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Review paper

Selectivity of 5-HT_3 receptor antagonists and anti-emetic mechanisms of action

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5-HT_3 receptor antagonists, ondansetron, granisetron and tropisetron are highly specific for the 5-HT_3 receptor and have a selectivity ratio of approximately 1000:1 compared with affinities for other receptors. Other 5-HT_3 receptor antagonists, largely those having a benzamide structure, are non-selective. These include metoclopramide, renzapride and zacopride which stimulate gastric motility via activation of 5-HT_4 receptors; metoclopramide is also a potent dopamine receptor antagonist. Selective 5-HT_3 receptor antagonists are a major advance in the treatment of chemotherapy- and radiotherapy-induced emesis in cancer patients. These agents inhibit emesis by blocking 5-HT_3 receptors on vagal afferent nerve terminals in the gastrointestinal mucosa and on terminals on the same vagal nerves in the vomiting system. Inhibition of acute emesis appears to be produced by blocking the initiation of the emetic reflex induced via 5-HT_3 receptors and by 5-HT released from enterochromaffin cells in the small intestine, as well as by blocking 5-HT_3 receptors in the hindbrain vomiting system.

Keywords: Emesis, chemotherapy, granisetron, 5-HT_3, ondansetron, tropisetron.

5-Hydroxytryptamine

5-Hydroxytryptamine (5-HT or serotonin) has been known to physiologists since the beginning of the century. It was recognized as a vasoconstrictor substance in serum which confounded attempts to perfuse isolated organs with blood. In 1948 it was isolated and identified chemically.[1] Subsequently, it was found to occur not only in blood platelets but also in the enterochromaffin cells of the gut and in neurons. However, the physiological effects of 5-HT baffled scientists for many years. Its actions varied between species and were often dependent on the experimental conditions.

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5-HT receptor classification

Research carried out by a number of groups showed that the different actions of 5-HT were mediated via different receptors. This was formalized into a generally accepted receptor classification in 1986.[2] This classification described three receptors for 5-HT (5-HT_1, 5-HT_2 and 5-HT_3) and the functional responses associated with them. Recently, a 5-HT_4 receptor involved in the modulation of gastrointestinal motility[3] and additional 5-HT_1 receptor subtypes in the central nervous system[4] have been identified.

5-HT_3 receptor antagonists as anti-emetics

The first selective 5-HT_3 receptor antagonist, MDL 72222, was described in 1984.[5] Subsequently, a number of 5-HT_3 receptor antagonists have been reported in the literature (Table 1). Interest in the therapeutic potential of 5-HT_3 receptor antagonists as anti-emetics was generated by two findings. Firstly, in 1978, it was shown that metoclopramide, which was used as an anti-emetic and is a selective dopamine receptor antagonist, also had significant activity at the 5-HT M receptor (or 5-HT_3 receptor).[6] Secondly, independent research groups at Glaxo and Sandoz, both in collaboration with Bradford University, and at Beecham established that 5-HT_3 receptor antagonists inhibited chemotherapy-induced emesis in ferrets.[7–11] These compounds are considerably more potent than metoclopramide in this model and did not cause any overt side-effects (Figure 1). This was in contrast to metoclopramide, which caused sedation even at doses which inhibited emesis by only 50%. This offered the possibility that selective 5-HT_3 receptor

Table 1. Selective and non-selective 5-HT_3 receptor antagonists

Selective	Non-selective
Ondansetron (GR38032)	Metoclopramide
Granisetron (BRL 43694)	Renzapride (BRL 24924)
Tropisetron (ICS 205-930)	Zacopride

antagonists would be anti-emetic in patients without inducing the distressing extrapyramidal reactions often associated with dopamine receptor antagonists such as metoclopramide. Initially, 5-HT_3 receptor antagonists have been investigated in the clinic against emesis induced by chemotherapy, as this is often extremely severe. Indeed, ondansetron, the first highly selective 5-HT_3 receptor antagonist to be developed and marketed, is extremely effective against emesis induced by chemotherapy or radiotherapy in cancer patients and is a major advance in the management of these patients.[12] Recent studies show that ondansetron is also effective against emesis following surgery[13] and co-trimoxazole administration to patients with AIDS.[14]

