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5-HT$_3$ Receptor Antagonists for the Prevention of Chemotherapy-Induced Nausea and Vomiting

A Comparison of Their Pharmacology and Clinical Efficacy

R. Elizabeth Gregory and *David S. Ettinger*

Johns Hopkins Oncology Center, Baltimore, Maryland, USA

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Summary

In the mid-1980s it was discovered that serotonin (5-hydroxytryptamine; 5-HT) was at least partially responsible for producing chemotherapy-induced nausea and vomiting. It was therefore realised that serotonin receptor blockade with serotonin 5-HT$_3$ receptor antagonists could inhibit chemotherapy-induced nausea and vomiting.

5-HT$_3$ antagonists have different chemical structures and receptor binding affinity. Granisetron, dolasetron and its major metabolite are pure 5-HT$_3$ antag-

onists, while ondansetron and tropisetron are weak antagonists at the 5-HT_4 receptor. Ondansetron has also been demonstrated to bind at other serotonin receptors and to the opioid μ receptor.

The half-lives of granisetron, tropisetron and the active metabolite of dolasetron are 2 to 3 times longer than that of ondansetron. These observations initially suggested that more frequent ondansetron administration would be required; however, it has now been shown that receptor blockade does not correlate with elimination half-life and all 5-HT_3 antagonists can be effectively administered once daily.

Clinical trials have been conducted that directly compare the 5-HT_3 antagonists. To compare these studies, it is necessary to assess trial design, including known risk factors for the development of chemotherapy-induced nausea and vomiting, and response criteria. Stratification for risk factors, use of strict efficacy criteria and randomisation to a blinded trial using an appropriate comparative regimen are essential for a well designed antiemetic trial.

Comparative clinical trials using various doses, routes and regimens of administration have been conducted with 5-HT_3 antagonists. Despite some trial design shortcomings, most of the studies show equal efficacy between the agents, especially in moderately emetogenic chemotherapy and mild, infrequently occurring adverse effects. The addition of steroids also appears to improve outcome. However, since many doses and regimens of ondansetron were used, further study is needed to determine the optimal regimen.

The efficacy of 5-HT_3 antagonists in controlling delayed nausea and vomiting from chemotherapy is less well studied. Further, there is no good scientific rationale for the use of 5-HT_3 antagonists in controlling delayed nausea and vomiting since serotonin has not been shown to be released during the delayed phase. In fact, most studies show no benefit or modest benefit of 5-HT_3 antagonists over placebo.

Because the 5-HT_3 antagonists perform similarly in the clinical setting, pharmacological differences do not seem to translate into therapeutic differences. There is also no appreciable difference in the incidence or severity of adverse effects among the 5-HT_3 antagonists. Determination of clinical use may then be driven by cost.

Until the introduction of serotonin (5-hydroxytryptamine; 5-HT) 5-HT_3 receptor antagonists, control of chemotherapy-induced nausea and vomiting was either inadequate or produced unacceptable adverse effects. 5-HT_3 antagonists have improved the control of nausea and vomiting without producing concomitant unacceptable adverse effects. There are currently four of these agents available worldwide and all four are deemed effective and safe, but each has different characteristics and has been studied under different clinical conditions. This report reviews the pharmacological differences and the comparative clinical trials with these 5-HT_3 antagonists to highlight their differences and clinical efficacy.

1. Pathophysiology of Chemotherapy-Induced Nausea and Vomiting

In order to understand the antiemetic pharmacology of 5-HT_3 antagonists, it is necessary to understand the pathophysiology of chemotherapy-induced nausea and vomiting. While the events leading to vomiting have been elucidated, the mechanisms that trigger nausea are less well understood.

1.1 The Mechanisms of the Emetic Response

Vomiting results from an intricate series of physiological events mediated by humoral factors and afferent fibres and both inhibition and excitation of somatic visceral musculature that are ultimately coordinated by the vomiting centre.[1,2] The emetic centre is a nucleus of cells located in the medulla and is the motor centre responsible for the coordination of emesis. Afferent input to the emetic centre originates from at least 4 sources; the chemoreceptor trigger zone (CTZ), the cortex, the vestibular apparatus and the gastrointestinal tract. Vomiting occurs when efferent impulses are sent from the emetic centre to the salivation centre, abdominal muscles, respiratory centre and cranial nerves.

