D_2-dopaminergic receptor and 5-HT_3 serotoninergic receptor antagonists having antiemetic profile

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Metoclopramide is the prototype of the orthopramide family and is used clinically as a stimulant of upper gastrointestinal motility and as an antiemetic. Its antiemetic potential is attributed mainly to the antagonist activity at D_2-dopaminergic receptors in the chemoreceptor trigger zone of the central nervous system. Besides, ondansetron was the first selective 5-HT_3 serotoninergic receptor antagonist used in clinics as an antiemetic. Herein, the antiemetic profile of different chemical classes of D_2-dopaminergic receptor and 5-HT_3 serotoninergic receptor antagonists will be discussed, which may be helpful in the development of potent antiemetic agents.

Keywords:
antagonists, antiemetic, D_2-dopaminergic receptor, 5-HT_3 serotoninergic receptor

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Introduction

Vomiting is the forceful repulsion of the contents of one's stomach through the mouth and sometimes the nose and it may result from many causes, ranging from gastritis or poisoning to brain tumor or elevated intracranial pressure. It is generally considered to be a protective mechanism by which undesirable substances are evacuated quickly from the gastrointestinal tract. Vomiting is different from regurgitation, although the two terms are often used interchangeably. Regurgitation is the return of undigested food back up the esophagus to the mouth, without the force and displeasure associated with vomiting. Nausea, which also has an impact on the gastrointestinal tract, is the sensation of discomfort in the upper stomach with the urge to vomit [1]. Persistent nausea may lead to loss of appetite and reduction of food uptake until the point of malnutrition and debilitation. Gastrointestinal infections (37%) and food poisoning are the most common causes of nausea and vomiting besides side effects from medications (3%) and pregnancy [1,2]. In 10% of people the cause remains unknown [2]. Prolonged and severe vomiting leads to hypochloremia, hypokalemia, alkalosis, and dehydration; it can even cause death, especially in children. Therefore, treatment should be directed mainly toward eliminating the causes of illness. This review focuses on the antiemetic agents that potentially act as antagonists to the D_2-dopaminergic and 5-HT_3 serotoninergic receptors.

Mechanism of emesis

The act of emesis is very complicated and involves a series of coordinated activities and changes in the respiratory and gastrointestinal musculature. It is usually preceded by salivation, nausea, malaise, lassitude, weakness, retching movements, and characteristic postures of the head and body adopted to final expulsion of vomitus [3,4]. This order of events indicates the existence of at least two central areas concerned with the vomiting act, namely, the chemoreceptor trigger zone (CTZ), which can be stimulated by chemical agents such as the dopaminergic apomorphine and transmits impulses to the vomiting centre itself, which is located in the reticular core of the medulla [2].

The latter center lies in proximity to the other centers such as inspiratory and expiratory centers, the vasomotor center, salivary nuclei, and vestibular nuclei. The action of all these centers may manifest as the act of vomiting [2]. Impulses from all these centers pass through the CTZ to the vomiting center, resulting in emesis [5–7].

Sites other than the CTZ may be effective in the stimulation of emesis. Thus, visceral afferent impulses mediated through the parasympathetic and sympathetic routes transmit to the vomiting center impulses that result in the genesis of vomiting [8,9].

Antiemetic agents

Antiemetic agents are drugs that are used for the prophylaxis, control, and prevention of nausea and vomiting. Emesis is the main symptom for motion sickness, during the first trimester in pregnancy, in the case of hyperemesis gravidarum, and of radiation sickness

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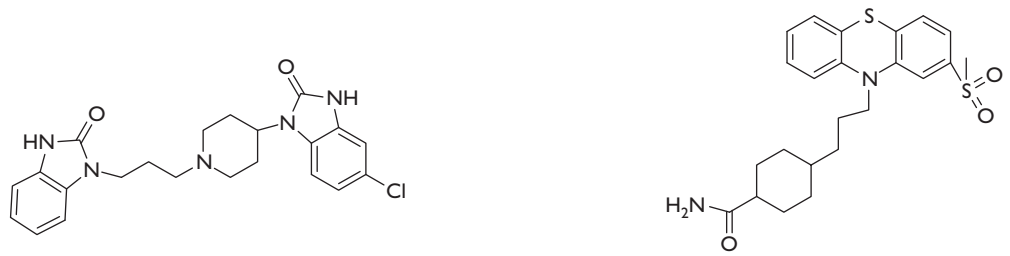
Figure 1