Effects of 5-HT_3 receptor antagonists on gastrointestinal motility

As described above, metoclopramide is predominantly a dopamine receptor antagonist, but it also has significant activity at 5-HT_3 receptors. It was postulated that the ability of metoclopramide to facilitate gastric emptying and contractions of stomach muscle might be due to antagonism of 5-HT_3 receptors.[15] Indeed, 5-HT_3 receptor antagonists may facilitate gastric emptying in some experimental models.[16] However, selective 5-HT_3 receptor antagonists are inactive in some functional motility models[16 19] and fail to enhance small intestine cholinergic transmission.[20] Furthermore, in normal volunteers, granisetron and ondansetron have been reported as having little or no effect on the motility of the stomach and small intestine[21 23] but do affect lower bowel function by slowing colonic transit[23] which is probably responsible for inducing mild constipation in some patients.[24,25]

Recent evidence suggests that stimulation of gut motility is mediated via 5-HT_4 receptor activation.[16,26,27] Indeed, the selective 5-HT_3 receptor antagonists, ondansetron, granisetron and tropisetron have no agonist activity at this receptor although tropisetron has moderate antagonist activity.[26] On the other hand, metoclopramide, zacopride and BRL 24924 (renzapride) stimulate gastric motility and are also 5-HT_4 receptor agonists.[26,28]

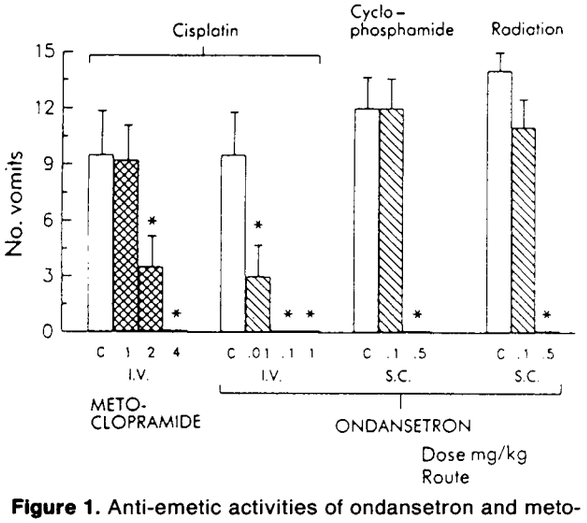

Figure 1. Anti-emetic activities of ondansetron and metoclopramide against cisplatin-, cyclophosphamide- and radiation-induced vomiting in ferrets (C = control). *$p < 0.01$.

Selectivity of 5-HT_3 receptor antagonists

Zacopride is a racemic mixture of r and s enantiomers and, unlike ondansetron, granisetron and tropisetron, it has been shown to induce emesis in ferrets at clinically relevant doses.[29] It has been suggested that the activity of zacopride at 5-HT_4 receptors is involved in its emetic response.[30] However, it is more likely to result from 5-HT_3 receptor activation mediated by the s enantiomer of zacopride, since it has been shown that, while the r enantiomer is a 5-HT_3 receptor antagonist, the s enantiomer has 5-HT_3 agonist activity.[31–33] Ondansetron is also a racemic compound but, in contrast to zacopride, both enantiomers are potent and selective 5-HT_3 receptor antagonists and have no affinity for 5-HT_4 receptors.