With respect to chemotherapy and radiation therapy, the CTZ, the gastrointestinal tract and the cerebral cortex have been identified as sources of afferent input to the emetic centre.[1,2] The cerebral cortex does not appear to provide input to the CTZ in acute chemotherapy-induced vomiting, but may stimulate the emetic centre in anticipatory vomiting. The gastrointestinal tract is directly connected to the emetic centre via the nucleus tractus solitarius and it also contains afferent fibres which terminate at the CTZ. Because of its location within the area postrema, the CTZ is exposed to both cerebrospinal fluid and the systemic circulation: thus, substances circulating in both of these fluids can stimulate the CTZ to release neurotransmitters. All of the afferent inputs received by the vomiting centre are controlled by neurotransmitters and their receptors.

1.2 Neurotransmitters and Receptors Involved in Chemotherapy-Induced Nausea and Vomiting

Dopamine, acetylcholine, histamine and serotonin are all neurotransmitters which are involved in the emetogenic pathways stimulated by radiation and chemotherapy.[2,3] Receptors for each of these neurotransmitters are found in abundance in the emetic centre, the CTZ and the gastrointestinal tract. Activation of these receptors by chemotherapy, metabolites and/or neurotransmitter release caused by chemotherapy may all be responsible for inducing nausea and vomiting.

The mechanism by which chemotherapy stimulates nausea and vomiting was only partially understood until that by which metoclopramide prevents nausea and vomiting was identified.[4] Before the discovery of 5-HT_3 receptors, it was assumed that dopamine receptor blockade was the mechanism by which metoclopramide produced its antiemetic activity. Only later was it discovered that high doses of metoclopramide were blocking 5-HT_3 receptors and that binding of serotonin to these receptors stimulated vagal afferent neurons supplying the upper gut.

Serotonin, found in high concentrations within the enterochromaffin cells in the gut,[1,5] is additionally located primarily in the CNS and platelets. 5-HT_3 receptors are widely distributed in peripheral tissues, the nucleus tractus solitarius and the CTZ where most vagal afferents enter the brain. Peripherally, chemotherapy and radiation cause release of serotonin from enterochromaffin cells which are found in the gut and which activate the abdominal vagal afferents.[6]

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[7] and is not affected by the administration of 5-HT_3 antagonists. Thus, peripherally, 5-HT_3 antagonists do not prevent release of serotonin, but bind to the 5-HT_3 receptors and prevent chemotherapy-induced nausea and vomiting by preventing agonism of the 5-HT_3 receptor by serotonin. The largest concentration of 5-HT_3 receptors in the CNS is the nucleus tractus solitarius and the area postrema where the CTZ is located and where vagal afferents enter the brain. Although not well characterised, it is also believed that 5-HT_3 antagonists may mediate nausea and vomiting by interaction with these central receptors.[8]

2. Comparative Pharmacology of the 5-HT$_3$ Receptor Antagonists

Since their discovery, several 5-HT$_3$ receptor antagonists have been identified and are listed in table I. Granisetron, ondansetron, tropisetron and dolasetron are the four drugs of this class that have been approved to date in different countries worldwide for the prevention of chemotherapy-induced nausea and vomiting. Although they all share a common mechanism of action in preventing nausea and vomiting, there are differences in their pharmacological profiles. The major differences are found in their chemical structure, 5-HT$_3$ receptor affinity, dose-response curve and pharmacokinetic profile. The 5-HT$_3$ antagonists have different chemical structures:[9] ondansetron is a carbazole derivative, while granisetron is an indazole, and tropisetron and dolasetron are indole moieties. Ondansetron exists as a racemic mixture of 2 enantiomers. The others are single molecular species without enantiomers.

2.1 Receptor Binding and Affinity

Using radioligand binding techniques and functional studies, at least 4 distinct serotonin receptor types (5-HT$_1$, 5-HT$_2$, 5-HT$_3$ and 5-HT$_4$), each with various subtypes, have been characterised.[10] The role of 5-HT$_3$ receptors in mediating chemotherapy-induced nausea and vomiting is discussed in section 1.2. 5-HT$_4$ receptors are responsible for the prokinetic activity in the gastrointestinal tract,[11] while the function of the other receptors and their subtypes is less clearly defined.

