments using radioactive ligands in the cerebral cortex of rats [28–30]. The dose stated in the product package insert of each drug for use in Japan was taken as the standard dose of each drug.

Calculation of receptor occupancy of 5-HT_3 antagonists

5-HT_3 antagonists bind to receptors by competing with serotonin, which is an agonist for 5-HT_3 receptors, and the efficacy of the antagonists is elicited by displacement of serotonin from 5-HT_3 receptors [13]. These molecular interactions can be represented as follows:

$$A + R \rightleftarrows AR, \quad K_A = A \times R/AR \tag{1}$$

$$B + R \rightleftarrows BR, \quad K_B = B \times R/BR \tag{2}$$

where R is the concentration of unoccupied receptors, A and B are the effective (unbound) concentrations of an agonist (serotonin) and an antagonist near 5-HT_3 receptors, respectively, and K_A and K_B represent the dissociation constants of the agonist and antagonist, respectively. The total receptor concentration (R_0) is the sum of the occupied and unoccupied receptors:

$$R_0 = R + AR + BR \tag{3}$$

The occupancy of 5-HT_3 receptors by the antagonists (Φ_B) can be expressed by the following equation:

$$\Phi_B = \frac{BR}{R_0} \times 100 \tag{4}$$

Substitution of Eqs. 1–3 into Eq. 4 gives the following equation:

$$\Phi_B = \frac{B}{K_B(1 + A/K_A) + B} \times 100 \tag{5}$$

Therefore, Φ_B can be predicted from the drug concentration near receptors and dissociation constants. The concentration of a 5-HT_3 antagonist near receptors (B) was approximated by the unbound drug concentration in plasma (Cp^f, nanomoles), since it can be assumed that drug transfer across capillary vessels is due to simple diffusion and there is no active transport process. Plasma unbound drug concentrations at steady-state (Css^f) were calculated from $AUC_{0-\infty}$ and f_u after intravenous or oral administration of each drug at the standard dose. Metabolites of each 5-HT_3 antagonist were not taken into consideration in this study, since their contribution to antiemetic efficacy is considered to be small. On the other hand, Φ_B should vary with change in concentration of serotonin (A) as an agonist. It was assumed that the value of A was smaller than that of K_A (150 n *M*) ($A \ll K_A$) [28] and that its variation after administration of a 5-HT_3 antagonist would not affect the value of Φ_B. Accordingly, Φ_B could be predicted by the following equation:

$$\Phi_B = \frac{B}{K_B + B} \times 100 = \frac{Cp^f}{K_B + Cp^f} \times 100 \tag{6}$$

Relationship between receptor occupancy of 5-HT_3 antagonists and antiemetic action after administration of cisplatin

We analyzed the relationship between the average receptor occupancy of 5-HT_3 antagonists (Φ_B) predicted as described above and antiemetic effects. We obtained complete vomiting inhibition rates from the antiemetic effects observed with preventive and curative intravenous administration and with preventive oral administration of 5-HT_3 antagonists after a single intravenous administration of cisplatin (not less than 50 mg/m^2) found in clinical studies conducted in Japan [35–45]. It was also assumed that each drug examined acted as a complete antagonist, and the antiemetic effect (E_B) of a 5-HT_3 antagonist after administration of an antineoplastic agent could therefore be expressed as a function of Φ_B.

$$E_B = f(\Phi_B) \tag{7}$$

Results

Pharmacokinetic and pharmacodynamic parameters of 5-HT_3 antagonists

$AUC_{0-\infty}$, f_u, and K_I values of each 5-HT_3 antagonist at standard (curative) doses obtained from the literature are shown in Tables 1 and 2. Table 1 summarizes the

Table 1 Pharmacokinetic and pharmacodynamic parameters of four parenteral 5-HT_3 antagonists

Drug	Dose (mg)[a]	$AUC_{0-\infty}$ (ng h/ml)	f_u	K_I (n*M*)
Granisetron hydrochloride	3	63.06 [14]	0.33 [23]	0.41 [28]
Ondansetron hydrochloride	4	153.2 [15]	0.12 [24]	1.3 [28]
Ramosetron hydrochloride	0.3	18.71 [16]	0.09 [25]	0.033 [29]
Azasetron hydrochloride	10	247.1 [17]	0.69 [26]	0.54 [28]

[a]Average/standard dose.

