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Review paper

5-HT_3 receptor antagonists, a new approach in emesis: a review of ondansetron, granisetron and tropisetron

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In recent years a new class of agents, the serotonin type 3 receptor antagonists, has been identified. This article reviews the preclinical, pharmacological and clinical data of ondansetron, granisetron and tropisetron, the first representatives of this group. Preclinical work showed that the drugs interfere with a variety of physiological processes, and hold promise for clinical utility in a wide range of areas. To date, these agents have proven, both in early clinical and comparative studies, to be potent antiemetic agents in patients receiving cisplatin and non-cisplatin chemotherapy as well as radiotherapy. In comparative studies the antiemetic efficacy mostly has been superior to conventional antiemetic drugs with regard to the acute chemotherapy-related symptoms; whereas their role in delayed emesis needs further investigation. This also applies for their role as an antiemetic in other types of nausea and vomiting (post-operative). Toxic effects have been modest, no extrapyramidal reactions have been reported. Potential clinical use in psychiatric disorders has been suggested, and the results of clinical trials are awaited.

Key words: Antagonists, antiemetics, chemotherapy-induced emesis, granisetron, 5-HT_3 receptor, ondansetron, tropisetron.

Introduction

The vasoactive alkylamine neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) (Figure 1) was first described by Rapport and Page in 1948.[1] It is mainly present in neurons in the central and peripheral nervous system, in platelets, and in enterochromaffin cells of the intestinal mucosa.[2] Evidence was first obtained for the existence of two types of serotonin receptors over 30 years ago.[3] A major step forward was the recent development of selective agonists and antagonists, enabling for these receptors the investigation of the interaction between 5-HT and its different membrane receptors. At present it is recognized that there are four main types of 5-HT receptor. Furthermore, the existence of subtypes or interspecies differences of the 5-HT, and 5-HT_3 receptors has been suggested.[2,4,5] Moreover some 5-HT receptors cannot be classified in one of these groups,[6] and the classification will therefore certainly undergo further adaptation in the near future.

The 5-HT_3 receptors are neuronal receptors coupled to cation channels, involved in the mediation of the von Bezold–Jarisch reflex;[7] in the provocation of pain from the blister base and intradermal flare response;[7] in nausea/vomiting and gastrointestinal motility;[2,8,9] and in anxiety, drug dependency, and schizophrenia.[10,11] These receptors were first identified on peripheral neurons, as in the sympathetic nerves innervating the heart, postganglionic neurons in the superior cervical ganglion, enteric neurons in the ileum and vagal afferent terminals.[12] Recently 5-HT_3 receptors have been found widespread through the central nervous system, with a high density in the (human) area postrema.[13,14]

Ondansetron (Zofran^R), granisetron (Kytril^R), and tropisetron (ICS 205-930) are the first representatives of a group of highly selective and competitive 5-HT_3 antagonists.[7,15,16]

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Chemistry

Ondansetron (1,2,3,9-tetrahydro-9-methyl 3-[(2-methylimidazole-lyl) methyl] carbazol-4-one hydrochloride dihydrate) (GR38032F), has been developed from methylcarbazolone, which in turn originally descended from a modification of the serotonin molecule (Figure 1). The pure drug is a white, crystalline powder with a molecular weight of 365.8 Daltons, and is stable over a wide range of relative humidities (e.g. 22–96%) at 30°C. At 20°C the solubility is 3.2% w/v in water, and 0.8% w/v in 0.9% saline.[15] Tropisetron [(3α-tropanyl)-1H-indole-3-carboxylic acid ester] (ICS 205-930), was derived from structural modification of 5-HT, using the indole moiety as the nucleus (Figure 1).[7] Granisetron (endo-*N*-(9-methyl-9-azabicyclo [3.3.1] nonan-3-yl)-1-methyl-1H-indazole-3-carboxamide) (BRL46394), however, was developed using metoclopramide as the chemical starting point. First the (diethylamino)-ethyl side chain underwent a restriction in the form of the azabicyclic tropane, and subsequently the aromatic nucleus was modified (Figure 1). The drug has a molecular weight of 348.9 Daltons and a solubility of >40 ng/ml in 0.9% saline at 20°C.[16]