Granisetron, dolasetron and its major metabolite have been identified as pure 5-HT$_3$ receptor antagonists. While binding of these agents may occur at other receptors, the affinity is extremely low compared with the binding that occurs at the 5-HT$_3$ receptor. Granisetron, for example, has >4000 to >40 000 times higher binding affinity for the 5-HT$_3$ receptor than any other receptor type that 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. In addition to 5-HT$_3$ receptor binding, ondansetron binds at 5-HT$_{1B}$, 5-HT$_{1C}$, α_1-adrenergic and opioid μ receptors and tropisetron binds to 5-HT$_4$ receptors.[12] 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$_3$ antagonists. In addition, receptor binding and affinity studies should be interpreted with caution: since they are performed *in vitro*, they may not reflect clinically important differences.

2.2 Dose-Response Curves with the 5-HT$_3$ Antagonists

Dose-response curves with 5-HT$_3$ antagonists have been compared in animal models and some differences have been identified.[13] Curvilinear dose-response curves were identified for granisetron, dolasetron and tropisetron in animal models. Dose-response is linear up to a point when subsequent increases in dose do not result in equivalent increases in response. Ondansetron has an unusual dose-response curve that produces an initial decrease in emesis followed by an increase, and it is not until the dose increases further that control of emesis is regained.[14] Differences in receptor binding and the surmountable antagonism of ondansetron by increasing concentrations of sero-

Table I. 5-HT$_3$ antagonists

Bemesetron[a]
Dolasetron[a]
GR-65630
Granisetron[a]
Ondansetron[b]
Renzapride[c]
Tropisetron[b]
Zacopride[c]
Zatosetron

a Pure 5-HT$_3$ receptor antagonist.
b Weak 5-HT$_4$ antagonist.
c Weak 5-HT$_4$ agonist.
Abbreviation: 5-HT = 5-Hydroxytryptamine (serotonin).

Table II. Comparative pharmacokinetics of 5-HT_3 antagonists in adults with cancer[15-20]

	Ondansetron	Granisetron	Tropisetron	Dolasetron[a]
Dose	0.15 mg/kg IV	40 μg/kg IV	10mg IV	0.6-3.0 mg/kg IV
$t_{½}$ (h)	3.9	9.0-11.6	7.3	7-9
CL (L/min)	0.398	0.24-0.43	0.96	0.42[b]
Vd (L)	160	154-228	554	109[b]

a Pharmacokinetic values reported for the active metabolite of dolasetron.

b Normalised to 70kg bodyweight.

Abbreviations: CL = clearance; IV = intravenous; $t_{½}$ = half-life; Vd = apparent volume of distribution.

tonin, not seen with granisetron or tropisetron, may account for the dose-response relationship observed with ondansetron.

2.3 Pharmacokinetic Differences

Some of the pharmacokinetic parameters of the 5-HT_3 antagonists are summarised in table II.[15-20] Granisetron and tropisetron have long elimination half-lives compared with that of ondansetron. Dolasetron, as the parent compound, has a short elimination half-life (0.13 to 0.24 hours), but it is rapidly metabolised to its active metabolite which has an elimination half-life similar to that of granisetron and tropisetron. Early clinical studies of dosage regimens took into consideration these differences in half-life; thus, ondansetron was initially administered 3 times daily compared with once daily for the other 5-HT_3 antagonists. It has now been demonstrated that ondansetron, as well as the other 5-HT_3 antagonists, can be effectively administered once daily[21-39] and that antiemetic efficacy persists long after their plasma concentrations are undetectable. This indicates that interactions at the receptor level, not plasma pharmacokinetics, are the most important criteria for defining efficacy.

Other than differences in half-life, other pharmacokinetic parameters of the 5-HT_3 antagonists are very similar. Thus, pharmacokinetic differences among these drugs are unlikely to contribute significantly to clinical differences in activity.

3. Interpreting Clinical Trials with Antiemetic Agents

3.1 Risk Factors for Developing Chemotherapy-Induced Nausea and Vomiting

There are known risk factors for the development of chemotherapy-induced nausea and vomiting. These are listed in table III.[40] The efficacy of antiemetics is influenced by variables such as the patient characteristics and the emetogenic potential of the chemotherapy. These variables should be considered carefully when examining studies of the efficacy of any antiemetic regimen.

