REVIEW

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Cancer chemotherapy-induced nausea and vomiting: role of mediators, development of drugs and treatment methods

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The development of serotonin 5-HT_3 receptor antagonists dramatically improved the treatment of chemotherapy-induced nausea and vomiting. Ondansetron, a serotonin 5-HT_3 receptor antagonist in combination with dexamethasone is widely used to treat chemotherapy-induced nausea and vomiting. This treatment regimen is effective against acute nausea and vomiting, but fails to control delayed nausea and vomiting. Metoclopramide along with other antiemetics are used to treat delayed nausea and vomiting. The high doses of metoclopramide needed may produce extra pyramidal side effects. The recent developments of 5-HT_3 and dopamine D_2 dual receptor antagonists have been found to exhibit a broad spectrum of activity against peripherally and centrally acting stimuli, but are not much effective against delayed emesis associated with chemotherapy. In various animal models, neurokinin NK_1 receptor antagonists showed promising results against acute and delayed emesis, but the clinical trials revealed that triple therapy (NK_1 receptor antagonist, 5-HT_3 receptor antagonist and dexamethasone) is superior than standard therapy (5-HT_3 receptor antagonist & dexamethasone) or NK_1 receptor antagonist alone, in controlling acute as well as delayed nausea and vomiting. Ginger, which is used traditionally for controlling emesis induced by various stimuli, also showed good activity against chemotherapy-induced nausea and vomiting in animal models. Non-pharmacological methods such as acupressure and acustimulation are good adjunct methods in treating nausea and vomiting. Since many mediators are involved in emesis induced by chemotherapy, cocktail treatment is proven to be more efficacious than a single drug, but increases treatment costs. So there is a need of further research in this field to get economically useful methods for the treatment of acute and delayed chemotherapy-induced nausea and vomiting.

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1. Introduction

Chemotherapy regimens for the treatment of cancer are unfortunately well known for their toxicity. Although some of their toxic effects may be life threatening, patients are often most fearful of the nausea and vomiting (N&V) caused by cancer chemotherapy. Prevention and control of N&V are paramount in the treatment of cancer

patients. N&V can result in serious metabolic derangements, nutritional depletion and anorexia, esophageal tears, deterioration of patient's physical and mental status, which prompts the patient to discontinue the potentially useful and curative antineoplastic treatment (Craig et al. 1987; Passik et al. 2001) Since the last decade, there is a lot of interest in developing new molecules for the treatment of chemotherapy-induced nausea and vomiting (CINV) and alternative methods like natural remedies and adjunct therapies such as acupuncture and acustimulation. This article discusses the role of various neurotransmitters/receptors in the process of CINV, development of drug molecules, which act on each receptor selectively, or combination of receptors and alternative methods for the management of CINV.

2. Physiology of emesis

Nausea and vomiting (N&V) are natural protective reflexes designed to eliminate toxins from the gastrointestinal tract (GIT) and to prevent further ingestion of the same substance. The process of vomiting is co-ordinated by the vomiting centre (VC) located in the medulla oblongata. Chemoreceptor trigger zone (CTZ) located in the area postrema (AP) of the fourth ventricle and nucleus tractus solitarius (NTS) of the vagus nerve are the most important relay centres for afferent impulses arising in the periphery (pharynx and GIT). CTZ can also detect circulating toxins directly from the blood and cerebrospinal fluid (CSF), as it is unprotected by the blood brain barrier. Vagal afferents from the liver may also play a role in the relay of information to the CTZ. Two additional areas, which send impulses to the VC, are the cerebral cortex (particularly in anticipatory N&V) and vestibular labyrinthine system (in motion sickness). In response to afferent impulses, VC sends efferent impulses to nuclei responsible for respiratory, salivary, and vasomotor activity as well as to both striated and smooth muscle, involved in the process of vomiting (Brunton 1996; Karim et al. 1996). In contrast to vomiting, the mechanism of nausea is not clearly defined and it has been believed that nausea may be due to low level activation of the vomiting pathway. With respect to chemotherapy and radiation therapy, the CTZ, the GIT (particularly enterochromaffin cells of the small intestinal mucosa are likely to be involved) and the cerebral cortex have been identified as sources of afferent input to the VC (Gregory and Ettinger 1998). GIT is connected to the VC, via the CTZ and NTS. Cerebral cortex stimulates the VC, in anticipatory N&V (Craig et al. 1987). The CTZ has high concentrations of serotonin (5-HT_3), dopamine (D_2) and opiod receptors, while the NTS is rich in enkephalin, histamine, and cholinergic receptors and also contains 5-HT_3 receptors (Brunton 1996). The neuronal pathways involved in the nausea and vomiting are represented in Fig. 1.

3. Classification of chemotherapy-induced nausea and vomiting

Anticipatory nausea and vomiting (ANV): ANV is nausea and/or vomiting which occurs prior to a new cycle of chemotherapy, in response to conditioned stimuli such as the smell, sight, and sound of the treatment room. ANV is a classically conditioned response that typically occurs after 3–4 prior chemotherapy treatments, following which the person experiences acute or delayed N&V.

Acute nausea and vomiting: N&V experienced during the first 24-hour period following chemotherapy administration.

Delayed (or late) nausea and vomiting: N&V that occurs beyond 24 hours following chemotherapy administration.

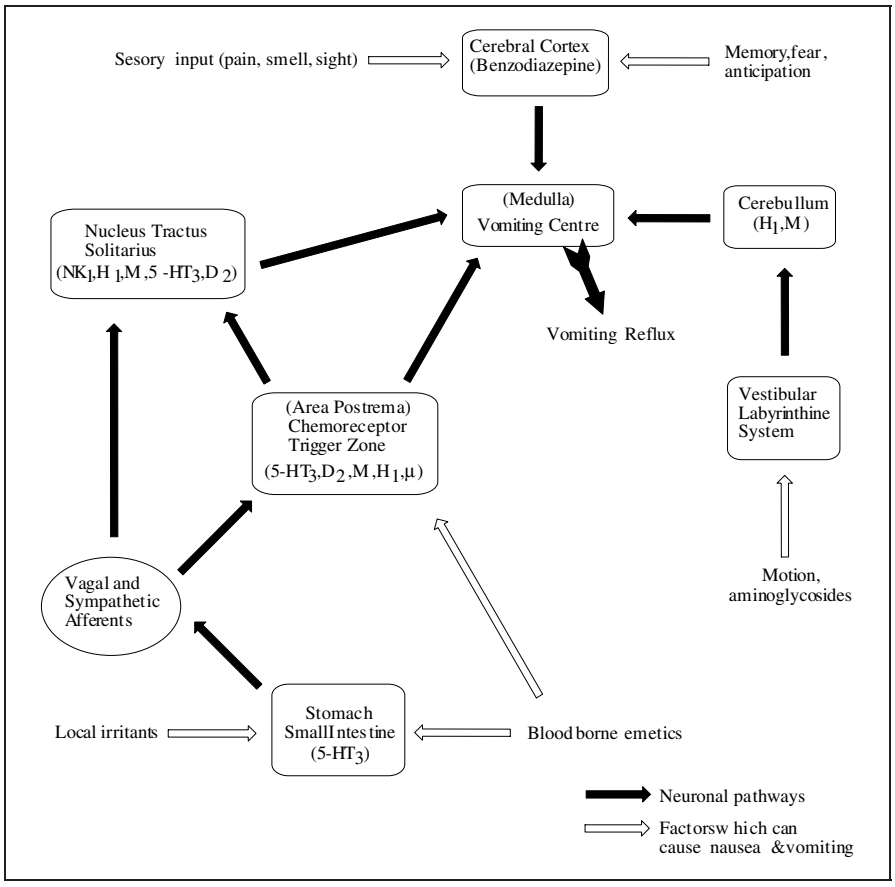


Fig. 1:
Neural pathways involved in the nausea and vomiting

This is considered as delayed, or late N&V. Delayed N&V is associated with cisplatin, cyclophosphamide, and other drugs (eg., doxorubicin, and ifosfamide) given at high doses or on 2 or more consecutive days.
Chronic nausea and vomiting: N&V that occurs in advanced cancer patients, which is associated with a variety of potential etiologies. A definite understanding of cause is not well known, nor well researched, but potential causal factors include gastrointestinal, cranial, metabolic, drug-induced (eg., morphine), cytotoxic chemotherapy, and radiation-induced mechanisms.
Breakthrough nausea and vomiting: N&V that occurs despite patients being treated with preventive therapy.
Refractory nausea and vomiting: N&V that occurs during subsequent cycles of chemotherapy when antiemetic propylaxis or rescue therapy has failed in earlier cycles.