Ondansetron has been reported to have very weak affinity for 5-HT_{1C}, α_1 and μ opioid receptors (pK_b 5.43–5.59). Similarly, antagonist activity at the 5-HT_{1A} and 5-HT_4 receptors has been described for granisetron and tropisetron respectively (pK_b 5.5 and 6.0). However, these compounds have a selectivity ratio of approximately 1000:1 for 5-HT_3 receptors (pK_b 8.3–10.2) compared with any other receptor type (Figure 2);[26,34 44]

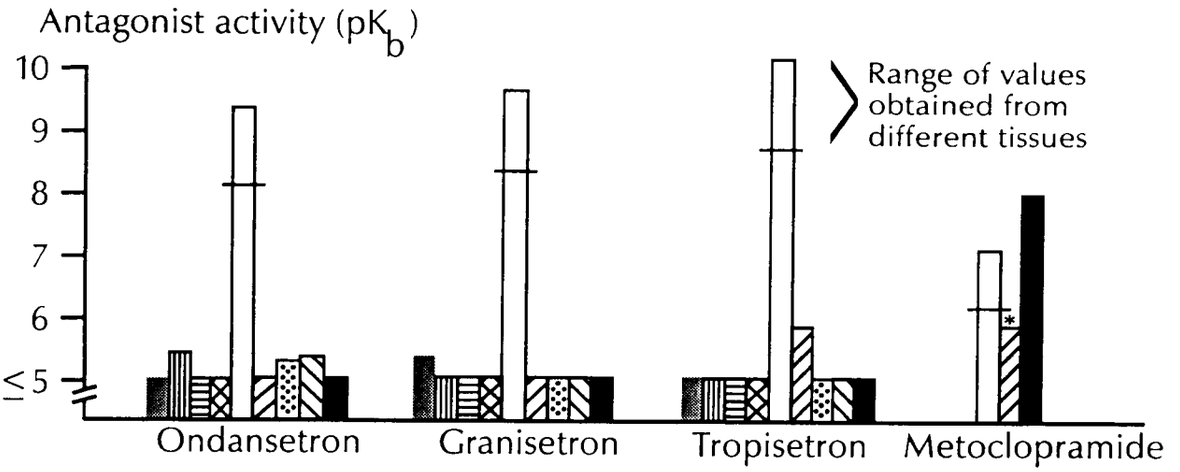

Figure 2. Selectivity of 5-HT$_3$ receptor antagonists:[26,34–45] ▨ = 5-HT$_{1A}$; ▥ = 5-HT$_{1C}$; ▤ = 5-HT$_{1D}$; ▩ = 5-HT$_2$; □ = 5-HT$_3$; ▨ = 5-HT$_4$; ⁘ = α_1; ▧ = μ; ■ = dopamine. *Agonist.

hence the affinity of these drugs for other receptors has no clinical significance.

Differences in the affinities of ondansetron, granisetron and tropisetron for 5-HT$_3$ receptors in different experimental conditions led to the suggestion that there are 5-HT$_3$ receptor subtypes.[45] However, current evidence suggests that these are related to species differences rather than the existence of receptor subtypes within the same species.[2,46]

It is interesting to note that 5-HT$_3$ receptor antagonists also have activity in behavioral models of psychiatric diseases. In these models, unlike the anti-emetic dose-response relationships, bell-shaped dose-response curves have been described for ondansetron, granisetron and other 5-HT$_3$ receptor antagonists; this characteristic is particularly pronounced with granisetron.[15,47,48] The reasons for this non-linear dose have yet to be elucidated. A similar response relationship does not occur for the anti-emetic effects of ondansetron and granisetron over the therapeutic dose range (Figures 1, 3 and 4).[49–52]