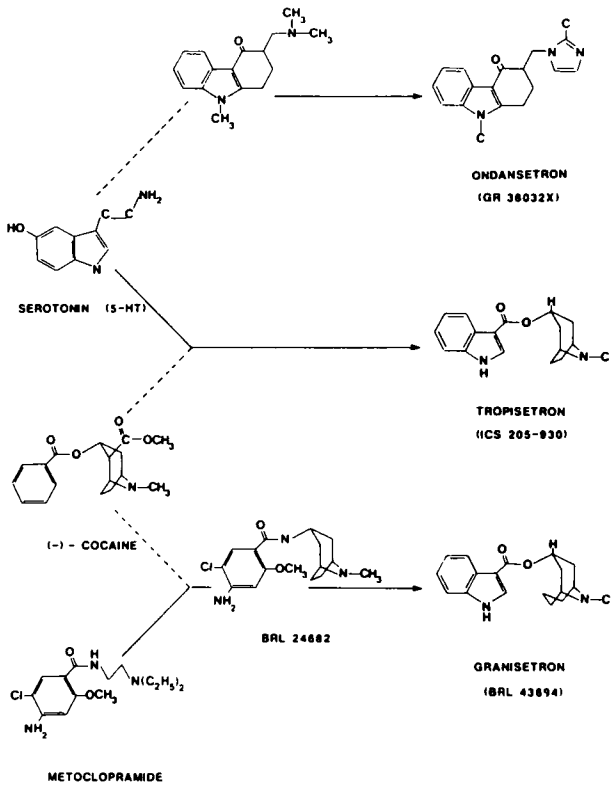

Figure 1. Chemical structure of several 5-HT_3 receptor antagonists.

The common structural feature of these agents is a 6,5 aromatic nucleus connected, via a carbonyl group and a 4-atom unit, to a basic nitrogen atom. It may be that this part adopts a similar configuration which is active at 5-HT_3 receptors.

Mechanism and site of action

In-vitro specificity of 5-HT_3 receptor antagonist activity

The potency of compounds in blocking the 5-HT_3 receptors located on peripheral neurons can be assessed in three different bioassay systems: the rat or rabbit vagus nerve, the rabbit heart and the guinea-pig ileum.[2] The affinity of the different 5-HT_3 receptor antagonists for central 5-HT_3 recognition sites is determined by radioligand binding techniques, using autoradiographic analysis.[13,14] As shown in Table 1, all three antagonists cause a blockade of the 5-HT_3 receptors at each of the three peripheral functional models as well as at central recognition sites. The dose of metoclopramide required for 5-HT_3 receptor antagonism was at least 100- to 1000-fold. Although it has been suggested that the different affinities for the various peripheral 5-HT_3 responses reflect the existence of 5-HT_3 receptor subtypes,[2,7,18] species differences and/or artefacts associated with drug penetration might account for some of the differences.[23] The selectivity of the activity at 5-HT_3 receptors was demonstrated by an absence of antagonistic effect at 5-HT_1-like and 5-HT_2 receptors. Additionally, the three agents were either inactive or only weakly active at a variety of non-5-HT_3 receptors such as $alpha_1$, $alpha_2$, and $beta_1$ adrenoceptors, muscarinic and nicotinic cholinergic receptors, gamma amino butyric acid, histamine H_1 and H_2 receptors, dopamine D_2 receptors, benzodiazepine and neurokinin receptors.[5,7,18,20] Weak activity was observed at the 5-HT_{1A} receptor subtype for granisetron,[20] and at the 5-HT_4 receptor for tropisetron.[6] Ondansetron binds to a second, lower-affinity site which is not related to 5-HT_3 receptors.[5] Overall, this makes the three agents selective, competitive antagonists at 5-HT_3 receptor sites.

Action on the cardiovascular system

The von Bezold-Jarisch reflex is a transient, dose-related and vagally mediated bradycardia and consequent hypotension, following depolarization

Table 1. Activity of different agents at 5-HT$_3$ receptor sites in various isolated tissues and the Bezold-Jarish reflex

5-HT$_3$ receptor site	5-HT	MCP[a]	Ond[b]	Gran[c]	Trop[d]	Ref
Peripheral (p_{A2})[e]						
Rabbit vagus		7.5, 7.7	9.4	—	10.2	17, 18
Rabbit heart		7.2, 6.8	10.5[f]	10.7	10.6	2, 7, 18, 20
Guinea-pig ileum		5.5	7.3, 7	8.1	7.9, 8.1	7, 18–20
Rat brain membranes						
Radioligand (K_i, nM)						
[^{3}H]quipazine	—	120	—	0.3	0.4	21
[^{3}H]GR65630	128	360	2.9	0.6	3.1	13
[^{3}H]zacopride	642	326	4.8	2.7	2.0	22
Bezold-Jarish	i.v.[g]	24[f]	0.4[f]	0.7	0.4	17, 19
Effect in rats	p.o.[h]	5.3	8.0			17
(ID_{50}, μg/kg)	i.v.	—	2.5	—	2.7	18
	p.o.	—	275.0	—	142.0	18
	i.v.	530	3.6	0.7	1.4	23

[a] Metoclopramide.
[b] Ondansetron.
[c] Granisetron.
[d] Tropisetron.
[e] $p_{A2} = -\log K_B$.
[f] Tested against 2-methyl-5-HT.
[g] Intravenous.
[h] Per os.