Dompridone(Motillum ®) **1**

Metopimazine **2**

Examples of D_2-receptor antagonist.

resulting during the treatment of tumors by irradiation and using cytotoxic drugs. In addition, postoperative vomiting can also occur, which may be due to the use of general anesthetics and opiate analgesics after surgical operations. Gastrointestinal irritation because of peptic ulcer and ulcerative colitis also leads to nausea and vomiting. Antiemetics include various classes and groups of drugs with versatile pharmacological mechanisms.

Dopaminergic antagonists

The neurotransmitter dopamine plays an important role in neural functions involving reward processes, approach behavior, economic decision making, adaptive behavior, motion, and cognition [10]. Dopamine receptors belong to two subclasses, with D_1 and D_5 receptors sharing homology and coupling with Gs and D_2, D_3, and D_4 receptors coupling with Gi.

Selective D_1-receptor antagonists have been studied as potential therapeutics for Parkinson's disease, psychotic behavior, substance abuse, and obesity [11] in animal models and in human clinical trials [12].

D_2-receptor antagonists were the first antiemetics used; these drugs are currently primarily used as rescue antiemetics. The primary reason for the ignorance of these drugs is frequent induction of extrapyramidal side effects such as akinesia, akathisia, and acute dystonic reactions. Domperidone **1** and metopimazine **2** are examples of D_2-receptor antagonists that are effective against nausea, which is a more troublesome chemotherapy-induced side effect than vomiting; these do not cause extrapyramidal side effects (Fig. 1) [13].

Phenothiazines

Phenothiazine was first synthesized by Bernthsen in 1883. In 1934 [14], it was found to possess insecticidal properties. Later, Hardwood *et al*. [15] discovered the anthelmintic activity of this compound in swine ascaridosis. In 1946, Halpern and Ducrot [16] screened various phenothiazine compounds for antihistaminic properties. The first compound with definite therapeutic value was promethazine **3**, which has proven antihistaminic as well as sedative and hypnotic properties [17].

In 1950, the first neuroleptic phenothiazine prototype, chlorpromazine **4**, was introduced. It possesses a large number of pharmacological activities such as adrenolytic, antidopaminergic, antihistaminic, antiserotonin, antimuscarinic, and antiemetic properties [18–22]. Subsequently, numerous phenothiazines have been introduced such as antiemetics with increased antiemetic potency, reduced cardiovascular effects, milder tranquilizing action, and decreased extrapyramidal side effects [23–25].

The difference in antiemetic activities between the neuroleptic phenothiazines is because of differences in the site of their sequestration in the central nervous system; however, they act predominantly on the CTZ.

Phenothiazines are classified into three groups according to the substituents on nitrogen: (i) aliphatic analogues, which bear acyclic groups; (ii) piperidines, which contain piperidine-derived groups; (iii) piperazine, which incorporate piperazine-derived substituents. The most relevant antiemetic phenothiazines (**3–15**) are illustrated in Table 1.