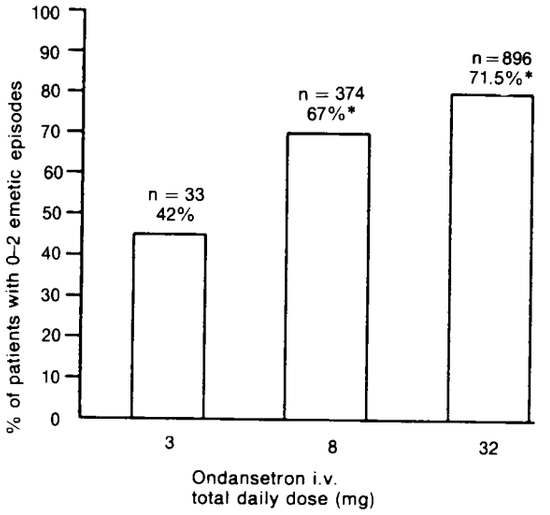

Figure 3. The anti-emetic efficacy of increasing doses of ondansetron against cisplatin-induced emesis (combined data from dose-ranging and dose comparative studies).[49–51]

*The total daily dose of ondansetron (8–32 mg) should be selected according to the emetogenic challenge and patient factors.

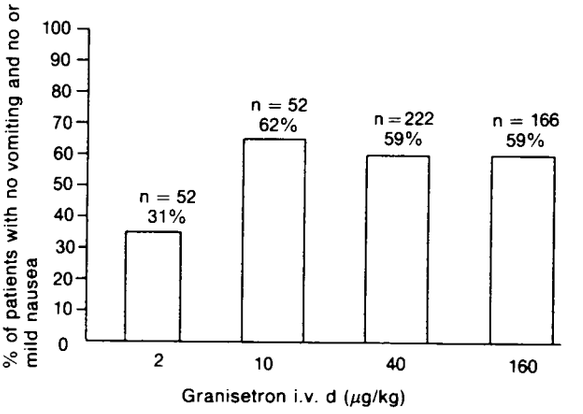

Figure 4. The anti-emetic efficacy of increasing doses of granisetron against cisplatin-induced emesis (combined data from dose comparative studies).[52]

Distribution of 5-HT$_3$ receptors

5-HT$_3$ receptors are densely located in areas known to be involved in the emetic reflex (Figure 5). Thus there are 5-HT$_3$ receptors on vagal afferent terminals,[40,53] which innervate the gastrointestinal mucosa, and on the same vagal afferent nerves located in the brain stem vomiting system (i.e. the dorsovagal nucleus, the nucleus of the solitary tract and the area postrema).[38,54,55]

Peripheral mechanisms

Large amounts of 5-HT (about 80% of the body's total 5-HT content) are contained in the enterochromaffin cells located close to vagal afferent terminals in the gastrointestinal mucosa. Evidence suggests that cancer chemotherapeutic drugs or radiation release 5-HT from these cells. Gunning *et al.*[56] found that cisplatin-induced damage and inflammation of the ferret gastrointestinal tract was accompanied by an almost 2-fold increase in the content of 5-HT and its metabolite 5-hydroxyindolacetic acid (5-HIAA) in the ileal mucosa. Since there was no change in noradrenaline levels in the same tissue it is unlikely that the change in 5-HT was caused by generalized tissue damage. Furthermore, Barnes *et al.*[57] found that cisplatin-induced emesis in ferrets could be prevented by pre-treating the animals with chlorophenylalanine, an inhibitor of 5-HT synthesis.

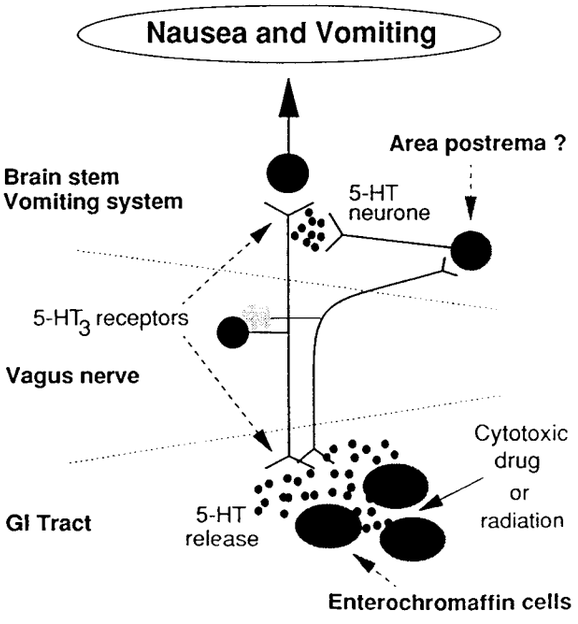

Figure 5. Sites of action of 5-HT$_3$ receptor antagonists as anti-emetics.