by various compounds of sensory nerve endings in the wall of the right ventricle. An intravenous (i.v.) injection of 5-HT[24] or 2-methyl-5-HT[18] in anesthetized rats is able to elicit this reflex, known to occur via 5-HT$_3$ receptors. This reflex is inhibited dose-dependently by ondansetron in anesthetized rats and cats.[18,19] This inhibitory activity was also observed in rats after granisetron,[20] and after tropisetron (Table 1)[7,19]. No other cardiovascular effects have been observed after therapeutic doses of ondansetron and granisetron in several animals.[18,25]

Actions on the gastro-intestinal system

Antiemetic properties in animals. Table 2 lists the antiemetic activity of ondansetron, granisetron, tropisetron, and metoclopramide investigated in ferrets and dogs after various emetic stimuli. Compared with the three 5-HT$_3$ receptor antagonists, the dose of metoclopramide required to prevent chemo- and radiotherapy-induced emesis was 50- to 500-fold. On the contrary, unlike metoclopramide, the serotonin antagonists do not protect against apo- and morphine-induced emesis, and motion sickness.[31] Ondansetron was able to re-establish antiemetic control once radiation-induced emesis had already began,[27] and granisetron could terminate chemotherapy-induced emesis within 5–30 s.[28] When comparing the potency and the antiemetic efficacy of the different 5-HT$_3$ antagonists some considerations should be made. No randomized studies have been performed with 5-HT$_3$ receptor antagonists. Moreover, studies from different laboratories are mostly not done under completely identical conditions. The importance of identical study designs and techniques may be apparent from the observation that the emetic potential of an agent varies with dose and route of administration,[31] and that the sensitivity of a certain species differs for various emetic stimuli.[31] Additionally, the study observation time should be sufficiently long in view of the latency time between the administration of some cytotoxic drugs and the onset of emesis.[23] The available data do not allow a careful comparison between those agents.

Effect on gastro-intestinal motility. In the guinea-pig, ondansetron, tropisetron and metoclopramide increased the gastric emptying rate (X-ray location of barium sulfate speroids) in a dose-dependent manner. Both 5-HT$_3$ antagonists (0.001–1 mg/kg) were more potent than metoclopramide (2–5 mg/kg).[33,34] The small-bowel transit time (breath hydrogen analysis) was not altered by ondansetron in the guinea-pig and rat.[33] In 10 healthy volunteers there was no change in gastric

Table 2. Activity of 5-HT_3 antagonists against emetic agents in animals

Emetic agent	Species	Route admin.	Ond[a]	Gran[b]	Trop[c]	MCP[d]	Ref
Cisplatin	ferret	i.v.	+	+	+	±	17, 26, 28, 29
		p.o.		+			23
		in AP[e]	+				27
	dog	i.v.	+	+	+		19, 30
		$4^{th}V$[f]		−			23
Cyclophosph	ferret	i.v.		+		±	8, 28
		s.c.	+	+		±	26, 31
Doxorubicin	ferret	i.v.		+		±	8, 28
Radiation	ferret	i.v.		+		±	8, 28
		s.c.	+	+			26, 31
		p.o.		+			28
	dog	i.v.		+			23
Apomorphine	ferret	s.c.	−	−			31
		i.v.				+	23
	dog	i.v.		−			28, 30
Morphine	ferret	s.c.		−			23
Motion sickness	human		−				32

[a] Ondansetron.
[b] Granisetron.
[c] Tropisetron.
[d] Metoclopramide.
[e] Area postrema.
[f] Ventricle.

emptying rate (radioisotope labeling method), small-bowel transit time (breath hydrogen analysis) and mouth-to-cecum transit time after ondansetron, 16 mg tds, as compared to placebo. In contrast the whole gut transit time (radio-opaque markers) was significantly prolonged to 55 h compared with 32 h in the control population ($p = 0.001$).[9] The latter observation was confirmed in 39 healthy men (39 versus 28 h). The most marked prolongation occurred in the left colon.[35] In healthy subjects, tropisetron was found to shorten mouth-to-cecum time (breath hydrogen analysis), and to enhance gastric emptying of a solid, but not of a semi-solid meal.[36] After the administration of tropisetron, secretory diarrhea in three patients with a carcinoid syndrome was reduced, but no effect was observed in two patients having VIP tumors.[37] Although further information is required, these data indicate that the 5-HT_3 receptor is involved in the regulation of gastro-intestinal motility.
intestinal motility.

Effect on the central nervous system

The development of selective 5-HT_3 receptors was warmly welcomed by investigators in psychiatry, enabling the study of serotonin and its potential central effects.