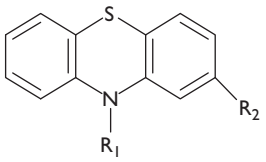
Butyrophenones

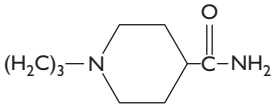
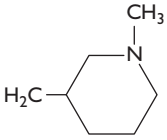
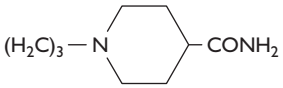
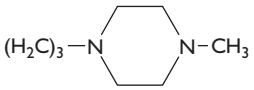
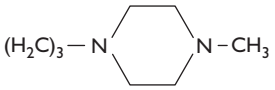
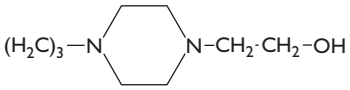
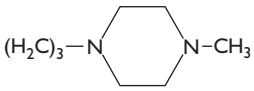
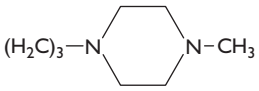
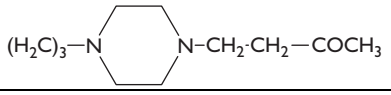
Neuroleptic drugs like droperidol **16** and haloperidol **17** are major tranquillizing drugs, which possess significant antiemetic activity as a result of their D_2-receptor antagonist properties, especially when administered through the intravenous and intramuscular routes [43]. However, side effects [44,45] such as drowsiness, dysphoria, delayed discharge, extrapyramidal reactions, restlessness, and anxiety after discharge have led to the current reluctance to use these agents in the outpatient setting. The structures of the commonly used antiemetic butyrophenones are depicted in Table 2.

Benzamides

Metoclopramide hydrochloride monohydrate (Primperan **21**; Table 3) is a benzamide derivative related to orthopramides class that belongs to the neuropsychotropic, antipsychotic neuroleptics (Table 3). It is a derivative of procainamide but it is virtually devoid of antiarrhythmic or local anesthetic activity in clinical doses [67]. It shows both central and peripheral

Table 1 Antiemetic phenothiazines (*3–15*)



	Name	R_1	R_2	References
Aliphatic analogues	Promethazine (**3**, Phenergan)	$-CH_2-CH(CH_3)N(CH_3)_2$	H	Couvoisier and colleagues [26,27]
	Chlorpromazine (**4**, Largactil)	$-(CH_2)_3N(CH_3)_2$	Cl	Delay and colleagues [28,29]
	Promazine (**5**, Sparine)	$-(CH_2)_3N(CH_3)_2$	CF_3	Wirth [30]
	Triflupromazine (**6**, Vesprin)	$-(CH_2)_3N(CH_3)_2$	H	Yale and colleagues [31,32]
Piperidines	Pipamazine (**7**, Mornidine)		Cl	Dobkin and Purkin [33]
	Mepazine (**8**, Pacatal)		H	Bowes [34]
	Metopimazine (**9**, Compazine)		SO_2CH_3	Jacob and colleagues [35,36]
Piperazines	Trifluoperazine (**10**, Stelazine)		CF_3	Tedeschi *et al.* [37]
	Thiethylperazine (**11**, Torecan)		SCH_2CH_3	Bourquin *et al.* [38]
	Perphenazine (**12**, Trilafon)		Cl	Hotovy and Kapff-Walter [39]
	Prochlorperazine (**13**, Campizine)		Cl	Gralla *et al.* [40]
	Fluphenazine (**14**, Prolixin)		CF_3	Kline and Simpson [41]
	Thiopropazate (**15**, Dartal)		Cl	Toldy *et al.* [42]

antiemetic activities. It is rapidly absorbed orally but has a wide range of oral bioavailability. It has a plasma half life of 4–6 h. In addition to its ability to block dopaminergic receptors at the CTZ, metoclopramide increases lower esophageal sphincter tone and enhances gastric and small bowel motility, thereby preventing delayed gastric emptying caused by opioid analgesics [68]. Although it is not effective in controlling motion sickness, metoclopramide has some peripheral cholinergic actions.

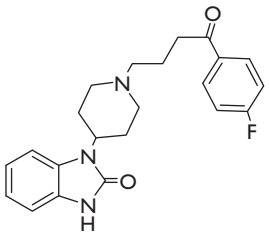
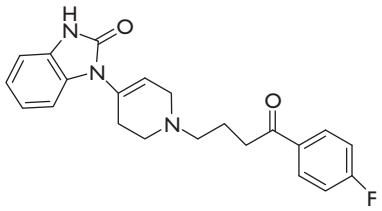
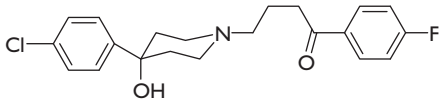
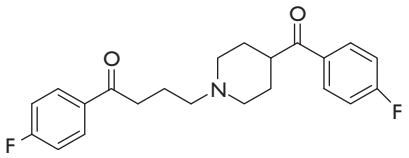
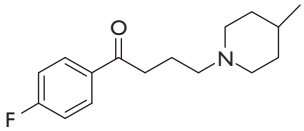
High doses of metoclopramide (1–2 mg/kg) are effective in managing chemotherapy-induced emesis [69]; however, this is associated with high incidence of dystonic reactions and extrapyramidal side effects.