4. Serotonin 5-HT_3 receptors

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter involved in various pharmacological effects in the peripheral and central nervous system (CNS) (Boess and Martin 1994). Fifteen 5-HT receptor subtypes belonging to 7 major classes (5-HT_1-5-HT_7) have been identified so far (Hoger and Martin 1997). The majority of 5-HT receptors belong to the G protein-coupled receptor family. The 5-HT_3 receptors, on the other hand, act through a pentameric cation channel and are present within the peripheral and CNS (Derkach et al. 1989). Since the last decade 5-HT_3 receptors have gained much attention because of the clinical use of 5-HT_3 receptor antagonists (RAs) in the treatment of CINV (Karim et al. 1996; Watters et al. 2001) and also in postoperative nausea and vomiting (PONV) (Jones and Blackburn 2002). Besides, a number of preclinical studies suggest that 5-HT_3 RAs can be used in the treatment of various CNS disorders like anxiety and cognitive dysfunction (Jones and Blackburn 2002).

4.1. Involvement of 5-HT_3 receptors in the CINV

In the early 1980s, the best available treatment for CINV was high dose metoclopramide (Gralla et al. 1981; Homesley et al. 1982) combined with a number of other drugs, such as lorazepam and dexamethasone. However, this treatment regimen was effective only in less than 60% patients and these drugs produce extra pyramidal side effects, which added to the patient's problem. The dose of metoclopramide is much higher than those required for gut motility effects, and other prokinetic agents failed to control CINV. Since dopamine antagonists are known to be useful antiemetics for a number of conditions, it was assumed that metoclopramide was effective through dopamine receptor blocking activity. However, other dopamine receptor antagonists did not appear to be as effective as metoclopramide against CINV. From these observations it can be tentatively concluded that the antiemetic action of metoclopramide against CINV, is not due to gut motility stimulation of dopamine antagonism (Andrews and Bhandari 1993). Metoclopramide was known to have other pharmacological properties including interactions with muscarinic receptors, α-adrenoreceptors and 'M' receptors (5-HT_3 receptors). Serotonin had not previously been implicated as part of the vomiting reflex pathway, but the discovery of ondansetron a selective 5-HT_3 RA without affinity for dopamine receptors, proved the involvement of 5-HT_3 receptors in the CINV (Tyers et al. 1993).

4.2. Mechanism of the antiemetic action of 5-HT_3 receptor antagonists

Serotonin (5-hydroxytryptamine, 5-HT) is found in high concentrations within the enterochromaffin cells in the gut (Gregory and Ettinger 1998; Rapepart and Sanger 1988), and is additionally located primarily in the CNS and platelets. In the CNS, highest density of receptors is present in the NTS, AP where the CTZ is located and where vagal afferents enter brain and also present in dorsovagal nucleus (Kilpatrick et al. 1987).

4.2.1. Peripheral site of action

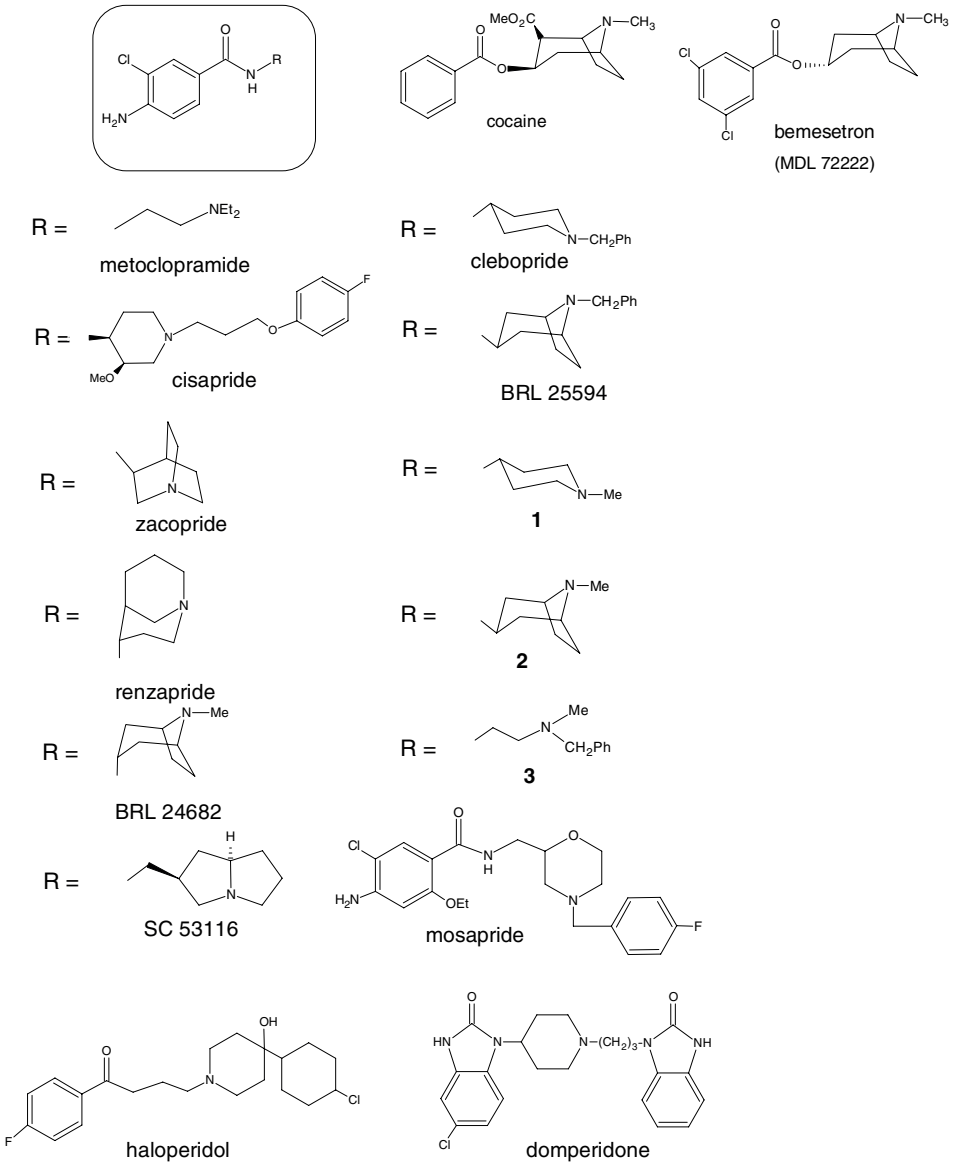
It has been revealed that cisplatin caused the released of serotonin from enterochreomaffin cells in the GIT (Guinning et al. 1987; Cubeddu et al. 1990), possibly as a result of free radical generation (Matsuki et al. 1993). The released serotonin, then activates the 5-HT_3 receptors on vagal afferent fibres, which stimulates the CNS that mediate emetic response. 5-HT_3 RAs, by blocking the afferent vagal pathways would prevent vomiting (Andrews et al. 1990).
It has been shown that urinary excretion and plasma concentrations of the major metabolite of serotonin, 5-hydroxyindole acetic acid (5-HIAA), is increased after administration of highly emetogenic chemotherapy (Alfieri and Cebeddu 1995) and is not affected by the administration of 5-HT_3 RAs. Thus, peripherally, 5-HT_3 RAs do not prevent the release of serotonin, but bind to the 5-HT_3 receptors and prevent CINV by preventing agonism of the 5-HT_3 receptors by serotonin.