In four of the five tested animal models predictive of anxiolytic activity (social interaction of rats in high-light conditions, aversion of mice for the light section of a light/dark box, anxiety-related behavior in marmoset and monkey), ondansetron showed a more potent activity than diazepam, and no sedation.[10] Similar anxiolytic activity was also demonstrated with tropisetron and granisetron in the same and another laboratory.[10,38] However, Johnston and File found in their studies only a weak anxiolytic effect for tropisetron and granisetron, and none for ondansetron.[39] The potential anti-psychotic activity of the three agents was suggested by the inhibition of the hyperactivity caused by an infusion of dopamine into the nucleus accumbens of rat or marmoset. The locomotor activity was not depressed and rebound hyperactivity did not occur after cessation of treatment. There was no explanation for the observation that the efficacy of the three compounds, particularly of granisetron and tropisetron, diminished at high doses.[40] In various animals ondansetron prevented some of the behavioral consequences of withdrawal from subchronic treatment with diazepam, alcohol, nicotine and cocaine. Chronic ondansetron use reduced alcohol consumption in alcohol-preferring rats and marmosets.[11]

Site of action

The major detectors of emetic stimuli are located in the gut and the area postrema, in which regions a high density of 5-HT$_3$ receptors has been observed.[12,14] A low dose of ondansetron, 0.01–1 μg, injected directly into the area postrema, inhibited cisplatin-induced retching and emesis in ferrets, compared to control animals.[41] These observations were confirmed for other 5-HT$_3$ receptor antagonists and indicate that at least one functional site for 5-HT$_3$ receptors in modulating the emetic response is the area postrema.

In ferrets it was shown that abdominal vagotomy as well as the three 5-HT$_3$ receptor antagonists markedly reduced or abolished emesis, evoked by total body irradiation and several cytotoxic drugs.[19,26,31] Serotonin and 5-hydroxyindole acetic acid are increased in the ileal mucosa after cisplatin,[26,42] while activation of vagal mechano- and chemoreceptor afferents by 5-HT is mediated by the 5-HT$_3$ receptor. These data indicate that 5-HT$_3$ receptor blockade may occur at abdominal visceral afferents to exert its antiemetic action. However, as yet, insufficient data are available to determine which (if either) of these sites of action is the clinically relevant one.[31] Although it may be clear that it is difficult to compare the different 5-HT$_3$ antagonists, a clear difference between the three agents does not appear from these data.

Pharmacology

Pharmacokinetics

Determination of ondansetron base and granisetron level in plasma is carried out using a high-pressure liquid chromatography (HPLC) procedure. Ondansetron is detected by UV absorption at 305 nm (detection limit 1 ng/ml, working range 1–20 ng/ml),[43] whereas for granisetron a fluorimetric detection is used (lower limit of determination, 0.1 ng/ml).[25] Most data on tropisetron have not yet been published.

Volunteer studies. The pharmacokinetic parameters, established in healthy subjects, after i.v. doses of granisetron ranging from 30 to 300 μg/kg,[44] and various oral and i.v. regimens of ondansetron[45] are summarized in Table 3. Generally plasma levels were related to dose. However, atypical plasma concentration–time profiles (e.g. delayed peak concentration, concentration plateau before the elimination phase) were observed in 30% of the subjects after ondansetron, and could not always be reproduced in the same person.[45] Even so, wide interpatient differences were seen after granisetron.[46] After oral administration of ondansetron absorption began after approximately 30 min, reaching peak levels at *ca* 1.5 h; the bioavailability was ±60%. At steady state there was no evidence

Table 3. Mean values for pharmacokinetic parameters after different i.v. and oral doses of ondansetron and granisetron in healthy subjects[43–45]

Dose level		C_{max} (ng/ml)	AUC (h.ng/ml)	$t_{1/2}$ (h)	V_d (l)	CL_P (ml/min)	CL_R (ml/min)
Granisetron (μg/kg)							
i.v.[a]							
40	(n = 4)	33.8	106.0	4.0	174	556.7	60
50–130	(n = 8)	0.7[c]	3.3[c]	5.5	210	778.3	67
270, 300	(n = 8)	0.7[c]	3.3[c]	5.9	244	781.7	67
Ondansetron (mg)							
i.v.							
8	(n = 16)	95.6	229.4	3.5	163	578.1	10.0
8 + 1/h	(n = 15)	125.2	885.1	3.7	–	601.8	16.9
8	(elderly = 16)	114	317	5.0		421.0	
p.o.[b]							
8	(n = 16)	31.2	133.0	3.2[d]	–	–	17.5
8 tds/5 days	(n = 16)	38.9	–	3.3[e]	–	–	15.6

[a] Intravenous.
[b] Per os.
[c] Dose-normalized mean values.
[d] n = 14.
[e] n = 9.

of undue accumulation. In elderly volunteers (>65 years) pharmacokinetic parameters were mostly similar, although there is a tendency for a reduced plasma clearance (421 ml/min) and a prolonged half-life (5 h).[43,45] Except for plasma levels and AUC values, there were no apparent dose-related changes in the pharmacokinetic parameters over the different dose schedules investigated for both agents, indicating linear pharmacokinetics.