3.1.1 Patient Characteristics

Studies that are not matched for the patient risk factors outlined in table III may be potentially biased. Patients with a prior history of long term

Table III. Risk factors for developing chemotherapy-induced nausea and vomiting

Age <50y
Female sex
Negative history of alcohol use
Susceptibility to motion sickness
Anxiety
Depression
Nausea and vomiting with previous cycles of chemotherapy
perspiration after the last chemotherapy treatment
sensation of warmth or heat after last chemotherapy treatment
post-treatment dizziness and lightheadedness
severity of post-treatment nausea and vomiting
no. of chemotherapy cycles received
lengthy chemotherapy infusions
delayed onset nausea and vomiting
abnormal taste sensations during chemotherapy administration

Table IV. Emetogenic potential (mg/m^2 body surface area) of commonly used chemotherapeutic agents (from Hesketh et al.,[40] with permission)

Level 5 (>90%)	Carmustine >250	Cisplatin ≥50
	Cyclophosphamide >1500	Dacarbazine
	Chlormethine (mechlorethamine)	Streptozocin
Level 4 (60-90%)	Carboplatin	Carmustine ≤250
	Cisplatin <50	Cyclophosphamide >750 ≤1500
	Cytarabine >1 g/m^2	Doxorubicin >60
	Methotrexate >1000	Procarbazine (oral)
Level 3 (30-60%)	Cyclophosphamide ≤750	Cyclophosphamide (oral)
	Doxorubicin 20-60	Epirubicin ≤90
	Altretamine [hexamethylmelamine] (oral)	Idarubicin
	Ifosfamide	Methotrexate 250-1000
	Mitoxantrone <15	
Level 2 (10-30%)	Docetaxel	Etoposide
	Fluorouracil <1000	Gemcitabine
	Methotrexate >50 <250	Mitomycin
	Paclitaxel	
Level 1 (<10%)	Bleomycin	Busulfan
	Chlorambucil (oral)	Cladribine (2-chlorodeoxyadenosine)
	Fludarabine	Hydroxycarbamide (hydroxyurea)
	Methotrexate ≤50	Phenylalanine mustard (oral)
	Thioguanine (oral)	Vinblastine
	Vincristine	Vinorelbine

alcohol intake have a decreased risk for the development of chemotherapy-induced nausea and vomiting,[41] while younger patients (<50 years old) and female patients are at an increased risk for the development of chemotherapy-induced nausea and vomiting.[42,43]

3.1.2 Chemotherapy Risk Factors

Certain chemotherapy regimens are more emetogenic than others. Table IV lists the emetogenic potential of commonly used chemotherapy agents.[40] Studies in which patients receive highly emetogenic chemotherapy are likely to show poorer results than those where the chemotherapy is only moderately emetogenic. Chemotherapy dose is an important factor to consider when evaluating the antiemetic efficacy of 5-HT$_3$ antagonists. Some chemotherapy agents may be highly emetogenic when given as a high dose and only moderately emetogenic when given in lower doses. In addition, combination regimens may be highly emetogenic while the individual agents that make up the combination regimen may have only moderate or low emetogenic potential. Therefore, the type and dose of chemotherapy should be considered when evaluating the efficacy of antiemetic agents.

3.1.3 Acute, Delayed or Anticipatory Nausea and Vomiting

Another consideration for assessing antiemetic efficacy is the postchemotherapy period being evaluated. For example, cisplatin causes acute nausea and vomiting that occurs over the first 4 hours after administration, followed by delayed emesis which may last for up to 7 days.[44] Cyclophosphamide in high doses usually does not precipitate initial episodes of nausea and vomiting until 12 to 24 hours after administration.[45] Nausea and vomiting that begins within the first 24 hours after chemotherapy is known as acute nausea and vomiting and, though it can be severe, is responsive to prophylaxis with antiemetic therapy. Delayed nausea and vomiting, occurring more than 24 to 96 or 120 hours after chemotherapy, and anticipatory nausea and vomiting, which is psychogenically mediated,[46] are distinctly different types of nausea and vomiting from the acute type. 5-HT_3 antagonists are not effective for anticipatory nausea and vomiting and are considerably less effective in the delayed setting. Familiarity with the patterns of nausea and vomiting associated with chemotherapy regimens is essential in interpreting clinical trial results.