4.2.2. Central site of action

Autoradiographic studies have revealed that 5-HT_3 receptor ligands bind with much higher density to the dorsal vagal complex (AP, NTS, dorsal motor nucleus of the vagus nerve) than to other brain regions, in ferrets (Higgins et al. 1989; Fozard 1987). These studies suggested that central 5-HT_3 receptors are also involved in CINV.
When the 5-HT_3 receptor agonist, 2-methyl-5-HT was injected by intracerebroventricular (i.c.v.) route, it has been observed to induce emesis in ferrets (Miller and Nonaka 1990). Cisplatin-induced emesis is fully prevented by surgical ablation of CTZ (Bhandari et al. 1989). Administration of ondansetron or other 5-HT_3 RAs into the area postrema or the fourth cerebral ventricle has been reported to inhibit emesis induced by peripherally or centrally administered cisplatin (Higgins et al. 1989; Smith et al. 1988; Kamato et al. 1993). These findings support that 5-HT_3 RAs act at CTZ in the AP of the fourth ventricle.

4.3. Developments of 5-HT_3 receptor antagonists

In 1957, a neuronally mediated, so-called 'M' receptor response to serotonin in the guinea pig isolated ileum preparation was observed (Gaddum and Picarelli 1957). After this many research groups worked on this receptor to explore its physiological functions. It has been reported the blockade of setotonin 'M' receptor by metoclopramide (Fozard and Mobarek Ali 1978) and also the pharmacology of MDL-72222 (Fozard 1984), which was a structural hybrid of two compounds, cocaine and metoclopramide, which were known to have 'M' receptor-blocking properties. It has been published that some tropane-substituted indoles showed potent and selective 'M' receptor antagonist



Serotonin 5-HT_3, 5-HT_4 and/or dopamine D_2 receptor antagonists

activity (Richardson et al. 1985). In 1986, the 'M' receptor was renamed as 5-HT_3 receptor (Bradley et al. 1986).

For many years, metoclopramide, a benzamide derivative has been widely used to treat the emesis induced by anticancer therapy, besides being used as a prokinetic agent (Pinder et al. 1976; Harrington et al. 1983). Pharmacologically, metoclopramide effects are believed to be due to a combination of relatively weak serotonin 5-HT_3 and dopamine D_2 receptors antagonisms and a serotonin 5-HT_4 receptor agonism. The weak affinity and lack of selectivity of metoclopramide for these receptors may be due to large number of conformations arising from the flexibility of the 2-(diethylamino)ethyl moiety. To develop potent 5-HT_3 receptor antagonists and/or 5-HT_4 receptor agonists that are devoid of significant D_2 receptor antagonistic activity, several research groups have modified the 2-(diethylamino)ethyl moiety of metoclopramide. Accordingly, benzamide with conformationally rigid amines such as piperidine, quinuclidine and quinolizidine have been reported (Kato et al. 1999). Thus, cisapride, mosapride, zacopride, renzapride, compound **1**, BRL 24682, SC 53116, and compound **2**, were found to exhibit good affinity for 5-HT_3 and/or 5-HT_4 receptors, whereas clebopride, BRL 25594 and compound **3**, having a benzyl group on the nitrogen atom in the amine moiety have shown high affinity for the D_2 receptors (Harada et al. 1995; Hirokawa et al. 1998a, 1998b, 2003.

In due course, the most familiar and clinically used 5-HT_3 RA, ondansetron, was introduced in 1990 by Glaxo, followed by granisetron in 1991 by Smithkline Beecham,

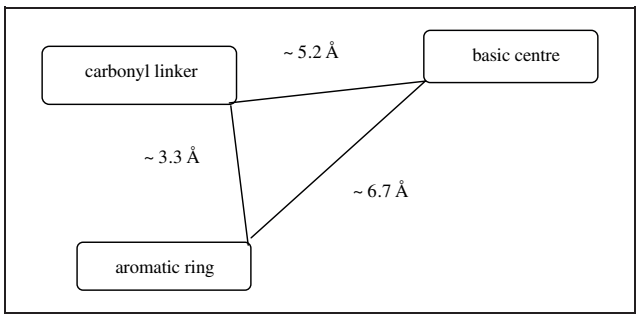
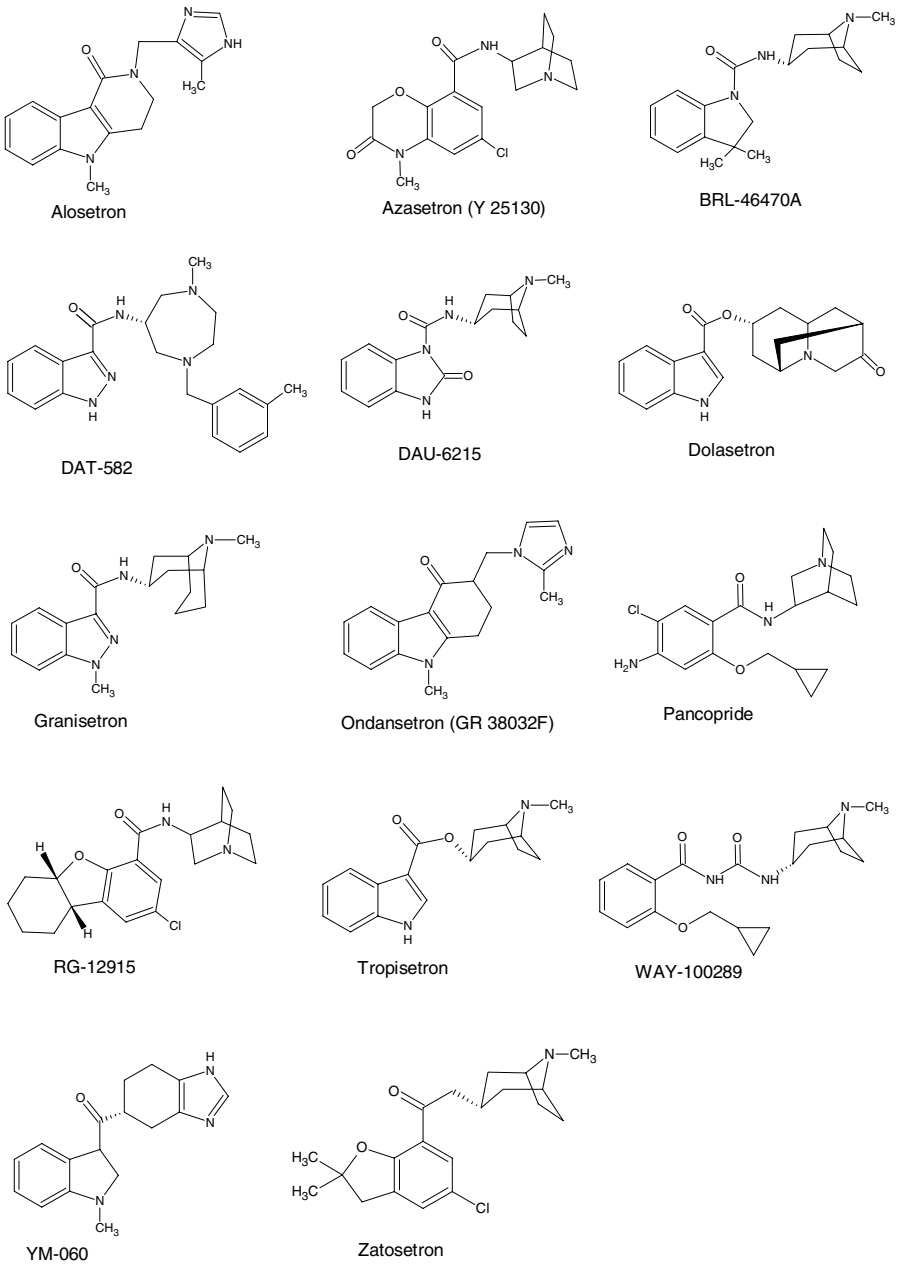