Clinical trials. Pharmacokinetic data were obtained in a small number of patients receiving emetogenic chemotherapy and i.v. either granisetron or ondansetron (Table 4). Plasma levels showed a similar wide inter-patient variability,[25,47–52] and appeared to be somewhat higher with ondansetron compared to those of healthy subjects.[45] Most of the pharmacokinetic data were not clearly different to those observed in healthy subjects, but plasma half-life of granisetron was prolonged (9–11.6 h).[25,52,53] All the pharmacokinetic parameters of ondansetron were 2- to 3-fold greater in elderly patients (>65 years) when compared to younger healthy subjects (<40 years). There was however no major accumulation indicating that dose adjustment is not necessary.[54] For both agents, although more pronounced for ondansetron, there was a trend toward a better antiemetic control or better protection against failure with higher AUC or plasma concentration.[47,48,50,53]

Metabolism

Ondansetron is widely distributed and metabolized, primarily by hydroxylation followed by glucuronide and sulfate conjugation. The major proportion of the drug (60%) is rapidly excreted in man via the urine with less than 10% of the parent drug recovered unchanged in the urine.[55] Granisetron is also extensively distributed and rapidly cleared, primarily by hepatic metabolism, as less than 15% of the parent compound was identified in the urine.[25]

Toxicology

Animal studies

An extensive series of toxicological tests was carried out in rodents and dogs, using dose levels of ondansetron from 30- to 100-fold higher than human doses, and at least 1000 times the dose required for 5-HT_3 receptor blockade *in vivo*, for as long as 18 months. Toxic effects, consisting of decreased blood pressure and heart rate, were observed at doses of 10 mg/kg i.v., whereas behavioral changes (ataxia, convulsions) occurred only at near-lethal doses (rats >30 mg/kg, dogs >12.5 mg/kg). At the higher dose levels transient increases of serum transaminases (max.50%) were observed, which were not accompanied by

Table 4. Mean values for pharmacokinetic parameters of ondansetron and granisetron in patients receiving emetogenic chemotherapy

Dose level		C_{max} (ng/ml)	AUC (h.ng/ml)	$t_{1/2}$ (h)	V_d (l)	CL (l/h/kg)	Ref
Granisetron (μg/kg)							
i.v.							
40	(n = 18)	37.5	350	10.6	2.2	0.21	25
range		11–124	66–1127	3–21	1–4	0.04–0.6	52
80	(n = 12)	67.7	359	9.7	3.3	0.48	25
Ondansetron (mg)							
i.v.							
0.15/kg × 3/day		119	1,590	3.9	1.68	23.9[a]	48
5 days	(n = 12)						
8 + 1/h	(n = 15)	109	1,415	–	–	19.6[a]	49, 50
10 + 2/h	(n = 19)	173	2,500			17.3	50
12 + 4/h	((n = 9)	276	4,517			18.4	50
p.o. elderly							
8 tds/4 days		118.0	500[b]	8.2			54
range	(n = 10)	92–151	275–998	5.6–9.4			

[a] l/h.
[b] AUC (0–8 h).

macro- and/or microscopic changes of the liver structure. A further, wide variety of toxicological studies did not show any indication for reproductive, genetic, teratogenic or oncogenic effects.[56] In rats the non-toxic level of granisetron was 3 mg/kg/day, the dose-limiting toxicity consisted of seizures and ECG changes at doses of 10 mg/kg; in dogs the maximum tolerated i.v. dose was 3 mg/kg.[25]

Human studies

No major adverse events were reported after the administration of ondansetron to 223 volunteers and 438 patients with psychiatric disorders, postoperative emesis and pain in more than 2000 occasions. Mainly two categories of symptoms appeared related to ondansetron, occurring more frequently in repeat (R) compared to single (S) dose studies. These were headache (S:17%, R:31%), and constipation/abdominal discomfort (S:1%, R:16%). Headache, however, was also often reported after repeat doses of placebo (S:5%, R:28%).[56] Similarly minor adverse effects were noticed after granisetron. Constipation was first encountered at a dose of 80 μg/kg, occurring in four out of eight volunteers at 160 μg/kg. Although headache was observed quite often after a placebo administration (9%), the incidence was higher with granisetron (15%).[46] Transient mild elevations of transaminases were reported occasionally with both drugs (ondansetron 5%), but also after placebo (12%).[46,56]

Clinical trials

Phase I/dose-escalating phase II studies

In cisplatin-containing regimens, dose-ranging antiemetic studies with ondansetron have been performed using continuous infusion schedules or intermittent bolus doses (Table 5). Pharmacokinetic modeling indicated that a consistent concentration above 30 ng/ml, thought to block all 5-HT$_3$ receptors, could be achieved with a bolus dose of 8 mg i.v. followed by an hourly infusion of 1 mg for 24 h, which was therefore used as the basis in European studies. The antiemetic efficacy of this and higher dose schedules showed a complete antiemetic control in 20–40% of the chemotherapy-naive and pretreated patients. A dose–response relationship was not established.[49,57] In dose-ranging trials in the United States the antiemetic efficacy of either three or six bolus doses of ondansetron (range 0.01–0.48 mg/kg) was evaluated at 2–8 h intervals.[58–63] Antiemetic response was poor with bolus doses below 0.1 mg/kg. The highest antiemetic response rate was obtained with bolus doses of 0.12–0.18 mg/kg. At higher doses, used in later trials, no improvement of results was seen. So far no schedule-dependent efficacy has been found. In multiple-day cisplatin regimens a dose of 0.15 mg/kg of ondansetron given three times at 2- or 6-h intervals showed complete control in 36–82% of the chemotherapy-naive patients and in 33–75% of the pretreated patients. An increased bolus dose of ondansetron (0.3 mg/kg) did not result in improved control.[48] There was a trend toward decreased activity on the third and fourth day of treatment, which is in contrast with other non-5-HT$_3$ antagonistic antiemetics.[60,64]