Table 2 Pharmacokinetic and pharmacodynamic parameters of five oral 5-HT_3 antagonists

Drug	Dose (mg)[a]	$AUC_{0-\infty}$ (ng h/ml)	f_u	K_I (n*M*)
Granisetron hydrochloride	2	46.51 [18]	0.33 [23]	0.41 [28]
Ondansetron hydrochloride	4	74.8 [19]	0.12 [24]	1.3 [28]
Ramosetron hydrochloride	0.1	2.895 [20]	0.09 [25]	0.033 [29]
Azasetron hydrochloride	10	215.1 [21]	0.69 [26]	0.54 [28]
Tropisetron hydrochloride	5	60.8 [22]	0.4 [27]	1.03 [30]

[a]Average/standard dose.

parameters for parenteral drugs, and Table 2 summarizes the parameters for oral drugs. As shown in Tables 1 and 2, the K_I values of the drugs examined differed by up to almost 40-fold, although the K_I value of each drug is lower than the 150 n *M* of serotonin. The $AUC_{0-\infty}$ values of the drugs examined differed by up to almost 80-fold.

Receptor occupancies of 5-HT_3 antagonists

Predicted values of average receptor occupancy (Φ_B) after intravenous administration of each 5-HT_3 antagonist at the standard dose are listed in Table 3, and those after oral administration are shown in Table 4. The value of Φ_B after intravenous administration was predicted to be relatively high (not less than 65%), although there were large differences in the standard dose K_I value and Css^f among the drugs examined. The value of Φ_B after oral administration was predicted to be more than 50%.

Table 3 Average 5-HT_3 receptor occupancies of four 5-HT_3 antagonists after intravenous administration of standard doses (*Cssf* unbound concentration of 5-HT_3 antagonists at steady-state, Φ_B average 5-HT_3 receptor occupancy of 5-HT_3 antagonist)

Drug	Dose (mg)	Cssf (n*M*)	Φ_B (%)
Granisetron hydrochloride	3	2.78	87.1
Ondansetron hydrochloride	4	2.61	66.8
Ramosetron hydrochloride	0.3	0.25	88.5
Azasetron hydrochloride	10	20.2	97.4

Table 4 Average 5-HT_3 receptor occupancies of five 5-HT_3 antagonists after oral administration of standard doses (*Cssf* unbound concentration of 5-HT_3 antagonists at steady-state, Φ_B average 5-HT_3 receptor occupancy of 5-HT_3 antagonist)

Drug	Dose (mg)	Cssf (n*M*)	Φ_B (%)
Granisetron hydrochloride	2	2.05	83.3
Ondansetron hydrochloride	4	1.27	49.5
Ramosetron hydrochloride	0.1	0.04	54.4
Azasetron hydrochloride	10	17.6	97
Tropisetron hydrochloride	5	3.56	77.6

Relationship between receptor occupancy of 5-HT_3 antagonists and antiemetic effects after administration of cisplatin

Regarding efficacy of 5-HT_3 antagonists in cisplatin therapy, the relationships between standard dose and plasma unbound drug concentrations at steady-state (Css^f) and complete vomiting inhibition rates for prevention or cure [35–45] were analyzed. No significant positive correlations were found in these relationships.

The relationships between average receptor occupancy (Φ_B) and complete vomiting inhibition rate for prevention and cure are shown in Fig. 1. Significant ($P < 0.05$) positive relationships were found between complete vomiting inhibition rate of the 5-HT_3 antagonists after intravenous and oral administration for prevention.