Fig. 2: Pharmacophore of 5-HT_3 receptor antagonists



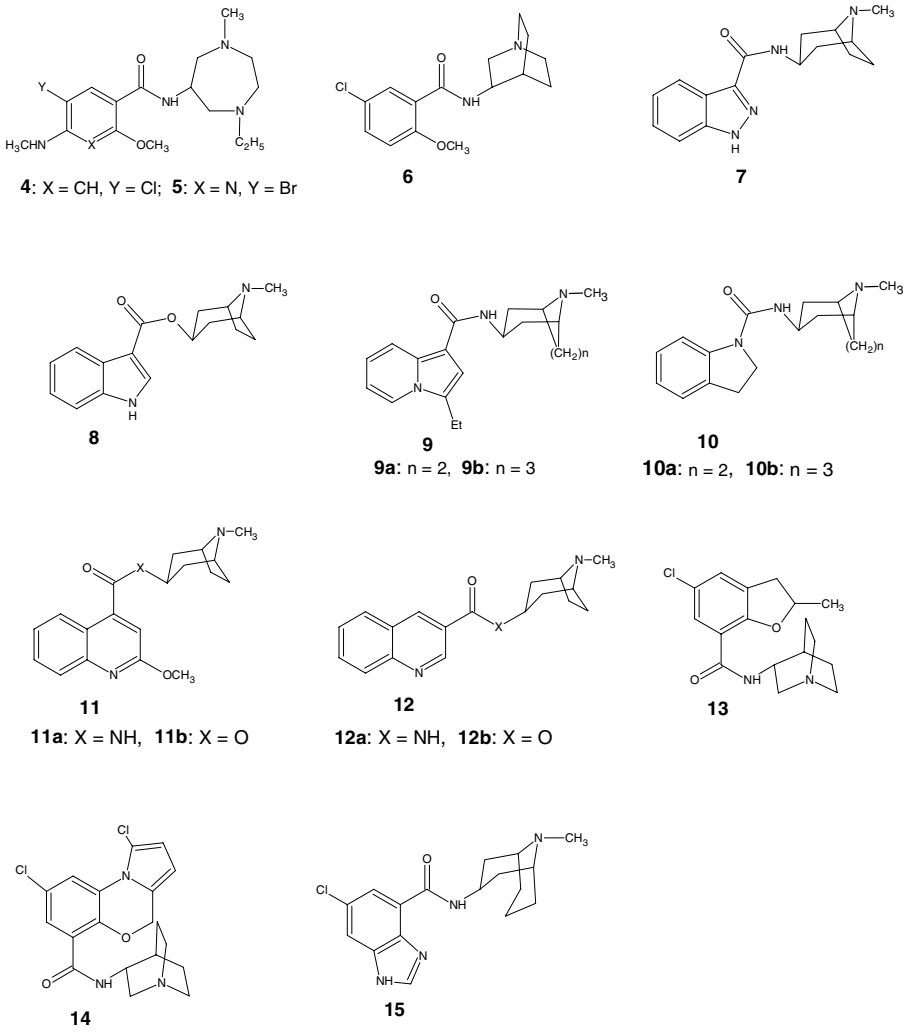
5-HT_3 receptor antagonists

tropisetron in 1992 by Sandoz and dolasetron by Marion Merrell Dow. All these drugs are currently available in many contries, whereas dolasetron is available in the UK and is now approvable in USA. Other 5-HT_3 RAs, alosetron, azasetron, BRL-46470A, DAT-582, DAU-5215, pancopride, RG-12915, WAY-100289, YM-060, zatosetron are yet to be commercialized.

4.4. Pharmacophore of 5-HT_3 receptor antagonists

Computer-based three-dimensional steric molecular models of the 5-HT_3 receptor pharmacophore have been developed on the basis of radio-ligand binding data using potent agents like ondansetron and granisetron. Perhaps the most well known and generally accepted 5-HT_3 pharmacophore consists of three components: an aromatic ring, a carbonyl-containing linking moiety, and an out of plane basic center in a specific spatial arrangement (Hibert et al. 1990, Fig. 2).

Since Hibert published his model in 1990, a number of molecules have been reported based on this model and also some refinements and extensions to this model have been proposed. Many research groups developed molecules based on this model. Beginning with the aromatic component, various modifications have been achieved namely substitution with phenyl (**4**) (Hirokawa et al. 1998a), (**6**) (Youssefyeh et al. 1992), pyridyl (**5**) (Hirokawa et al. 2003), indazoles (**7**) (Robertson et al. 1990), indole (**8**) (Rosen et al. 1990), indolizine (**9**) (Bermudez et al. 1990b), indoline (**10**) (Bermudez et al. 1990a), quinoline (**11**) (Hayashi et al. 1992), (**12**) (Hayashi et al. 1993), dihydrobenzofuran (**13**) (Kuroita et al. 1994), benzoxazine (**14**) (Kato et al. 1995) and benzimidazole (**15**) (Lopez-Rodriguez et al. 1996). Concerning the basic amine component a number of sterically hindered and conformationally rigid aliphatic azabicyclics like tropane (**7**) (Robertson et al. 1990), (**9a**) (Bermudez et al. 1990b),



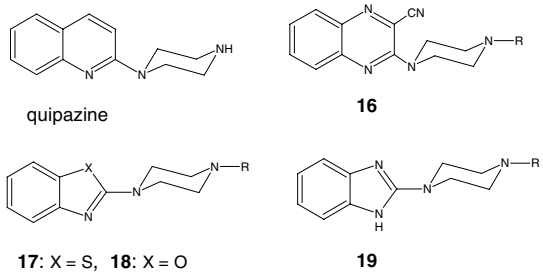
Structure of 5-HT_3 receptor antagonists based on the pharmacophore

(**10**) (Bermudez et al. 1990a), (**11**) (Hayashi et al. 1992), (**12**) (Hayashi et al. 1993), granatane (**9b**) (Bermudez et al. 1990b), (**10b**) (Bermudez et al. 1990a), quiniclidine (**6**) (Youssefyeh et al. 1992), (**13**) (Kuroita et al. 1994), (**14**) (Kato et al. 1995) and monocyclics like 1,4-diazepine (**4**) (Hirokawa et al. 1998a; Hirokawa et al. 1998b), (**5**) (Hirokawa et al. 2003) have been studied. Amides (**11a**) (Hayashi et al. 1992), (**12a**) (Hayashi et al. 1993) and esters (**11b**) (Hayashi et al. 1992) and (**12b**) (Hayashi et al. 1993) have been studied for carbonyl linking moiety.

It has been hypothesized that the carbonyl moiety is not essential in the pharmacophore for high affinity. This component could serve as a hydrogen-bonding region (Rosen et al. 1990). One of the 5-HT_3 ligands that proved this concept is quipazine, which exhibits 5-HT_3 antagonist properties (Round and Wallis 1987) as well as an agonist character in some preparations (Emerit et al. 1993). Although quipazine lacks a carbonyl group, the negative electrostatic potential energy field generated by the quinoline nitrogen may resemble that generated by a carbonyl group (Laguerre et al. 1994). Indeed, it has been anticipated that the lone pair of the quipazine nitrogen may play a role equivalent to the carbonyl oxygen (Hibert et al. 1990). Based on this hypothesis, different heteroaryl piperazines viz., piperazinylquinoxaline (**16**) (Monge et al. 1993; Lasheras et al. 1996), piperazinylbenzothiazole (**17**) (Monge et al. 1994), piperazinylbenzoxazole (**18**) (Monge et al. 1994), piperazinylbenzimidazole (**19**) (Orjales et al. 1997) have been studied for 5-HT_3 antagonistic activities. Among these derivatives piperazinylquinoxaline (**16**) showed good 5-HT_3 antagonistic activities in the isolated guinea pig ileum as well as in radioligand binding studies (Monge et al. 1993; Lasheras et al. 1996).

4.5. Receptor binding and affinity

Granisetron, dolasetron and its major metabolite have been identified as selective 5-HT_3 RAs with extremely low or



Structure of heteroaryl piperazines as 5-HT_3 receptor antagonists

no affinity towards other receptors. Granisetron, for example has 4000 to 40000 times higher binding affinity for the 5-HT_3 receptors than any other receptor type, which has been studied. The major metabolite of dolasetron, has an affinity for the 5-HT_3 receptor that is 23 to 64 times greater than that of the parent compound (Gregory and Ettinger 1998). In addition to 5-HT_3 receptor binding, ondansetron binds at 5-HT_{1B}, 5-HT_{1C}, α_1-adrenergic and opioid μ receptors (Van Wijngaarden et al. 1990). The affinity of ondansetron for the 5-HT_3 receptor is 250 to 500 times that of other receptors. Despite the differences in chemical structure, receptor binding and affinity, these properties do not appear to have an effect on the therapeutic activity or adverse effect profiles of the 5-HT_3 RAs. In addition, several prospective, randomized comparison trials have shown bio-equivalence between ondansetron and granisetron (Navari et al. 1995), as well as between ondansetron and dolasetron (Hesketh et al. 1996), and granisetron and dolasetron (Audhuy et al. 1996). The same level of therapeutic efficacy has been observed among these agents.