In phase I/II studies 10 μg/kg of granisetron showed no antiemetic efficacy. At a dose of 40 μg/kg complete control was obtained in 38–55% of the patients, both in cisplatin and non-cisplatin-based chemotherapy. A dose escalation up to 160 μg/kg did not increase the antiemetic response.[25,65–68] Obviously postponement of the granisetron infusion for 2, 4, 6 h had no impact on its efficacy.[52] Preliminary results with oral granisetron, at doses of 1 and 2.5 mg bd, indicate that it is also effective.[69] Up to now, only a few data on tropisetron have been published. Doses of 5–40 mg and 5–48 mg/m^2 have been tested, and again there was no dose–response relationship. Five or 10 mg of tropisetron seemed to be as effective as the higher doses (Table 5).[70–73]

In a further five open trials ondansetron was administered to 107 evaluable patients (65 chemotherapy-naive, 42 with refractory emesis), receiving non-cisplatin chemotherapy (e.g. cyclophosphamide >500 mg/m^2, doxorubicin >50 mg/m^2, ifosfamide 5 g/m^2). A loading dose of 8 mg (oral, i.v. or partly i.v./oral) was given before chemotherapy, and followed by 4 mg 6-hourly or 8 mg 8-hourly for 2–4 days. The combined results showed complete protection in 69% of the chemotherapy-naive patients and in 67% of the patients with previously refractory emesis.[74] There was no clear difference between the various treatment schedules. Different doses of oral ondansetron (2 mg qds, 4 mg tds/qds, 8 mg tds) were administered to 54 evaluable patients receiving radiotherapy to the upper abdomen (field >100 cm^2). The 2 mg dose was not effective in single-exposure irradiation; higher ondansetron doses (4, 8 mg) completely controlled emesis in 59% and 62% of patients. With fractionated irradiation complete antiemetic control occurred in 33% of the

Table 5. Antiemetic results of 5-HT_3 antagonists in emetogenic chemotherapy, open phase I and early phase II studies

Number	Prior treatment no/yes	Antiemetic dose	Cisplatin dose (mg/m^2)	Antiemetic response *n* (%)			Ref
				CR[a]	MR[b]	F[c]	
Ondansetron							
Continuous infusion (mg)							
42	n/y	8 + 1/h/24h	70–120	16 (38)	8 (19)	18 (43)	57, 49
6	n/y	10 + 2/h/24h	100–120	2 (33)	1 (17)	3 (50)	49
10	n/y	12 + 4/h/24h	100–120	2 (20)	1 (10)	7 (70)	49
7	n	12 + 3/h/18h	>99	2 (28)	2 (28)	3 (44)	57
Intermittent bolus doses (mg/kg)							
23	n/y	0.04–0.35 × 3 2-hourly	60–120	8(35)	14 (61)	1 (4)	58
38	n/y	0.01–0.48 × 3 4-hourly	>59	17 (45)	13 (34)	8 (21)	59
10	n	0.18 × 3 2-hourly	>99	3 (30)	2 (20)	5 (50)	60
10	n	4-hourly	>99	4 (40)	2 (20)	4 (40)	60
39	n/y	6-hourly	>59	22 (57)	11 (28)	6 (15)	59, 61
36		8-hourly	>99	18 (50)	8 (22)	10 (28)	61
17	n	0.18 × 6 4-hourly	>99	7 (41)	4 (24)	6 (36)	62
79[d]	n	0.15, 0.3 × 3 4-hourly	>99	41 (52)	12 (15)	26 (33)	63
Granisetron (μg/kg)							
22	n/y	10–40	20–100	12 (54)	4 (18)	6 (28)	65
13	n	40, 80	25–120	7 (54)	5 (38)	1 (8)	25
9	n	40, 80	Doxo[e]/CTX[f]	5 (55)	4 (45)	0	25
20	n/y	40–100	13 pts > 50 various CT[g]	9 (45)	4 (20)	7 (35)	66
32	y	100	66–120	12 (38)	9 (28)	11 (34)	67
149	n	40	>49	92 (62)	24 (16)	33 (22)	68
147	n	160	>49	93 (63)	20 (14)	34 (23)	68
Tropisetron (mg)							
22	n/y	12–48/m^2	10 pts > 99 various CT	8 (36)	5 (22)	9 (42)	70
22	y	5–20/m^2	75–100	7 (31)	5 (23)		71
25	n/y	10–40	60–100	33 (59)	17 (30)	6 (11)	72
(56 courses)							
100	n	5–40	>50	54 (54)	23 (23)	23 (23)	73