An important clinical study by Cubeddu *et al.*[58] has provided supportive evidence for the role of 5-HT in chemotherapy-induced emesis. This study measured the urinary output of 5-HIAA in patients receiving cisplatin chemotherapy together with either ondansetron or placebo. In patients given placebo, the rise in urinary 5-HIAA correlated with the onset and development of emesis. The amount of urinary 5-HIAA produced by patients in this study can only be accounted for by release of 5-HT from enterochromaffin cells. Moreover, similarity between the urinary 5-HIAA levels in the placebo and ondansetron groups suggests that 5-HT$_3$ receptor antagonists do not affect the release or metabolism of 5-HT but antagonize its action on vagal afferent neurons.

Further clinical evidence suggesting that the release of 5-HT from the enterochromaffin cells lasts for just a few hours following cisplatin chemotherapy comes from a study by Marty *et al.*[59] This study compared the efficacy of ondansetron and metoclopramide in the prevention of cisplatin-induced emesis. Ondansetron was superior to metoclopramide in preventing acute emesis over the first 24 h. Interestingly, the time course of emesis in patients receiving metoclopramide showed that the maximum emetic response occurred 4–5 h following cisplatin; over this time ondansetron was effective (Figure 6). Recently it has been shown that a single intravenous dose of ondansetron (8–32mg) given before cisplatin chemotherapy is as effective as the 24-h infusion schedule used in the study of Marty *et al.*[60] Furthermore, single doses of granisetron are also effective for the control of acute emesis.[61] These findings, together with the relatively short half-life of ondansetron and granisetron (3–4 h),[62,63] suggest that 5-HT is released for just a few hours following cisplatin chemotherapy, probably until the 5-HT content of the enterochromaffin cells is depleted. The action of 5-HT$_3$ receptor antagonists over this time therefore prevents acute emesis.

Central mechanisms

The importance of central 5-HT$_3$ receptors has been demonstrated in ferrets. Low doses of on-