4.6. Pharmacokinetic differences

Granisetron and tropisetron have long elimination half-lifes compared to that of ondansetron. Dolasetron, as the parent compound, has a short elimination half-life (0.13 to 0.24 h), but it is rapidly metabolised to its active metabolite, which has an elimination half-life similar to that of granisetron and tropisetron. Some of the pharmacokinetic parameter of the 5-HT_3 RAs is summarized in the Table. Early clinical studies took these differences in half-life into consideration for the dosage regimens; thus ondansetron was initially administered two times daily compared with once daily for the other 5-HT_3 RAs. It has now been demonstrated that ondansetron, as well as the other 5-HT_3 RAs, can be effectively administered once daily and that the antiemetic efficacy of the compounds persists long after their plasma concentrations are undetectable. This indicates that interactions at the receptor level and not plasma pharmacokinetics are the most important criteria for defining efficacy (Gregory and Ettinger 1998). Other than difference in half-life, other pharmacokinetic parameters of the 5-HT_3 RAs are very similar. Thus, pharmacokinetic differences among these drugs are unlikely to contribute significantly to clinical differences in activity.

5. Dopamine receptor

Over the last few decades, substantial evidence has been obtained indicating that central dopaminergic systems play an important role in the regulation of emesis in humans, ferrets, and dogs. The availability of selective agonists towards dopamine receptor subtypes may prove useful in understanding the role of individual dopamine receptor subtypes in emesis. It is well known that the dopamine agonist apomorphine causes emesis in ferrets, dogs and humans (King 1990). Experiments with dogs have revealed that apomorphine induced emesis may be mediated by dopamine D_2 receptors in the CTZ, located in the AP (King 1990). However, some studies have also reported that apomorphine has equal affinity for dopamine D_2, D_3 and D_4 receptor sites (Seeman and Van Tol 1994). Thus, it is not clear whether that apomorphine-induced emesis is mediated by dopamine D_2 receptors and/or dopamine D_3 and D_4 receptors.

Administration of the *R*(+)-enatiomer of 7-hydroxy-*N,N*-di-n-propyl-2-aminotetralin (7-OH-DPAT), caused emesis in ferrets, whereas the, *S*(−)-enantiomer of 7-OH-DPAT, even at higher doses failed to induce emesis in the ferrets used (Yoshikawa et al. 1996). It has been reported that *R*(+)-7-OH-DPAT had about 40–70 fold more affinity for dopamine D_3 receptors than *S*(−)-7-OH-DPAT. Moreover, the affinity of *R*(+)-7-OH-DPAT for the dopamine D_3 receptor was approximately 60–200 fold higher than that for the D_2 receptor (Damsma et al. 1993; Rivert et al. 1994). In addition, the emesis induced by *R*(+)-7-OH-DPAT was found to be abolished by *S*(−)-eticlopride, a dopamine D_2 and D_3 receptor antagonist. Thus, these findings suggest that D_2 receptors may be involved in *R*(+)-7-OH-DPAT induced emesis in ferrets.

There are no reports whether dopamine D_1 receptor agonists can induce emesis in experimental animals. In one study (Yoshikawa et al. 1996), the selective dopamine D_1 receptor agonist, SKF 38393, did not cause emesis even at higher doses in ferrets. It has been reported that the affinity of *R*(+)-7-OH-DPAT for the dopamine D_1 receptor was approximately 10000 fold lower than that for the D_3 receptor (Levesque et al. 1992). These results clearly indicate that dopamine D_1 receptors are probably not involved in *R*(+)-7-OH-DPAT induced emesis in ferrets.

Pretreatment with dopamine D_2 and D_3 receptor antagonists, *S*(−)-eticlopride and domperidone, inhibited the retching and emetic episodes induced by *R*(+)-7-OH-DPAT in ferrets. However, pretreatment with clozapine, a dopamine D_4 receptor antagonist, did not inhibit the emesis induced by *R*(+)-7-OH-DPAT in ferrets, and *R*(+)-7-OH-DPAT has 1000 fold lower affinity for dopamine D_4 receptor than for dopamine D_3 receptor (Levesque et al. 1992). Therefore, these results indicate that *R*(+)-7-OH-DPAT induced emesis is not mediated via the dopamine D_4 receptor subtype.

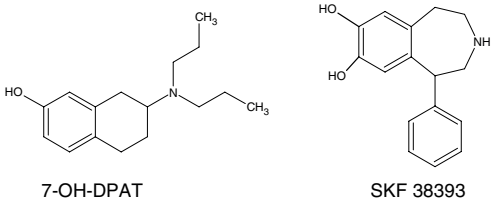
5.1. Central dopaminergic mechanism

Apomorphine is known to produce its emetic effect via the CTZ in the area of the brainstem. For example, it has been shown that apomorphine injected into the AP can induce emesis in ferrets and dogs (King 1990; Harding

Table: Comparative pharmacokinetics of 5-HT_3 RAs in adults with cancer (Lazarus et al. 1990; de Bruijn 1992)

	Ondansetron	Granisetron	Tropisetron	Dolasetron[a]
Dose	0.15 mg/kg, iv.	40 μg/kg, iv.	10 mg iv.	0.6–3.0 mg/kg, iv.
$t_{1/2}$ (h)	3.9	9.0–11.6	7.3	7.9
CL (L/min)	0.398	0.24–0.43	0.96	0.42
Vd (L)	160	154–228	554	109

[a] Pharmacokinetics values reported for the active metabolite of dolasetron
Abbreviations: CL = clearance; iv = intravenous; $t_{1/2}$ = half life; Vd = apparent volume of distribution



7-OH-DPAT SKF 38393

Dopamine receptor ligands

et al. 1997). In addition, the ablation of the AP causes inhibition of apomorphine-induced emesis in dogs (Harding et al. 1997; Carpenter 1990). From these reports, it is suggested that the emetic effect of apomorphine is mediated by central dopaminergic mechanisms. When *R*(+)-7-OH-DPAT was administered into the cerebral ventricle of ferrets, it caused emesis immediately. When administered i.c.v., the emetic effect of *R*(+)-7-OH-DPAT was more than 100 fold more potent than when the drug was given by s.c. injection. Furthermore, *S*(−)-eticlopride administered into the fourth cerebral ventricle, prevented emesis induced by s.c. administration of *R*(+)-7-OH-DPAT. I.c.v. administration of *S*(−)-eticlopride was about 100 fold more potent than s.c. administration in inhibiting the *R*(+)-7-OH-DPAT induced emesis (Yoshikawa et al. 1996). Therefore, these findings indicate that *R*(+)-7-OH-DPAT produces it's emetic effect by an action on central dopamine D_3 receptors in ferrets.

To further confirm the role of central site, the effect of ablation of the AP or vagatomy on *R*(+)-7-OH-DPAT induced emesis in ferrets has been studied (Yoshikawa et al. 1996). In this study, the destruction of the AP markedly abolished the emetic response to s.c. administration of *R*(+)-7-OH-DPAT in ferrets. These findings suggested that the CTZ is essential for the emetic actions of *R*(+)-7-OH-DPAT. These results were supported by the previous report that ablation of the AP prevents emesis induced by central acting agents such as apomorphine, loperamide and nicotine (Carpenter 1990; Bhandari et al. 1992; Beleslin and Krstic 1986). It is known that the vagal nerve also plays an important role in the emesis induced by peripherally acting stimuli such as copper sulphate and cytotoxic drugs (Andrews et al. 1990). In an experiment, abdominal vagotomy, markedly reduced the emetic response induced by cisplatin and no effect on *R*(+)-7-OH-DPAT induced emesis in ferrets (Damsma et al. 1993). These findings also confirm that *R*(+)-7-OH-DPAT exerts its emetic effect through dopamine D_3 receptors located in the AP.