[a] Complete response.
[b] Major response.
[c] Failure.
[d] Results of the 0.015 mg/kg dose not included (CR:15%).
[e] Doxorubicin.
[f] Cyclophosphamide.
[g] Chemotherapy.

patients receiving 2 mg qds and in 83% with a dose of 4 mg qds.[75]

Comparative studies

Highly emetogenic chemotherapy (cisplatin > 50 mg/m^2). The comparison of the efficacy of 3 i.v. doses of ondansetron (0.15 mg/kg) given at 4-h intervals with metoclopramide (2 mg/kg) given three times 2-hourly showed a complete control of 40% with ondansetron and of 30% with metoclopramide ($p = 0.07$).[76] The results of two double-blind, crossover studies comparing the antiemetic efficacy of a continuous infusion of ondansetron (8 mg + 1

mg/h/24 h) with metoclopramide (3 mg + 4 mg/kg/8 h) in 171 naive patients demonstrated similar results which were significantly in favor of ondansetron with regard to nausea and control of acute emesis ($p < 0.02$) (Table 6).[77,78] Recent data indicate that a single bolus dose of 8 mg of ondansetron is as effective as a dose of 32 mg, either given as a single bolus or a continuous infusion (CR: 55%, 58%, 57%, respectively; unpublished data.)[79] Three different trials investigated the antiemetic efficacy of a single dose of either granisetron or tropisetron in comparison with a combination of dexamethasone and metoclopramide; the latter was given as either a continuous infusion or a bolus dose regimen (Table 6). In these studies the single dose of each 5-HT$_3$ antagonist was as effective as the combination regimen; an additional dose of granisetron was able to relieve breakthrough symptoms in most of the patients.[80–82] The addition of dexamethasone to ondansetron significantly increased antiemetic control (CR: 91% versus 64%, $p < 0.05$).[83]

The incidence of delayed emesis was less after ondansetron (16 mg tds) compared to placebo.[76] Compared to metoclopramide, the control of delayed emesis was not different with either ondansetron or tropisetron.[78,82] In fact, metoclopramide showed a better control of delayed nausea than ondansetron.[78]

Moderately emetogenic chemotherapy (non-cisplatin or cisplatin 20–50 mg/m^2). In three different double-blind studies the antiemetic efficacy of ondansetron and metoclopramide has been compared in mainly female patients receiving non-cisplatin chemotherapy. Acute nausea was better controlled with ondansetron. Complete control of acute emesis varied between 60 and 66% with ondansetron versus 27–49% with metoclopramide ($p < 0.001$). Delayed emesis occurred less after ondansetron

Table 6. Results of 5-HT$_3$ antagonists in highly emetogenic chemotherapy (phase II/III trials)

Number	Male Female	Platin dose (mg/m^2)	Antiemetic dose		Antiemetic response *n* (%)				Ref
			(1) 5-HT$_3$ antagonist	(2) Comparative drug	(1) CR[a]	(1) MR[b]	(2) CR	(2) MR	
Acute cisplatin emesis									
			Ond[c] (mg)	MCP[f] (mg)					
274	209	>99	0.15/kg × 3	2 × 3/2-h	58 (40)	37 (30)	41 (30)	30 (22)	76
	98			2 × 3/3-h					
76	41	80–100	8 + 1/h/24h	3 + 4/kg/8h	35 (46)	22 (29)	12 (16)	20 (26)	77
	56								
95	53	50–100	8 + 1/h/24h	3 + 4/kg/8h	41 (44)	27 (28)	21 (22)	18 (19)	78
	68								
305	165	50–100	8 + 1/h/24h		(58)	(18)			79
	140		32		(57)	(15)			79
			Gran[d] (μg/kg)						
234	63	>49	40	MCP 3 + 4/kg/	80 (70)	17 (15)	83 (69)	10 (8)	80
	37			8h + Dex[g] 12 mg					
149		>49	80	MCP 2/kg × 5	34 (46)		33 (44)		81
				Dex 20 mg					
				Diphenh					
			Trop[e] (mg)	MCP (mg)					
253		>49	5 i.v.	3/kg × 2	80 (63)	30 (24)	79 (63)	29 (23)	82
				Dex 20 mg					
Delayed cisplatin emesis									
45			Ond 16 tds	placebo	significant difference on day 4				76
79			Ond 8 tds	MCP 20 tds	28 (36)	16 (21)	29 (37)	24 (30)	78
216			Trop 5 od	MCP 10 tds	(61–91)		(76–90)		82

[a] Complete response.
[b] Major response.
[c] Ondansetron.
[d] Granisetron.
[e] Tropisetron.
[f] Metoclopramide.
[g] Dexamethasone.