It has been successfully used to treat dyspepsia, gastrointestinal disorders, including irritable colon syndrome, and spastic constipation [67].

This gastroprokinetic activity is attributed to the release of acetylcholine upon stimulation of 5-HT_4 receptors, whereas the antiemetic activity is attributed to the antagonistic activity at both 5-HT_3 serotoninergic and D_2-dopaminergic receptors in the CTZ of the central nervous system. In addition, it stimulates orthograde peristalsis, leading to suppression of the bile reflux, with subsequent promotion of healing of gastric ulcers and prevention of relapse. However, metoclopramide does not accelerate healing of duodenal ulcers [70].

The antiemetic activity of metoclopramide as an antiapomorphine drug is 35 times greater and more selective than that of chlorpromazine [71]. Further, it shows no sedative action at its antiemetic doses [71]. However, at large doses it produces extrapyramidal side effects. It exerts its antiemetic activity through

Table 2 The commonly used antiemetic butyrophenones (*16–20*)

Name	Structure	References
Benperidol **16**		Bobon *et al.* [46]
Droperidol **17**		Domino *et al.* [47]
Haloperidol **18**		Granger and Albu [48]
Lenperone **19**		Nakra *et al.* [49]
Melperone **20**		Grözinger *et al.* [50]

central [72,73] and peripheral [74] dopamine receptor antagonism. Moreover, metoclopramide is ineffective against motion sickness and emesis occurring in labyrinthine episodes [71].

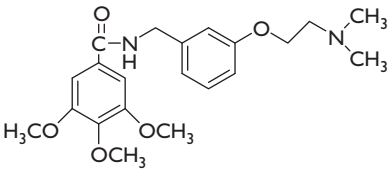
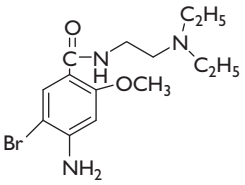
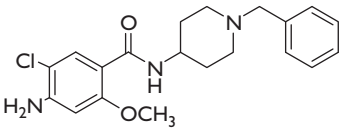
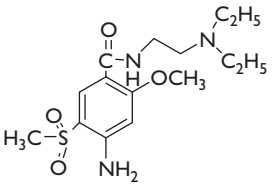
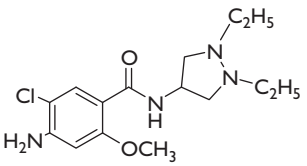
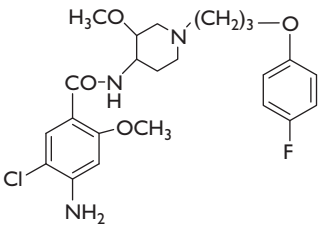
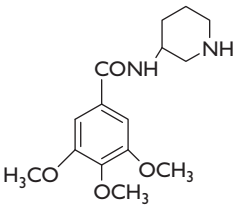
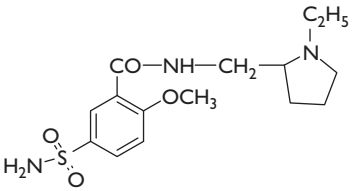
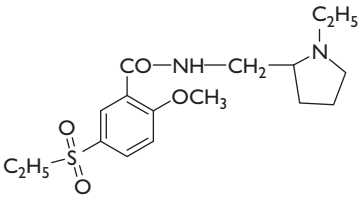
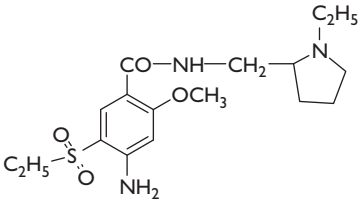
Orthopramides possess three common structural elements required for binding to the receptor site: an aromatic moiety, a carbonyl group or carbonyl group bioisosteres, and a basic nitrogen atom. The weak affinity and lack of selectivity of metoclopramide for dopaminergic and serotoninergic receptors can be explained by the large number of permissible conformers because of the flexibility of its amino chain. Accordingly, Aboul-Enein and colleagues [75,76] studied certain molecular modifications of metoclopramide, which imply (i) a change in the substituents of the aromatic ring, (ii) structural variations in the amine moiety, and (iii) an increase in the lipophilicity through a change in the vicinal carbon atom of the basic nitrogen to a cyclohexane ring (**22–24**; Fig. 2).