Discussion

When drug action is elicited by specific receptors, it is important to clarify kinetically the relationship between drug concentration in the region of the site of action of the drug and binding of the drug to receptors. Therefore, receptor occupancy of a drug is considered to be a rational index of curative effectiveness. In this study, we predicted the average receptor occupancy by integrating pharmacokinetic and pharmacodynamic parameters after administering 5-HT_3 antagonists, aiming to establish the relationship between Φ_B and efficacy.

In this study, we assumed that 5-HT_3 receptor antagonists are transported across capillary walls by simple diffusion, not mediated by a special transport mechanism, and that drug permeability across vessels is not the rate-determining step for exhibiting their efficacy. Thus, the drug concentration in the intercellular space of the small intestine was assumed to be equivalent to the plasma unbound drug concentration. Confirmation of the validity of this assumption would require

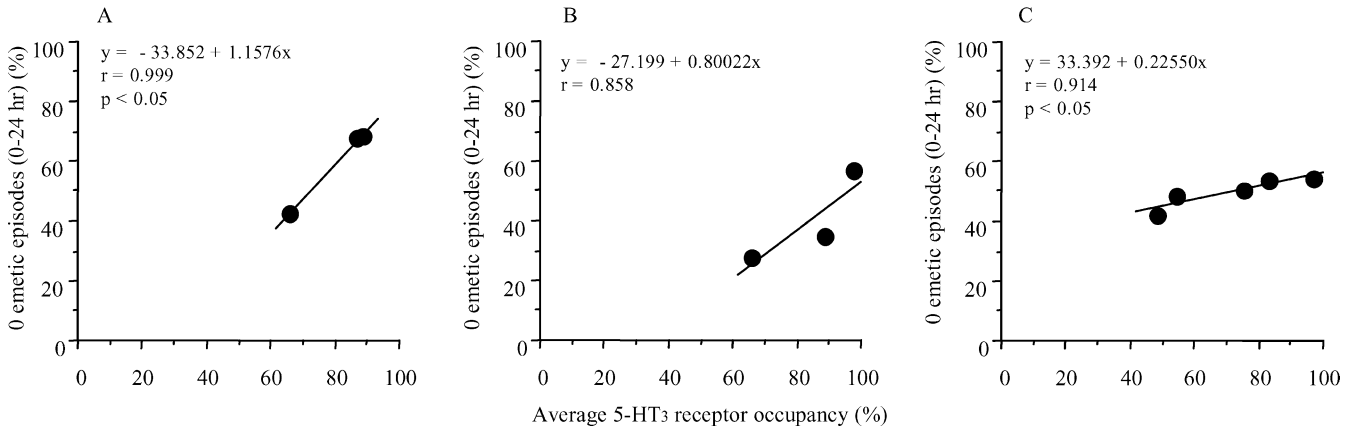

Fig. 1 Relationships between antiemetic effects and average receptor occupancy of 5-HT_3 antagonists: **A** intravenous administration for prevention; **B** intravenous administration for cure after development of vomiting; **C** oral administration for prevention

measurements of unbound drug concentrations in the gut using a microdialysis technique. No such data are currently available.

The data used in this study were obtained from many reports. Pharmacokinetic data were obtained from reported results of clinical studies using standard doses, and data on receptor binding affinity were obtained from reported results of studies using the same animal species and the same tissue region.

Organ-derived and species-derived differences in the K_I values (as receptor dissociation constants) among the many 5-HT_3 antagonists are shown in Fig. 2. The relationship between K_I values in the rat cerebral cortex and intestine is shown in Fig. 2A, and the relationship between K_I values in the rat intestine and human jejunum is shown in Fig. 2B. Significant correlations were found in both relationships, with correlation coefficients of 0.93 ($P < 0.001$) and 0.90 ($P < 0.01$), respectively, suggesting that organ-specific and species-specific differences in the K_I values of 5-HT_3 receptors are small [46]. Moreover, it has been reported that there is a good correlation between the K_I value in the cerebral cortex and the pA_2 value of the depolarization reaction in the vagus nerve of the rat [29]. Therefore, the use of the K_I value in the cerebral cortex in this study seems to have been appropriate.