3.2 Definition of Efficacy

Interpreting the comparative efficacy of antiemetics is made difficult by the fact that the efficacy criteria in clinical trials are not consistent. Complete, major and minor responses are defined in terms of the number of episodes of vomiting or retching and the severity of nausea. The number of vomiting episodes and retches and the nausea assessment scales that define each degree of response vary from study to study. This makes direct comparison of the antiemetic efficacy of 5-HT_3 antagonists difficult. In the past, complete responses have been defined as no episodes of vomiting or retching and no or mild nausea. Major responses have been defined as less than 2 vomiting episodes or retches and/or mild to severe nausea, while minor responses were 2 to 4 vomiting episodes or retches. Failures were most often defined as >4 episodes of vomiting of a 24 hour period of time. Many studies are designed to look at the episodes of emesis as the primary end-point, and may not consider nausea as an end-point when, in fact, patients may find nausea to be more disturbing than vomiting. It is most appropriate to evaluate nausea and vomiting separately, and to base efficacy statements on both parameters.

3.3 Clinical Trial Design

Placebo arm trials of antiemetics are considered unethical, since effective regimens are available for preventing chemotherapy-induced nausea and vomiting. The efficacy of new agents or their use in different doses, regimens or setting is determined by using another antiemetic regimen as the comparative regimen. If the comparative regimen is suboptimal, bias may be created in favour of the study regimen. Well designed trials should use the most effective available antiemetic regimen as the comparator in antiemetic trials. Patients and investigators also should be blinded to prevent bias, especially since nausea and patient preference are both subjective outcomes.

4. Comparative Efficacy of 5-HT_3 Antagonists for Controlling Acute Nausea and Vomiting

All currently marketed 5-HT_3 antagonists have been demonstrated to be efficacious in preventing acute chemotherapy-induced nausea and vomiting with both moderately and highly emetogenic chemotherapy regimens. They also have greater efficacy and less toxicity than other classes of agents for treating this problem. Clinically important differences among the 5-HT_3 antagonists have been difficult to demonstrate. Table V summarises studies that have been conducted to directly compare efficacy among the 5-HT_3 antagonists currently available for patient use.

4.1 Comparative Clinical Trials of 5-HT_3 Antagonists in Acute Nausea and Vomiting

In an open label study by Bonneterre et al.[21] there was no statistically significant difference found in the complete control of either nausea or vomiting by either ondansetron or granisetron during the first 24 hours after moderately emetogenic chemotherapy. 90% of the patients were female, most undergoing treatment for breast cancer. This study also compared delayed emesis control on days 2 to 5 and found no difference between the groups (granisetron 37%, ondansetron 32%) over this period, despite the administration of oral doses of ondansetron for 3 days after the first day of chemotherapy in the ondansetron arm. There was no patient preference expressed for either of the treatments and no difference in adverse events.

A second study by Noble et al.[22] compared the efficacy of ondansetron and granisetron in a placebo-controlled design. Patients were receiving

Table V. Comparative studies of 5-HT_3 antagonists for acute nausea and vomiting

Antiemetic agents (mg)	Chemotherapy	No. of pts	Study design	24h complete control (%)		Reference
				emesis	nausea	
OND 8 IV + 8 PO q8h × 3	Moderately emetogenic	150[a]	Randomised, open, crossover	77	47	21
GRA 3 IV				72	54	
OND 8 IV tid × 5 days	5-day fractionated cisplatin (mean 19.2 mg/m^2/day)	309[a]	Randomised, double-blind, crossover	89.1; cycle 1 86.4; cycle 2 40; 5-day		22
GRA 3 IV × 5 days				91.5; cycle 1 82.6-cycle 2 44 - 5 day		
OND 0.15/kg × 3	Cisplatin ≥60mg/m^2 (median 81.4mg/m^2)	987[a]	Randomised, double-blind	39	40	23
GRA 10 μg/kg				38	39	
GRA 40 μg/kg				40	42	
OND 8 IV	Cisplatin ≥50mg/m^2 (median 78mg/m^2)	496[a]	Double-blind, randomised parallel	59	56	24
OND 3 IV				51	48	
GRA 3 IV				56	56	
OND 8 IV + 8 PO bid × 4 days	Moderately emetogenic	488[a]	Randomised, double-blind double dummy	78	51	25
OND 8 PO + 8 PO bid × 4 days				78	55	
GRA 3 IV				81	54	
OND 24 IV	Cisplatin >70mg/m^2 (mean 84mg/m^2)	182	Randomised, open label	52	74	26
GRA 3 IV				49	79	
OND 16 IV	Moderately emetogenic	164		69	50	26
GRA 3 IV				67	45	
OND 24 IV divided dose + 8 bid day 2	Cisplatin ≥50mg/m^2	86[a]	Randomised, open label, crossover	67		27
GRA 3 IV				72		
OND 0.15/kg IV × 3	Highly (HE) and moderately (ME) emetogenic	118	Randomised, open	54-HE 67-ME		28
GRA 40 μg/kg				62-HE 73-ME		
OND 8 IV + DEX 20 IV	Cisplatin ≥50mg/m^2 (median dose 75mg/m^2)	966[a]	Randomised, double-blind	79	72	29
GRA 3 IV + DEX 20 IV				80	72	
TRO 5 IV + 5 PO days 2-6	Cisplatin >50mg/m^2	231[a]	Randomised, double-blind	54	66	30
OND 32 IV + 24 PO days 2-6				65	62	
TRO 5 IV + DEX 10 IV	Moderately emetogenic	39	Randomised, crossover	97*		31
OND 8 IV + 8 PO × 2 + DEX 10 IV				82*		
TRO 5 IV + 5 PO qd × 4 days	Moderately emetogenic	40	Randomised, open, parallel	45	60	32
OND 8 IV + 8 PO tid × 4 days				35	50	
GRA 3 IV	Moderately emetogenic	122[a]	'Allocated to group', parallel	66[b]	30[b]	33
OND 16 IV + 8 PO × 2				69[b]	39[b]	
TRO 5 IV + 5 PO × 4 days				72[b]	44[b]	
OND 24 IV	Cisplatin > 80mg/m^2	86[a]	Randomised, open label, crossover	65		34
GRA 3 IV				72		
TRO 5 IV				44*		