These compounds were evaluated for their dopamine D_2-receptor antagonistic activity *in vivo* by measuring their ability to inhibit apomorphine-induced chewing "Zwansgnagen" in rats. Among these compound, **24** possessed an ED_{50} of 5.94 μmol/kg, being nearly two-fold more potent than the previously reported cyclohexane-based dopamine D_2-receptor antagonist **23** (ED_{50} = 11.66 μmol/kg). Molecular simulation study of **24**, including fitting to the three-dimensional model of dopamine D_2-receptor antagonists using Discovery Studio 2.5 programs showed high-fit values [75]. The experimental dopamine D_2-receptor antagonistic activity was consistent with the findings of the molecular modeling study. Other substituted benzamides (Table 3) that have been evaluated as antiemetics include trimethobenzamide (**25**, Tigan), clebopride (**27**), cisapride (**30**), and alizapride (**39**) [77]. Trimethobenzamide is an antiemetic having some structural similarities to both reserpine and antihistamines [78] as well as to orthopramides. It possesses one-tenth to one-twentieth of the antiemetic activity of chlorpromazine. Its antiemetic action is primarily on the CTZ. Trimethobenzamide does not cause depression at very high doses. It has no sedative, hypotensive, or extrapyramidal effects; moreover, it shows no antihistaminic activity, and it proved effective against vomiting from various causes [79,80].

Cisapride **30** has a greater ability than metoclopramide to reverse morphine-induced gastric stasis and is not associated with extrapyramidal side effects. However, cisapride does not prevent the decrease in lower esophageal tone following antagonism by neostigmine in the form of neuromuscular blockade and has lesser antiemetic activity than metoclopramide.

It is worth mentioning that metoclopramide and its congeners, besides being potent antiemetics, show neuroleptic, antidyskinetic, and antiulcer effects, also

Table 3 Antiemetic benzamides *25–39* (orthopramides)

Name	Structure	References
Trimethobenzamide **25**		Report of the Workgroup on Vaccines [51]
Bromopride **23**		Fontaine and Reuse [52]
Clebopride **27**		Cuena Boy and Macia Martinez [53]
Tiapide **28**		Fontaine and colleagues [52,54]
Dazopride **29**		Lunsford and Cale [55]
Cisapride **30**		Van Daele and colleagues [56,57]
Troxipide **31**		Burnton and colleagues [58,59]
Sulpiride **32**		Laville and Margarit [60]
Sultopride **33**		Bruguerolle *et al.* [61]
Amisulpride **34**		Florvall and Oegren [62]