Table 7. Antiemetic results of 5-HT_3 receptor antagonists in moderately emetogenic chemotherapy (phase II/III trials)

Number	Male Female	Platin dose (mg/m^2)	Antiemetic dose		Antiemetic response *n* (%)				Ref
			(1) 5-HT_3 antagonist	(2) Comparative drug	(1) CR[a]	(1) MR[b]	(2) CR	(2) MR	
		Chemo	Ond[c] (mg)	MCP[d] (mg)					
68		FAC[e]/FEC[e]	Ac[f]: 4 i.v./4 p.o.	60 i.v. + 20 p.o.	23 (66)	7 (20)	9 (27)	5 (15)	84
			Del[g]: 8 tds	20 tds	33 (58)	13 (23)	28 (49)	9 (16)	
82		EC/AC	Ac: 8 i.v.	60 i.v.	26 (65)	6 (15)	17 (41)	9 (21)	84
		±F	Del: 8 tds	20 tds	29 (76)		25 (68)		
109		EC	Ac: 8 p.o.	60 i.v.	30 (60)	6 (12)	28 (47)	8 (14)	84
			Del: 8 tds	20 tds	(69)		(65)		
225	79	carbopl	Gran[i] 40 μg/kg	Chlorprom	80 (70)		55 (49)		86
	149	CTX[h]		Dex[k] 12 mg					
		platin <50							

[a] Complete response.
[b] Major response.
[c] Ondansetron.
[d] Metoclopramide.
[e] F = 5-fluorouracil, A = doxorubicin, C = cyclophosphamide, E = epirubicin.
[f] Acute.
[g] Delayed.
[h] Cyclophosphamide.
[i] Granisetron.
[k] Dexamethasone.

compared to metoclopramide, but this difference was not always statistically significant.[84] The combined data showed a superiority of ondansetron above metoclopramide on days 2 and 4 ($p = 0.001$, $p = 0.013$). Recently it has been shown that a twice-daily oral administration of 8 mg of ondansetron is as effective as a three times a day dose, for the first 24 h as well as for the following 2 days.[85] Compared with a combination regimen of chlorpromazine and dexamethasone, granisetron showed significantly better control of acute nausea and emesis in patients receiving moderately emetogenic chemotherapy (CR: 70% versus 49%, $p = 0.001$)[86] (Table 7).

Table 8. Percentage of adverse effects in comparative trials[56,88,89]

%	Ond $n = 338$	MCP $n = 156$	Gran $n = 982$	Compar[a] $n = 233$
Headache	17	8.5	14	5
Diarrhea	15	22.5	1	6
Constipation	3.5	1	4	1
Sedation	3	4	2	10
Abd. discomfort	25	2	0	
Extrapyramidal reactions	0	5	0	
Akathisia	0	3	0	

[a] Comparative antiemetic.

Radiotherapy. Ondansetron, at a dose of 8 mg tds, provided superior control in the prevention of acute nausea and emesis following radiotherapy compared to 10 mg of metoclopramide tds. Because the latter dose is not optimal, further studies are warranted.[87]

Adverse effects

Clinical symptomatology. The assessment of a causal relation of a side effect with an antiemetic drug in chemotherapy trials may be difficult because of the underlying disease and the use of cytotoxic drugs with intrinsic toxicities. It is therefore more realistic to consider the side-effect profile in comparative trials. The reported side effects for 5-HT_3 antagonists were generally minor and transient (Table 8). Furthermore, they were similar irrespective of the type of chemotherapy, but the frequency was lower in less emetogenic chemotherapy. Consistent adverse events in comparative trials were headache and constipation; no extrapyramidal reactions were seen whilst on treatment with a 5-HT_3 antagonist.[56,88,89] In multiple-day trials with ondansetron the incidence of adverse events was increased, with diarrhea occurring less (6% versus 23%) and constipation more frequently (11% versus 0%).[88]

Laboratory findings. Occasional minor changes in liver function tests have been noted (transaminases) with ondansetron which were not dependent on dose, treatment duration, or route of administration. At the moment this is rather thought to be associated with the cisplatin dose.[88] Similarly, no major abnormalities have been reported with granisetron and tropisetron.[89]

Conclusion

Serotonin 5-HT$_3$ receptor antagonists are a new class of drugs with an established antiemetic efficacy in the prevention of radiotherapy- and acute chemotherapy-induced emesis. They protect against delayed emesis induced by moderately emetogenic chemotherapy, but their role in delayed cisplatin-induced nausea and vomiting requires further investigation. A major advantage of the compounds is their ease of administration and the absence of extrapyramidal reactions. Their interference with gastro-intestinal motility which appears from the recorded constipation needs attention. Besides headache, no other causally related adverse effects or laboratory changes have been observed. Finally, the three compounds discussed do not appear to be essentially different, either in antiemetic activity or in safety profile.

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