It is thought that the concentration of released serotonin around 5-HT_3 receptors differs among antineoplastic drugs. Since data on amounts of serotonin released by antineoplastic drugs at the gastrointestinal mucous membrane were not available, it was not possible to take this possible difference into consideration in this study. It has been reported that the concentrations of serotonin and its metabolite, 5-HIAA, in plasma do not change but that urinary 5-HIAA excretion increases after antineoplastic treatment in cancer patients experiencing nausea and vomiting [47, 48]. Therefore, determination of time courses of the amounts of serotonin released by antineoplastic agents would be required for detailed analysis.

The predicted average receptor occupancy of all of the drugs examined in this study were relatively high (more than 65%) after intravenous administration and more than 50% after oral administration. These results can be explained by the spare receptor theory. Linear relationships were found between average receptor occupancy and complete vomiting inhibition rates of all of the 5-HT_3 antagonists used in cisplatin therapy, with

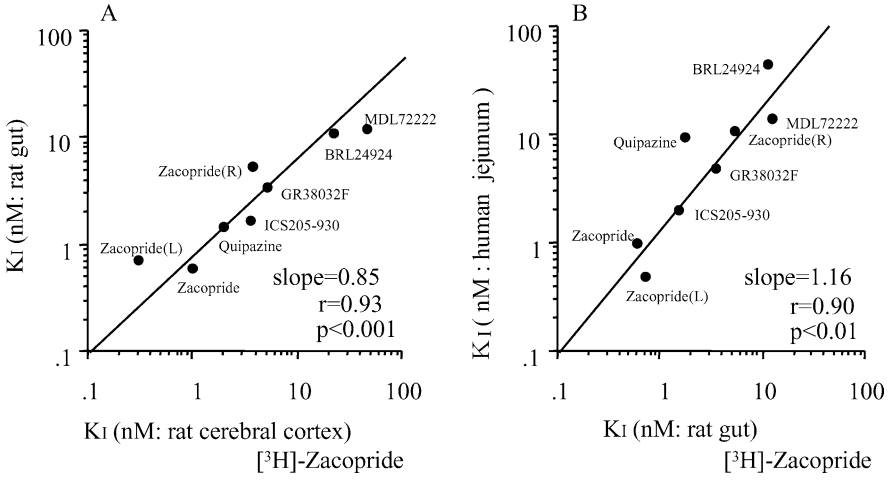

Fig. 2 Difference in 5-HT_3 receptor dissociation constants between rat and human. **A** Relationship between K_I values in rat cerebral cortex and rat gut; **B** relationship between K_I values in rat gut and human jejunum

correlation coefficients of 0.99 and 0.91 ($P < 0.05$) after intravenous and oral administrations for prevention, respectively. These results suggest that 5-HT_3 receptor occupancy is an appropriate index of clinical efficacy of 5-HT_3 receptor antagonists, with higher receptor occupancy indicating more extensive antiemetic action. Concerning ondansetron, dosage differs between Japan (4 mg for oral and intravenous administration) and the US (24 mg for oral administration and 32 mg for intravenous administration). The average receptor occupancy after these dosages in the US have been found to be 85.4% for oral administration and 94.1% for intravenous administration, respectively. This suggests that the dosage of ondansetron in Japan is low.

The analysis based on the receptor occupancy theory of the antiemetic effect of a 5-HT_3 receptor antagonist used in this study should be very useful for not only estimating the rational dosage regimen but also determining the standard dose of a new drug using experimental data obtained from a preclinical study.