From the clinical point of view, dopamine receptor antagonists such as phenothiazines, butyrophenones and benzamides, which have affinity for dopamine D_2 and D_3 receptors, are useful against emesis associated with administration of anti-parkinsonian drugs, loperamide, morphine and apomorphine. However, these dopamine receptor antagonists have little or weak effects on emesis induced by anticancer therapy and on postoperative nausea. Metoclopramide, which has weak affinity for dopamine D_2 and 5-HT_3 receptors, considerably inhibited the emesis triggered by *R*(+)-7-OH-DPAT, apomorphine, morphine, cisplatin, cyclophosphamide, and doxorubicin. However, this inhibition was not complete except for emesis induced by *R*(+)-7-OH-DPAT and apomorphine. In addition, the traditional antiemetic agent domperidone, a peripheral dopamine D_2 receptor antagonist, has been shown to be effective for the treatment of chronic upper gastrointestinal distress and the prevention of N&V resulting from variety of causes. However, this drug shows only minimal effect against CINV (Yoshikawa et al. 2001).

6. Dopamine-serotonin dual receptor antagonists

Dopamine D_2 and D_3 receptor antagonists are useful against centrally acting emetic stimuli such as apomorphine, loperamide, anti-parkinsonian drugs, etc., but failed to control the N&V associated with chemotherapy (Costall et al. 1990). 5-HT_3 RAs clinically proved to be useful against CINV but do not block all the components of the emesis induced by cytotoxic drugs or by centrally acting emetic stimuli (Yoshikawa et al. 2001). Thus, compounds which target both these receptor sites could serve as broad antiemetic agents. Clinical and experimental studies showed that PONV are not completely inhibited by dopamine RAs or 5-HT_3 RAs alone, but a combination of these two antiemetics was more effective than monotherapy (McKenzie et al. 1996; Wynn et al. 1993). Metoclopramide has antiemetic properties both in low doses as a dopamine antagonist and in high doses as a serotonin antagonist. However, high doses may precipitate undesirable extra pyramidal reactions and akathisia. These evidences suggest that dual dopamine D_2 and 5-HT_3 receptor antagonists may be more useful as antiemetics with a broad spectrum of activity than classical antiemetics which act on each receptor separately.

It has been reported that the *R*-isomer of compound **4** showed potent affinity for both 5-HT_3 and D_2 receptors (Hirokawa et al. 1998a, 2002) (IC_{50}: 2.86 nM and 34.6 nM), while the *S*-isomer of compound **4** was found to be a potent and selective 5-HT_3 RA and showed less affinity for D_2 receptors (IC_{50}: 1.49 nM and 320 nM). Metoclopramide was found to possess less affinity towards both the receptors (IC_{50}: 228 nM and 444 nM), while ondansetron showed good affinity for 5-HT_3 receptors than D_2 receptors (IC_{50}: 1.54 nM and >1000 nM). In the *in vivo* pharmacological screening, (*R*)-**4** completely inhibited apomorphine (1.0 mg/kg, po) induced emesis in dogs with an ED_{50} value of 0.13 mg/kg, po), which was *ca*. 4-fold more than that of metoclopramide (0.45 mg/kg, po). Next, (*R*)-**4** was evaluated for its ability to inhibit the Von Benzold-Jarisch reflux induced by 2-methyl-5-HT in rats. The 5-HT_3 receptor antagonistic activity of (*R*)-**4**, ondansetron and metoclopramide were characterized by IC_{50} values of 1.4, 2.8 and 181 μg/kg, iv., respectively. From the above results, it was concluded that (*R*)-**4** exhibits a strong affinity for the dopamine D_2 and the 5-HT_3 receptors and a potent antagonistic activity in the *in vivo* biological assay for both the receptors.

In another study it has been reported that the *R*-isomer of compound **5** showed potent affinities for both the receptors (Hirokawa et al. 2003, 1998b). The affinities of (*R*)-**5** for 5-HT_3 and dopamine D_2 receptors are approximately 3 fold higher than those of the corresponding benzamide (*R*)-**4** (IC_{50}: 1.20 and 6.88 nM Vs 2.86 and 34.6 nM, respectively). The (*S*)-**5**, showed almost similar affinity for 5-HT_3 but less affinity for dopamine D_2 than those of (*R*)-**5** (IC_{50}: 1.28 and 1.22 nM Vs. 1.20 and 6.88 nM, respectively). (*R*)-**5** also showed good affinity for dopamine D_3 receptors and no affinity for 5-HT_4 receptor (IC_{50}: 1.13 and >10 000 nM). *In vivo*, (*R*)-**5** completely inhibited apomorphine (1.0 mg/kg, po) induced emesis in dogs with an ED_{50} value of 0.12 mg/kg, po, which was *ca* 4-fold more than that of metoclopramide (0.45 mg/kg, po). (*R*)-**5** also significantly inhibited morphine induced emesis in dogs with an ID_{50} value of 14.2 μg/kg, iv, and 136 μg/kg, po. The antiemetic effect of (*R*)-**5** was as potent as that of haloperidol (ID_{50}: 20.2 μg/kg, iv and 122 μg/kg, po) and ca 20-fold stronger than that of metoclopramide (283 μg/kg, iv and 722 μg/kg, po). On the other hand, ondansetron did not cause 50% inhibition even at the high dose of 1 mg/kg, iv. Moreover, morphine-induced emesis model in dogs was used to evaluate the antiemetic activity against postoperative nausea, because morphine is a well known emetogenic agent in man in the postoperative setting (Palazzo and Strunin 1984). (*R*)-**5** also acted as an antagonist for dopamine D_3 receptors, by inhibiting hypothermia in

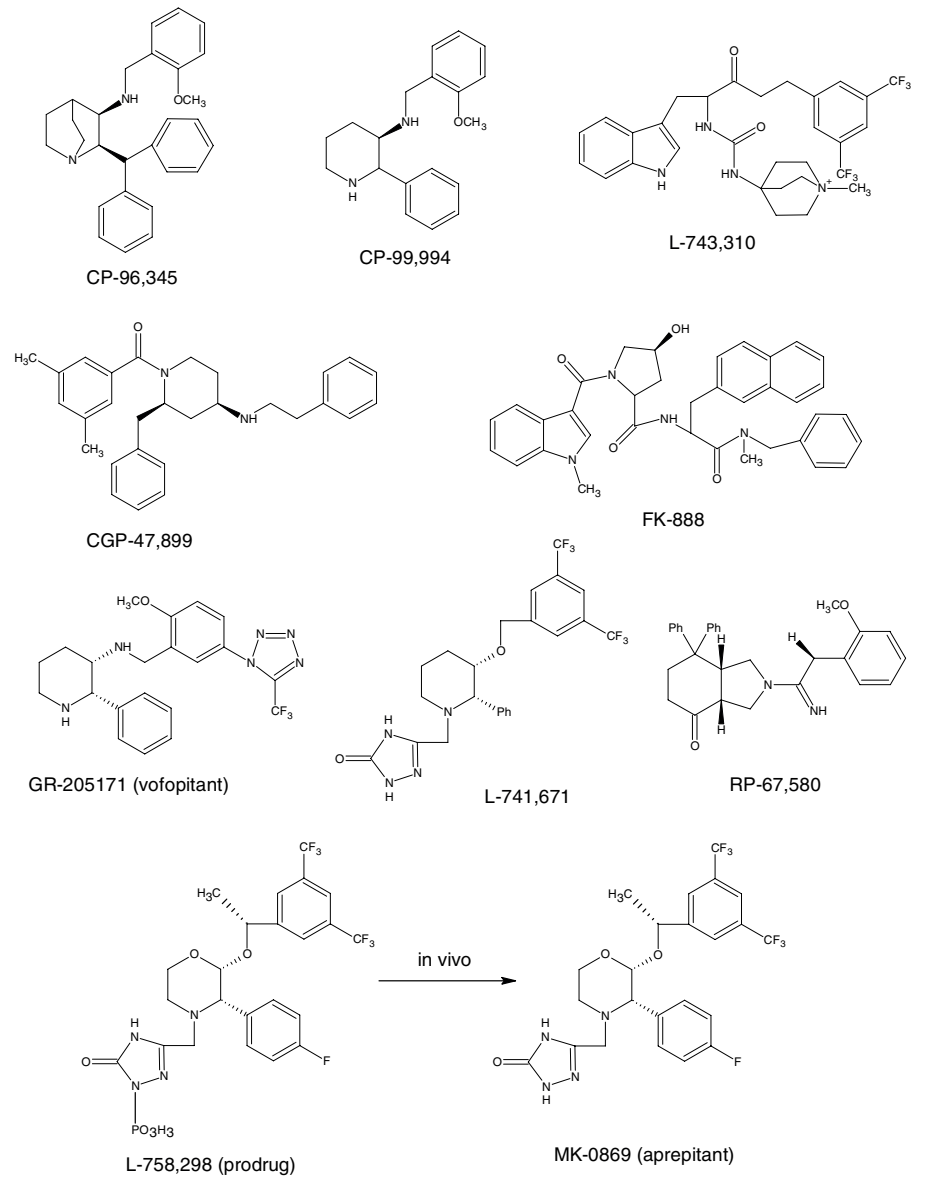
mice induced by R(+)-7-OH-DPAT, a selective dopamine D_3 agonist. In the ferret animal model, (*R*)-**5**, ondansetron and metoclopramide dose dependently inhibited cisplatin induced emesis with ID_{50} values of 17.6 μg/kg, iv. 16.0 μg/kg, iv. and 605 μg/kg, iv. respectively. Moreover, oral administration of these compounds significantly inhibited emesis in ferrets with ID_{50} values of 27.1 μg/kg, po, 27.2 μg/kg, po, and 1250 μg/kg, po, respectively. From the above results, it was concluded that (*R*)-**5** exhibits a strong affinity for the dopamine D_2, D_3 and the 5-HT_3 receptors and potent activity in the *in vivo* biological assay for these receptors than the corresponding benzamide derivative (*R*)-**4,** ondansetron and metoclopramide. Therefore, (*R*)-**5** is expected to be a broad antiemetic agent.