Table V. Contd

Antiemetic agents (mg)	Chemotherapy	No. of pts	Study design	24h complete control (%)		Reference
				emesis	nausea	
OND 8 IV	Moderately emetogenic	130	Randomised, open label, crossover twice	69*	17	35
GRA 3 IV				80*	42	
TRO 5 IV				75	15	
OND 32 IV	Cisplatin ≥70mg/m^2	609[a]	Randomised, double-blind	43		36
DOL 1.8/kg IV				44		
DOL 2.4/kg IV				40		
DOL 1.8/kg IV	Cisplatin ≥80 mg/m^2	474	Randomised, double-blind	54	43	37
DOL 2.4/kg IV				47	44	
GRA 3 IV				48	42	
DOL 2.4/kg ± DEX 8 PO, then DOL 200 PO ± DEX 8 × 6 days	Moderately emetogenic	696[a]	Randomised, double-blind, 2 × 2 factorial comparative	56*		38
OND 32 ± DEX 8 PO, then OND 8 PO bid ± DEX 8 × 6 days				65*		
DOL 25 PO	Moderately emetogenic	309	Randomised, double-blind	45		39
DOL 50 PO				49		
DOL 100 PO				49		
DOL 200 PO				61		
OND 8 PO × 4				72		

a Naïve (i.e. patients who had not received prior chemotherapy)

b 5-day assessment period.

Abbreviations and symbol: bid = twice daily; DEX = dexamethasone; DOL = dolasetron; GRA = granisetron; IV = intravenously; OND = ondansetron; PO = orally; qd = once daily; tid = 3 times daily; TRO = tropisetron; * p < 0.05.

fractionated cisplatin or ifosfamide administered over a 5-day period. Efficacy was evaluated after the first and second cycles and for the 5-day treatment period. Complete control rates of between 80 and 90% were achieved over the 24-hour period following both cycle 1 and cycle 2. However, the 5-day assessment control rate was 40 to 44%. For all assessment periods there was no statistically significant difference between the 2 treatment groups. Interestingly, there was a statistically significant difference ($p = 0.048$) in patients who expressed a preference for either of the two, with 26% of patients preferring ondansetron and 34% preferring granisetron; however, there was no difference reported in the incidence or severity of adverse effects or efficacy between the 2 groups and thus the reason for the difference in patient preference is unclear.