References

1. Urushizaki I (1990) Side effects by anticancer drugs and their treatments. Jpn J Cancer Chemother 17:1959
2. Merrifield KR, Chaffee BJ (1989) Recent advances in the management of nausea and vomiting caused by antineoplastic agents. Clin Pharm 8:187
3. Laszo J (1983) Nausea and vomiting as major complications of cancer chemotherapy. Drugs 25 [Suppl 1]:1
4. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, Tattersall MH (1983) On the receiving end—patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol 19:203
5. Joss RA, Brand BC, Buser KS, Cerny T (1990) The symptomatic control of cytostatic drug-induced emesis. A recent history and review. Eur J Cancer 26 [Suppl 1]:2
6. Sridhar KS, Donnelly E (1988) Combination antiemetics for cisplatin chemotherapy. Cancer 61:1508
7. Andrews PL, Rapeport WG, Sanger GJ (1988) Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol Sci 9:334
8. Mitchelson F (1992) Pharmacological agents affecting emesis. Drugs 43:295
9. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL (1990) Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 322:810
10. Tortorice PV, O'Connell MB (1990) Management of chemotherapy-induced nausea and vomiting. Pharmacotherapy 10:129
11. Yamada Y, Sawada Y, Takayanagi R, Ito K, Nakamura K, Iga T (1993) Prediction of therapeutic doses of antipsychotic drugs as dopamine D2 receptor antagonists: approach based on receptor occupancy theory. Xenobio Metabol Dispos 8:247
12. Yamada Y, Sawada Y, Ito K, Nakamura K, Iga T (1993) Prediction of therapeutic doses of β-adrenergic receptor blocking agents based on quantitative structure-pharmacokinetic/pharmacodynamic relationship. Biol Pharm Bull 16:1251–1259
13. Marr HE, Davey PT, Bartlett AJ (1991) Emerging differences between 5-HT3 receptor antagonists. Anticancer Drugs 2:513
14. Kumakura H, Koyanagi J, Nisioka Y, Sato M, Nakajima T, Nakahira K, Tateno M (1990) Phase I study of granisetron (second report)—pharmacokinetics of granisetron following single and repeat intravenous drip infusion in Japanese healthy volunteers. J Clin Ther Med 6 [Suppl 5]:25
15. Kumagai Y, Nakashima H, Kotegawa T, Shiga T, Ohira H, Oribe H, Koike Y, Ohashi K, Ebihara A, Murayama M (1992) Phase I study ondansetron (the 2nd report)—single intravenous dose study and continuous drip infusion dose study in healthy volunteers. J Clin Ther Med 8:1505
16. Nakashima M, Kanamaru M, Miura Y, Takeshige T, Atsuta Y (1994) A phase I study of YM060 in healthy male volunteers—single-dose intravenous administration. Jpn J Clin Exp Med 71:2461–2468
17. Igarashi S, Tanaka K, Yamamura H, Sawai K, Isobe M, Masui H, Kataoka H, Isikawa M, Oka T (1992) Phase I study of Y-25130, a new 5-HT3 receptor antagonist—single intravenous administration. Clin Rep 26:2535