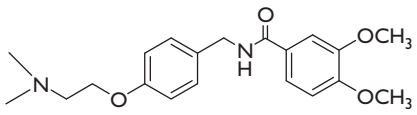
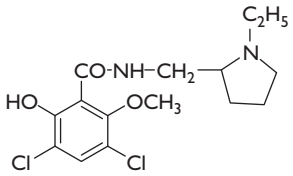
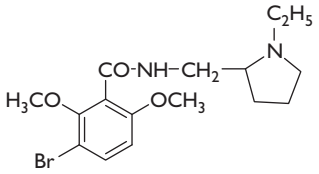
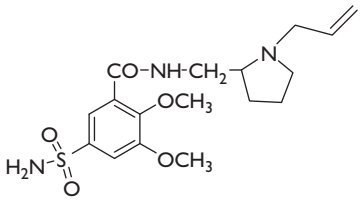
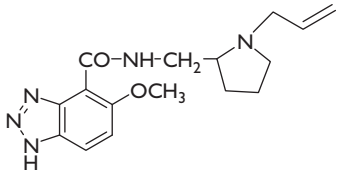
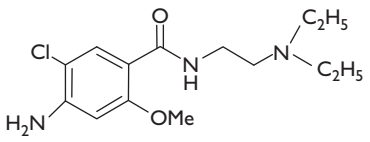
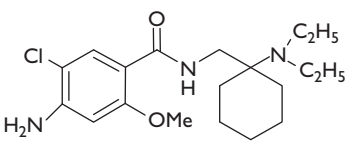
Name	Structure	References
Itopride **35**		Florvall *et al.* [63]
Raclopride **36**		Florvall and colleagues [63,64]
Remoxipride **37**		Florvall *et al.* [63]
Veralipride **38**		Thominet *et al.* [65]
Alizapride **39**		Bleiberg *et al.* [66]

Figure 2

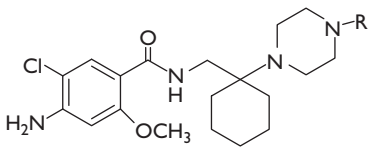


Metoclopramide

21

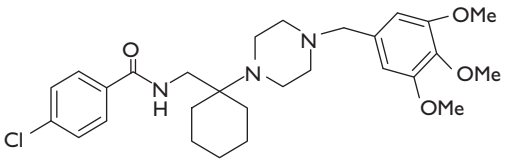


22



R = C_2H_5
R = $CH_2C_6H_5$
R = $CH_2C_6H_2(OCH_3)_3$
R = $CH(C_6H_5)_2$

23



24

Metoclopramide and structurally related compounds.

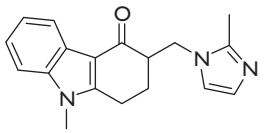
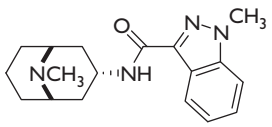
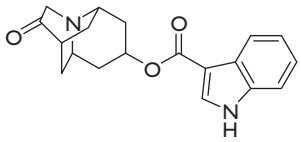
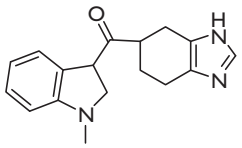
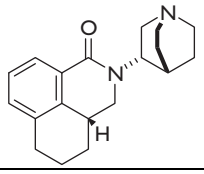
being useful as nonhormonal therapeutic agents in severe cases of menopausal disorders [67,81].

5-HT_3 serotoninergic receptor antagonists

5-HT_3 antagonists are a class of medications that act as receptor antagonists at the 5-HT_3 receptor, a subtype of the serotonin receptors found at the terminal ends of the vagus nerve and in certain areas of the brain. They are used as antiemetics in the prevention and treatment of nausea and vomiting. They are particularly effective in controlling nausea and vomiting caused by cancer chemotherapy and are considered the gold standard for this purpose [82].

5-HT_3 receptors are present at several critical sites involved in emesis, including vagal afferents, the solitary

Table 4 The 5-HT_3 receptor antagonists commonly used as antiemetics

Name	Structure	References
Ondansetron (**40**, Zofran)		Gan [86]
Granisetron (**41**, Kytril)		Gebbia *et al.* [87]
Dolasetron (**42**, Anzemet)		Hainsworth *et al.* [88]
Ramosetron (**43**, Nasea)		Rabasseda [89]
Palonosetron (**44**, Aloxi)		Gebbia *et al.* [87]

tract nucleus, and the area postrema itself. Serotonin is released by the enterochromaffin cells of the small intestine in response to chemotherapeutic agents and may stimulate the vagal afferents (through the 5-HT_3 receptor) to initiate the vomiting reflux. 5-HT_3 receptor antagonists suppress vomiting and nausea by preventing serotonin from binding to the 5-HT_3 receptors. The highest concentration of 5-HT_3 receptors in the central nervous system is found in the solitary tract nucleus and CTZ, and 5-HT_3 antagonists may also suppress vomiting and nausea by acting at these sites [59].