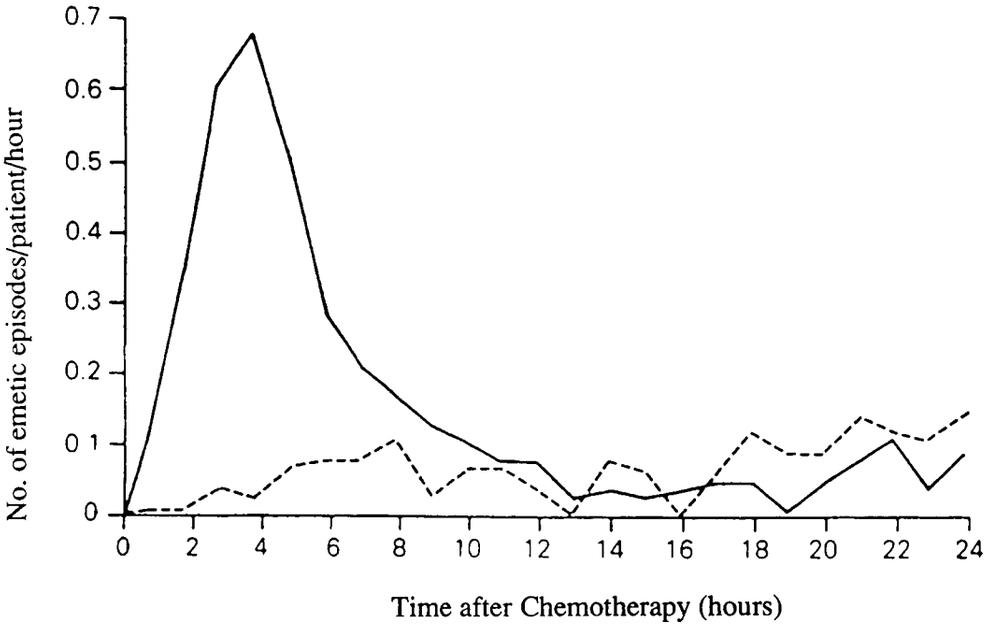

Figure 6. Episodes of emesis with metoclopramide (——) and with ondansetron (- - -) during the 24 h after cisplatin administration (n = 76).

dansetron or MDL72222 injected directly into the area postrema causes a dose-related inhibition of vomiting and retching.[64] However, there is the question as to the source of 5-HT which activates these central receptors. It is unlikely that 5-HT released from the enterochromaffin cells reaches the vomiting system via the plasma as 5-HT is rapidly metabolized. The ventral surface of the area postrema has neurons which contain 5-HT.[65] It is therefore possible that a direct action of cytotoxic drugs or even activation of vagal afferents causes 5-HT to be released from these cells. This then activates 5-HT$_3$ receptors located presynaptically on terminals of the vagus nerve within the vomiting system.

Peripheral and central mechanisms of action

The abolition of chemotherapy-induced emesis in ferrets following abdominal vagotomy[66] suggests that chemotherapeutic drugs have a peripheral site of action which is of primary importance. However, Pratt *et al.*[67] have shown that after bilateral or unilateral vagotomy in ferrets there is a decrease in the number of 5-HT$_3$ receptors in the brain stem. Therefore, not only is the peripheral input to the vomiting system prevented by vagotomy but also any possible role for central 5-HT$_3$ receptors is eliminated. Interestingly, in this context, the injection of the 5-HT$_3$ agonist, 2-methyl 5-HT, into the area postrema of non-vagotomized ferrets does not induce emesis.[64] An explanation for these observations is that 5-HT acts both centrally and peripherally in a synergistic manner so that activation of 5-HT$_3$ receptors at both sites is necessary to induce emesis. However, antagonism of 5-HT$_3$ receptors at one or both of these sites prevents emesis.

The effectiveness of a single intravenous dose of ondansetron[60] and granisetron[61] in the prevention of cisplatin-induced emesis over the first 24 h following treatment suggests that inhibition of the initiation of the emetic reflex is adequate for control of acute emesis following cisplatin. However, other trigger mechanisms may operate to recruit central 5-HT$_3$ receptors over the first 24 h and subsequently over the following 7 days when delayed emesis is known to occur. Indeed, a single dose of granisetron given before chemotherapy does not protect patients for 7 days.[61,68] Stimulation may come from areas such as the area postrema (Figure 5), and/or stores of 5-HT in the enterochromaffin cells may be replenished and contribute to delayed emesis. Furthermore, ondansetron has been shown to be effective in controlling emesis when given on days 2–5 following cisplatin and non-cisplatin chemotherapy.[69,70]

Summary

Selective 5-HT_3 antagonists, ondansetron, granisetron and tropisetron have a selectivity ratio of approximately 1000:1 for 5-HT_3 receptors compared with any other receptor type. Other non-selective 5-HT_3 receptor antagonists, including metoclopramide, renzapride and zacopride, stimulate gastric motility via activation of 5-HT_4 receptors.

Selective 5-HT_3 receptor antagonists appear to prevent acute emesis by blocking the initiation of the emetic reflex produced via 5-HT_3 receptors and 5-HT release from enterochromaffin cells in the gastrointestinal tract, as well as by blocking 5-HT_3 receptors in the hindbrain vomiting system.

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