18. Okada H, Kudoh S, Miyazaki R, Izumi K, Kumakura H, Ito S, Yasuda E, Nishioka Y, Nagamatsu S, Nakamichi N (1993) Bioequivalence study of tablet and capsule formulations of granisetron and pharmacokinetics following oral administration at 2 mg in healthy Japanese subjects. Jpn Pharmacol Ther 21:1771
19. Kumagai Y, Nakashima H, Kotegawa T, Shiga T, Ohira H, Oribe H, Koike Y, Ohashi K, Ebihara A, Murayama M (1992) Phase I study of ondansetron (the 1st report)—single and multiple oral dose studies in healthy male volunteers. J Clin Ther Med 8:1495
20. Nakashima M, Kanamaru M, Miura Y, Takeshige T, Atuta Y (1995) Phase I study of oral YM060. Jpn J Clin Exp Med 72:2912
21. Hoshida E, Ono Y, Oshiba S, Kitamura A, Isobe M, Mori H, Kadobe Y, Shimomukai T, Wakiya M (1996) Phase I study of azasetron hydrochloride (Y-25130) tablet—single dose and multiple dose studies. J Clin Ther Med 12:2483
22. Nomiyama T, Tanaka S, Masuda N, Nakashima A, Aizawa T, Morikawa H, Fujino A, Miwa T (1995) Phase I study of tropisetron capsules in healthy volunteers—single administration. Clin Rep 29:1523
23. Haddock RE, Hidham FC, Pope JA, Woods FR, Allen A, Pierce DM, Zussman BD, Nishioka Y, Kumakura H, Ito S (1990) Kinetics of granisetron hydrochloride—distribution, metabolism and excretion in rats and dogs following intravenous administration. Clin Rep 24:6821
24. Hallifax D, Shaw RJ, Skidmore IF, Barrow A, Colthup PV, Toshimitsu Y, Kiminami J (1992) Studies on the metabolic fate of ondansetron hydrochloride (I)—absorption, distribution, and excretion after oral and intravenous administration to rats and dogs. Clin Rep 26:1337
25. Kawabata Y, Sakiyama H, Muto S, Ueda S, Morihisa K, Yano S, Hamada Y, Maehara A, Nakamura T, Takano S, Yamamoto T, Asayama Y, Murakami H, Terasaki H, Miura H, Takeshige T (1994) Clinical evaluation and pharmacokinetics of YM060 against the nausea and vomiting induced by anticancer drug—phase III clinical study. Nishinihon J Urol 56:1445
26. Azasetron interview form (1998) Welfide Co. http://www.taiho.co.jp/medical/di/data/6302/63020201.pdf
27. Lee CR, Plosker GL, McTavish D (1993) Tropisetron: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. Drugs 46:925–943
28. Sakamori M, Takehara S, Setoguchi M (1992) High affinity binding of Y-25130 for serotonin 3 receptor. Folia Pharmacol Jpn 100:137
29. Ito H, Akuzawa S, Tsutsumi R, Kiso T, Kamato T, Nishida A, Yamano M, Miyata K (1995) Comparative study of the affinities of the 5-HT3 receptor antagonists, YM060, YM114 (KAE-393), granisetron and ondansetron in rat vagus nerve and cerebral cortex. Neuropharmacology 34:631
30. Gehlert DR, Schober DA, Gackenheimer SL, Mais DE, Ladouceur G, Robertson DW (1993) Synthesis and evaluation of [^{125}I]-(S)-iodozacopride, a high affinity radioligand for 5HT3 receptors. Neurochem Int 23:373
31. Clark AJ (1926) The reaction between acetyl choline and muscle cells. J Physiol 61:530
32. Ariens EJ (1954) Affinity and intrinsic activity in the theory of competitive inhibition. Arch Int Pharmacodyn 99:32