5-HT_3 serotoninergic receptor

5-HT_3 antagonists are most effective in prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), especially that caused by highly emetogenic drugs such as cisplatin. When used for prevention and treatment of CINV, they may be administered alone or, more frequently, in combination with a glucocorticoid, usually dexamethasone. They are usually administrated intravenously, shortly before administration of the chemotherapeutic agent [60], although some authors have argued that oral administration may be preferred [83]. The concomitant administration of an NK_1 receptor antagonist, such as aprepitant, significantly increases the efficacy of 5-HT_3 antagonists in preventing both acute and delayed CINV [84].

5-HT_3 antagonists are also indicated in the prevention and treatment of radiation-induced nausea and vomiting, when needed, and postoperative nausea and vomiting. Although they are highly effective at controlling CINV – they stop symptoms altogether in up to 70% of people and reduce them in the remaining 30% – they are only as effective as other agents in controlling postoperative nausea and vomiting.

Current evidence suggests that 5-HT_3 antagonists are ineffective in controlling motion sickness [85]. A randomized, placebo-controlled trial of ondansetron **40** to treat motion sickness in air ambulance personnel showed subjective improvement, but it was statistically insignificant.

Chemical structures of the first generation 5-HT_3 receptor antagonists [86] can be categorized into three main classes (Table 4).

Carbazole derivatives

Ondansetron **40** was the first 5-HT_3 antagonist; it was developed by Glaxo around 1984. Its efficacy was first established in 1987 in animal models [90]. Several studies have demonstrated that ondansetron produces an antiemetic effect equal to or superior to that of high doses of metoclopramide; however, ondansetron has a superior toxicity profile compared with dopaminergic antagonist agents [88,91]. Ondansetron (0.15 mg/kg) is administered intravenously 15–30 min before chemotherapy, and this dose is repeated every 4 h for two additional doses.

Ondansetron is not approved for use in children younger than 4 years. Its clearance is diminished in patients with severe hepatic insufficiency; therefore, such patients should receive a single injectable or oral dose no higher than 8 mg. The major adverse effects of ondansetron include headache, constipation or diarrhea, fatigue, dry mouth, and transient asymptomatic elevation

in liver function tests (alanine and aspartate transaminases), which may be related to concurrent cisplatin administration.

Indole derivatives

Dolasetron **42** was first mentioned in the literature in 1989 [92]. Both oral and injectable formulations of dolasetron are administered for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses. Dolasetron should be administered intravenously or orally at 1.8 mg/kg as a single dose ~30 min before chemotherapy [87].

Indazole derivatives

Granisetron **41** was developed around 1988 [93]. It has demonstrated the same efficacy and safety margin as ondansetron in preventing and controlling nausea and vomiting at broad-range doses (e.g. 10–80 μg/kg and empirically 3 mg/dose) especially in patients receiving emetogenic chemotherapy, including a high dose of cisplatin [94].

Ramosetron **43** is only available in Japan and certain Southeast Asian countries as of 2008. It has a higher affinity for the 5-HT_3 receptors than do the older 5-HT_3 antagonists, and it maintains its effects over 2 days. It is therefore significantly more effective against delayed CINV [89]. In animal studies, ramosetron was also effective against irritable bowel syndrome-like symptoms [95].

Palonosetron **44** is the newest 5-HT_3 receptor antagonist. It shows antiemetic activity at both central and gastrointestinal sites. In comparison with the older 5-HT_3 antagonists, it has a higher binding affinity to the 5-HT_3 receptors, a higher potency, a significantly longer half life (~40 h; four to five times longer than that of dolasetron, granisetron, or ondansetron), and an excellent safety profile. A dose finding study demonstrated that the effective dose was 0.25 mg or slightly higher [87].

Conclusion

Antiemetics include various classes and groups having versatile pharmacological mechanisms. This review deals with D_2-dopaminergic receptor and 5-HT_3 serotoninergic receptor antagonists possessing antiemetic potential, which could be considered as biocandidates in the development of new antiemetics or targets for extensive molecular modifications in order to accentuate some of their effects and attenuate or abolish side effects.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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