7. Substance P (SP) receptor antagonists

The principal members of the mammalian peptide tachykinins are substance P (SP), neurokinin A and neurokinin B, which bind selectively to the three corresponding neurokinin receptors, NK_1, NK_2 and NK_3. Among these tachykinins, SP has gained much attention due to its agonistic action on NK_1 receptor, which is believed to be involved in the emetic pathway.

SP is found in neurons, particularly in vagal afferent fibers innervating the brainstem NTS (which send impulses to VC) and the AP, when exogenous SP applied to cells in the NTS induces emesis (Gardner et al. 1996). SP acts via the G-Protein coupled NK_1 receptors to generate an inositol phosphate second messenger and thereby exert its biological effects (Otsuka and Yoshioka 1993).

Although early antagonists based on modifications of SP itself did provide peptide reagents useful in the laboratory, a real breakthrough in this field came with the discovery of nonpeptide antagonists. The first of these resulted from SAR studies around a lead structure discovered by empirical file screening with optimization of this template resulting in the potent and NK_1 selective CP-96,345 ($IC_{50} = 0.77$ nM in human IM-9 cells). The disclosure of a structurally-related piperidine with increased potency at the NK_1 receptor CP-99,994 indicates additional optimization in this series of antagonists. Subsequently, several



NK_1 receptor antagonists

structurally unrelated nonpeptide SP antagonists have been reported including RP-67,580 ($IC_{50} = 4.16$ nM for NK_1 binding in rat brain) and CGP-47,899 ($IC_{50} = 10$ nM). Fermentation screening has also yielded structurally novel NK_1 antagonists with cyclic peptide FK 224 showing a mixed spectrum of NK_1 ($IC_{50} = 37$ nM) and NK_2 ($IC_{50} = 72$ nM) antagonism. Modification of FK-224 resulted in the compound FK-888 with enhanced potency and selectivity at the NK_1 receptor (Snider and Lowe 1997).

7.1. Broad spectrum of activity of NK_1 receptor antagonists

Studies in the ferret, cat, house musk shrew and dog have characterized the broad spectrum antiemetic effects of several NK_1 RAs [eg., CP-99,994 (Watson et al. 1995), CP-122,721 (Gonsalves et al. 1996), L-741,671 (Tattersall et al. 1996), L-743,310 (Tattersall et al. 1996), GR203040 (Gardner et al. 1995), GR205171 (Gardner et al. 1996), L-758,298 (Tattersall et al. 2000) and MK-0869 (Tattersall et al. 2000)] both centrally (eg., morphine, apomorphine, loperamide, ethanol) and peripherally (eg., cisplatin, intragastric copper sulphate, abdominal vagal afferent stimulation) acting emetic agents (Watson et al. 1995; Gonsalves et al. 1996; Tattersall et al. 1996; Gardner et al. 1995; Gardner et al. 1996; Tattersall et al. 2000). Interestingly, NK_1 RAs act differently from 5-HT_3 RAs in a sense that the latter do not inhibit emesis elicited by central stimuli such as apomorphine (McLean 1996). Therefore, NK_1 RAs represent not only a new group of compounds for the treatment of emesis, but may also have a wider spectrum of efficacy compared with 5-HT_3 receptor antagonists (Tavorath and Hesketh 1996). In addition, NK_1 RAs prevented both acute and delayed vomiting induced by cisplatin in the ferret, whereas, 5-HT_3 RAs prevented only acute vomiting in this model (Tattersall et al. 2000). It has been reported that NK_1 RA, aprepitant (L-754,030, MK-0869) and its water soluble phosphoryl prodrug, L-758,298, inhibited acute and delayed cisplatin-induced emesis in a ferret animal model (Tattersall et al. 2000). The antiemetic activity of aprepitant also appeared to be enhanced by combination with either dexamethasone or the 5-HT_3 RA, ondansetron. Aprepitant also showed high affinity for ferret and hNK_1 receptors (IC_{50} (nM) ferret 0.7; human 0.1; rat 4.0). It showed poor affinity towards hNK_2 and hNK_3 receptors (IC_{50} (nM) 4500 and 300 respectively). Aprepitant is a selective antagonist for the NK_1 receptor and has no affinity for 5-HT_3 or D_2 receptors (Tattersall et al. 1996).

7.2. Central action of NK_1 receptor antagonists

SP is co-localised with serotonin in enterochromaffin cells in the GIT, and SP levels in the peripheral circulation were elevated following cisplatin administration in humans (Matsumoto et al. 1999). SP has been shown in animals to cross the blood-brain barrier, which raises the possibility that SP of peripheral origin may act centrally to induce emesis (Freed et al. 2001). The efficacy of a particular compound is significantly dependent on brain penetration indicating a central action of NK_1 RAs and the need of brain penetrating compounds for putative therapeutic use (Rupnaik et al. 1997). Injection of the NK_1 RAs, CP-99,994 or MK-0869 (aprepitant), directly into the vicinity of the NTS neurons inhibited cisplatin-induced emesis in ferrets (Tattersall et al. 1996). These results suggests that NK_1 RAs may exert their main antiemetic action by depressing the neural activity of the NTS neurons, with possibly some antiemetic effects from peripheral sites through blockade of the NK_1 receptors located on the vagal terminals in the gut (Minami et al. 1998, 2001).