33. Nickerson M (1956) Receptor occupancy and tissue response. Nature 178:697
34. Stephenson RP (1956) A modification of receptor theory. Br J Pharmacol 11:379
35. Furue H, Oota K, Taguchi T, Niitani H, Ogawa N (1990) Clinical evaluation of granisetron against nausea and vomiting induced by anticancer drug (II)—multi-centered, placebo-controlled, double-blind comparative study. J Clin Ther Med 6 [Suppl 5]:25
36. Ohta J, Taguchi T, Furue H, Niitani H, Ota k, Tsukagoshi S, Ariyoshi Y, Ikeda M, Akasaka Y, Suminaga M, Nukariya N, Yamamura H (1992) Anti-emetic effect and safety of single dose of ondansetron injection in double-blind comparison study with placebo. Jpn J Cancer Chemother 19:2041
37. Mori S, Takaya K, Shineha R (1994) Clinical evaluation of YM060 against nausea and vomiting induced by anticancer drugs. J Adult Dis 24:2257
38. Ikeda M, Taguchi T, Ota K, Furue H, Niitani H, Tsukagoshi S, Ariyoshi Y, Akasaka Y, Ohta J, Suminaga M, Nukariya N, Yamamura H (1992) Evaluation of SN-307 (ondansetron), given intravenously for the treatment of nausea and vomiting caused by anti-cancer drugs including cisplatin—a placebo-controlled, double-blind comparative study. Jpn J Cancer Chemother 19:2071
39. Noda K, Ikeda M, Yoshida O, Yano S, Taguchi T, Shimoyama T, Nakashima M (1994) Clinical evaluation of YM060 against nausea and vomiting induced by anticancer drugs (phase III study). Jpn J Clin Exp Med 71:2765
40. Niitani H, Ota K, Taguchi T, Takeuchi M, Tsukagoshi S, Furue H, Furuse K, Machida T, Wakui A, Sakuma A, Sakurai K, Wakunaga T (1992) Clinical evaluation of Y-25130 against nausea and vomiting induced by anticancer drugs—multi-centered, placebo-controlled, double-blind comparative study. Jpn Pharmacol Ther 20:2525
41. Suminaga M, Furue H, Ohta K, Taguchi T, Niitani H, Ogawa N (1993) Clinical evaluation of granisetron for nausea and vomiting induced by anticancer drugs—multi-centered placebo-controlled double-blind comparative study. Jpn J Cancer Chemother 20:1211
42. Ariyoshi Y, Ota K, Taguchi T, Furue H, Niitani H, Tsukagoshi S, Ikeda M, Akasaka Y, Ohta J, Suminaga M, Nukariya N, Yamamura H (1992) Anti-emetic effect and safety of ondansetron tablet in double-blind comparison with placebo. Jpn J Cancer Chemother 19:2057
43. Taketani Y, Yoshikawa H, Ueda K, Sonoda T, Hasumi K, Matuzawa M, Imanishi Y, Kasamatu T, Kaneko M, Kawabata M, Kinoshita K, Kimura Y, Shimizu K, Sugase M, Sugimoto M, Taniguchi I, Nagasaka T, Muronosono E (1996) Phase III clinical trial of YM060 tablet in nausea and emesis by anti-cancer drugs—clinical evaluation of single oral administration. Obstet Gynecol (Tokyo) 9:1297
44. Tominaga T, Furuse K, Fukuda T, Yamaguchi T, Hourai H, Oizumi K, Genga K, Sakuma A, Niitani H (1996) Clinical evaluation of azasetron tablets against nausea and vomiting induced by anticancer drugs—multicenter double blind test with ondansetron tablets as control. J Clin Ther Med 12:3089
45. Kondo M, Furue H, Taguchi T, Niitani H, Machida T, Akasaka Y, Ohta J, Suminaga M, Nukariya N, Kusunoki T (1995) Clinical phase III study of tropisetron capsules in the treatment of nausea and vomiting induced by anti-cancer drug; a placebo-controlled, multicenter, double-blind comparative study. Jpn J Cancer Chemother 22:1223
46. Pinkus LM, Sarbin NS, Gordon JC, Munson HR Jr (1990) Antagonism of [^{3}H]zacopride binding to 5-HT3 recognition sites by its (*R*) and (*S*) enantiomers. Eur J Pharmacol 179:231
47. Barnes NM, Ge J, Jones WG, Naylor RJ, Rudd JA (1990) Cisplatin induced emesis: preliminary results indicative of changes in plasma levels of 5-hydroxytryptamine. Br J Cancer 62:862
48. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Malave JJ (1992) Changes in serotonin metabolism in cancer patients: its relationship to nausea and vomiting induced by chemotherapeutic drugs. Br J Cancer 66:198