7.3. Comparison of clinical efficacy of 5-HT_3 receptor antagonists and NK_1 receptor antagonists

The initial clinical studies using the NK_1 RAs demonstrated that the addition of and NK_1 RAs (CP-122,721, CJ-11,794, MK-0869) to the standard therapy (5-HT_3 RA and dexamethasone) prior to cisplatin chemotherapy improved the control of acute emesis compared to the standard therapy alone and improved the control of delayed emesis, compared to placebo. In addition, as a single agent, L-758,298 had a similar effect on cisplatin-induced acute emesis as ondansetron but was superior in the control of delayed emesis (Kris et al. 1997; Cocquyt et al. 2001; Navari et al. 1999; Hesketh et al. 1999). Subsequent studies showed that the combination of aprepitant and dexamethasone was similar to the standard therapy in controlling acute emesis, but inferior in controlling acute emesis compared to triple therapy (aprepitant, 5-HT_3 RA, dexamethasone) (Belle et al. 2002; Campos et al. 2001).
Recently the antiemetic efficacy of aprepitant and standard therapy over more than one cycle of chemotherapy has been studied (de Wit et al. 2004). The data were obtained from two multicenter, randomized, double-blind, placebo-controlled studies with identical design and treatment regimens. Cancer patients receiving a first cycle of cisplatin-based (≥ 70 mg/m^2) chemotherapy were randomized to one of two treatment groups as follows: the standard therapy group received ondansetron 32 mg, iv., and dexamethasone 20 mg on day 1 and dexamethasone 8 mg, b.i.d. on days 2–4. The aprepitant group received aprepitant 125 mg, ondansetron 32 mg, iv., and dexamethasone 12 mg on day 1, aprepitant 80 mg and dexamethasone 8 mg on days 2–3, and dexamethasone 8 mg on day 4. The completed response (no emesis, no rescue) of the aprepitant group in both studies were significantly higher in both the acute period [(61%) ($n = 516$)] and the delayed period [(59%) ($n = 89$)] compared to that in the acute period [(46%) ($n = 522$)] and delayed period [(40%) ($n = 78$)] of the standard therapy. The author concluded that, patients who receive aprepitant in addition to standard therapy had consistently better antiemetic protection that was well maintained over multiple cycles of highly emetogenic chemotherapy compared with patients who received standard therapy alone.
In another clinical trial, it has been observed that patients who received 5-HT_3 RAs had better protection of N&V, occurred within 12 h, whereas patients who received NK_1 RAs had better protection of N&V, occurred after 12 h. Patients who received both drugs had superior control of symptoms compared with patients who received one or the other (Hesketh et al. 2003). This study provides substantial evidence for the involvement of separate pathophysiological mechanisms in CINV. Serotonin mediates the early vomiting process that occurs within 12 h following cisplatin-based chemotherapy, after which time substance P acting at NK_1 receptors becomes the dominant mediator for vomiting.
These results suggest that serotonin may heavily influence the 'early' acute emesis while substance P is a primary mediator of 'later' acute and delayed emesis. Currently, the combination of a 5-HT_3 RA, NK_1 RA, and dexametha-

sone has been shown to provide better control of acute and delayed emesis among the existing therapy options.
Although the efficacy of aprepitant has been proven, there is a need for further studies on the effectiveness in subsequent cycles of chemotherapy. As treatment guidelines often include metoclopramide for the prevention of delayed emesis, aprepitant should be compared with such regimens. At present aprepitant can only be used with highly emetogenic chemotherapy, including high-dose cisplatin.

8. Other receptors/neurotransmitters involved in CINV

8.1. Corticosteroids

The antiemetic action of glucocorticoids to reduce chemotherapy-induced emesis has been hypothesized to involve partly a reduction of prostaglandin synthesis via inhibition of phospholipase A_2 and by preventing cyclooxygenase-2-expression (Sam et al. 2001). This hypothesis is supported by studies in the piglet showing the antiemetic activity of cyclo-oxygenase inhibitors to reduce cisplatin-induced emesis (Girod et al. 2002); besides reports that depict a reduction of radiation-induced emesis in dogs (Carpenter et al. 1986).
Steroids are sometimes used as single agents against mild to moderate emetogenic chemotherapy, but are more often used in antiemetic drug combinations (Chiara et al. 1987). Dexamethasone is a drug of choice in N&V in patients receiving radiation to the brain as it reduces cerebral edema. Antiemetic efficacy in patient receiving cisplatin rises from 40–50% to 80% when dexamethasone is co-administered with a 5-HT_3 RA or metoclopramide. With moderately emetogenic agents such as cyclophosphamide, the rate of complete control rises to over 90% when a 5-HT_3 RA is co-administered with dexamethasone (Carpenter et al. 1986).

8.2. Benzodiazepines

Benzodiazepines such as lorazepam and alprazolam, by themselves are not very effective antiemetics, but their sedative, amnesic and antianxiety effect can be helpful in reducing the anticipatory component of N&V (Greenberg et al. 1987). In addition, they markedly decrease the severity of extra pyramidal side effects, associated with dopaminergic receptor antagonist.

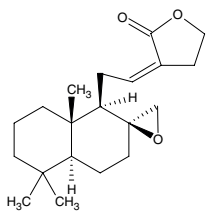
8.3. Cannabinoids

Cannabinoids presumably target higher CNS centers to prevent mild to moderate N&V. Dronabinol (Δ-9-tetrahydro cannabinol) may be used as a prophylactic agent in patients receiving chemotherapy when other antiemetic medications are not effective. Generally cannabinoids are not used as first line antiemetics because of their side effects, dysphoria, hallucinations, sedation, etc. It has been proposed that synthetic cannabinoids may activate the μ-opiate receptor in a so called 'antiemetic' centre, which is supposed to keep the VC in an inhibited state (Vincent et al. 1983; Costello and Borison 1977).

9. Alternative methods for the management of CINV

9.1. Natural remedies for CINV

Powdered rhizome of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has long been used in traditional medicine for alleviating the symptoms of gastrointestinal disorders.



Galanolactone

It has been reported that ginger is used in the treatment of excessive and uncontrolled vomiting occurring in the first trimester of pregnancy (Fisher-Rasmussen et al. 1990), experimentally-induced motion sickness (Stewart et al. 1990) and cisplatin-cyclophosphamide-induced emesis in *Suncus murinus* (Yamahara et al. 1989). It has been published that the acetone extract of ginger contains a diterpenoid, galanolactone, which possesses 5-HT_3 receptor antagonist activity (Huang et al. 1991). However, it is not known whether antagonism of galanolactone is selective or non selective for the receptor. The free radical scavenging activity of gingerol (one of the main constituent of ginger) has also been reported (Krishnakantha and Lokesh 1993). Free radicals play an important role in chemotherapy-induced emesis; antioxidants, eg., glutathione, tiopronin, vitamin C and vitamin E, prevented cisplatin-induced emesis in dogs (Gupta and Sharma 1996). Hence, the antiemetic action of ginger against cisplatin-induced emesis is probably due to 5-HT_3 receptor blocking action and/or free radical scavenging activity. As well accepted traditional medicine, ginger is worth for further clinical evaluation as an antiemetic against CINV.

9.2. Adjunct therapy for CINV

Evidence is emerging that stimulation of acupuncture points, particularly the Neiguan (P6) acupuncture point (located on the inside of the wrist) is helpful in controlling N&V (Mayer 2000; Roscoe and Matterson 2002), while no theory that is generally accepted by the scientific community adequately explains how stimulation of the P6 acupuncture point reduces N&V. However, studies have shown the efficacy of needling (acupuncture), mild electrical stimulation (acustimulation), or constant pressure (acupressure) to the P6 acupuncture point reduces N&V associated with motion sickness (Hu et al. 1995; Bertolucci and Didario 1995), anesthesia (Fan et al. 1997; Harmon et al. 1999), pregnancy (Dealoysio and Penacchioni 1992; Slotnick 2001) and chemotherapy (Dundee et al. 1991; Roscoe et al 2002).
The efficacy of acupressure and acustimulation wristbands for the relief of CINV was studied by the Behavioral Medicine Unit, University of Rochester Cancer Center, New York, USA. In this study (Roscoe et al. 2003), ninety participants were randomly assigned to receive standard treatment (control group), standard treatment with acupressure band or standard treatment with acustimulation band. Patients receiving acustimulation showed better control of N&V, compare to control group. Patients receiving acupressure band showed better tolerance to nausea on the day of treatment, compared to control group. However, these bands did not show any significant effect in delayed N&V. It cannot be ascertained from this study, why these bands were helpful on the day of treatment but not on the following days. It may be related to the fact that the acute

and delayed N&V have different etiologies, as evidenced by the fact that the 5-HT_3 class of antiemetics is more effective than the old line antiemetics for CINV but are less effective than the older drugs for the control of delayed N&V.

10. Conclusion

There is a considerable development in the treatment of acute N&V associated with cancer chemotherapy. Cocktail treatment is proven to be more efficacious than the administration of a single drug, since many receptors/neurotransmitters are involved in the pathway of CINV. The main disadvantage with the currently available treatment is high cost, which many patients cannot afford. Still the delayed phase of N&V is a challenging task to scientists as none of the currently available drugs can completely abolish the delayed N&V. Nonpharmacological strategies to manage N&V are also found to be beneficial. These include acupuncture and acustimulation, which may positively alter a patient's perception of the chemotherapy experience, but not necessarily alter emetic episodes. These strategies are perhaps more useful in treating anticipatory N&V but may also enhance a pharmacologic treatment program as well. There is a need of further research in the treatment of CINV, to achieve the goal of most effective, convenient and economical antiemetics for the management of chemotherapy-induced nausea and vomiting.

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