Other studies have compared different dosage strategies of ondansetron and granisetron. Navari et al.[23] compared the initial manufacturer's approved dose of ondansetron in the US (0.15 mg/kg intravenously) with 2 doses of granisetron, one of which was the approved dose in Europe (40 μg/kg intravenously) and the other a dose which had been found to be equally efficacious in other studies (10 μg/kg intravenously). The design was a rigorous test of antiemetic efficacy because the mean dose of cisplatin that patients received was 81.4 mg/m^2, but most of the patients were male. The results showed equal efficacy among all 3 arms for both nausea and vomiting; however, the efficacy rates (30 to 40%) were low in all 3 arms. This is perhaps the result of very strict criteria used to define complete control (no vomiting, retching, nausea or use of rescue medications) and the high median dose of cisplatin that patients received. A subset analysis was performed in 267 patients who had received ≥100 mg/m^2 of cisplatin. Total control was achieved in 28 and 33% of patients receiving low dose and high dose granisetron, respectively, and in 25% of patients receiving ondansetron, although patient numbers are probably too small to draw valid conclusions.

Ruff et al.[24] conducted a study directly comparing 2 different doses of ondansetron (8 or 32mg) with granisetron 3mg in a group of patients receiving cisplatin. The study was randomised and blinded and patients were crossed over. Both nausea and emesis were assessed during the 24-hour period after chemotherapy. Again, there was no statistically significant difference between the 2 agents when assessing complete control of nausea or vomiting, or in either of the parameters analysed separately. This study also found no statistically significant difference in patient global satisfaction. The results of this study are somewhat difficult to interpret because 14% of patients received <50 mg/m^2 of cisplatin despite an eligibility criteria to receive ≥50mg/m^2. Also, as in many of the other comparative studies, rescue medication use for breakthrough nausea or vomiting was not reported. These results are interesting because the low dose of ondansetron was found to be as efficacious as the higher ondansetron dose and the granisetron 3mg dose. As will be demonstrated in other studies, the optimum dose and regimen for ondansetron has not yet been clearly identified.

The study by Stewart et al.[25] is another test of lower doses of ondansetron and demonstrates that an all-oral administration of ondansetron may be equally as efficacious as an intravenous-plus-oral regimen in moderately emetogenic chemotherapy. In this study, patients on the ondansetron arms received ondansetron 8mg either intravenously or orally before chemotherapy, followed by oral ondansetron 8mg twice daily for 4 days after chemotherapy in both arms. The third arm of patients received granisetron 3mg on day 1 only and placebo over the next 4 days. The 5-day assessment period showed no difference among the groups for emetic episodes, but the intravenous-plus-oral ondansetron arm was superior to the granisetron arm for nausea: 33 *vs* 25%, respectively.

This study has important caveats. First, 26% of the patients in the granisetron arm were rescued with other antiemetics or withdrawn from the study due to lack of response when comparing efficacy for emetic episodes over the 5-day study period, compared with 11% for the intravenous ondansetron arm; however, there was no difference in nausea control for the same period among the 3 groups. The oral ondansetron group had a significantly higher percentage of patients who required rescue or withdrawal compared with the intravenous ondansetron due to lack of emesis control on day 1.

Secondly, this is the only study comparing usual doses of granisetron with ondansetron that has demonstrated a statistically significant difference in any efficacy parameter – a decrease in nausea over the total 5-day period being found in the intravenous-plus-oral ondansetron arm. A possible explanation is that a large percentage of patients received cyclophosphamide-containing regimens and it is known that emesis may not begin until 12 to 24 hours after that agent has been administered. A more likely explanation is that the additional doses of oral ondansetron received over the 4-day period may account for the improved efficacy and may signal the need for later administration of a 5-HT_3 antagonist after regimens containing high doses of cyclophosphamide.

Other studies comparing ondansetron and granisetron in both highly and moderately emetogenic chemotherapy have been published[26-29] and the results have shown that both are efficacious in controlling acute nausea and vomiting and there is no statistically significant difference between the two. In the study by Martoni et al.,[27] there was a strong patient preference for granisetron; however, the patient numbers were small, the study was open-label and no explanation can be given for the difference since efficacy and tolerability were the same for both the ondansetron and granisetron regimens.

The control rates of these 2 agents in acute nausea and vomiting have also been shown to be augmented by the addition of dexamethasone in patients receiving highly emetogenic chemotherapy.[29] Patients had a 79 and 80% complete control rate with ondansetron and granisetron, respectively, when intravenous dexamethasone 20mg was added before treatment. These results have been confirmed in studies that have compared dexamethasone, 5-HT$_3$ antagonists and the combination of the two.[47,48] These studies also demonstrate that there is no difference between an 8mg dose of ondansetron and a 3mg dose of granisetron, when combined with dexamethasone.

Although not approved for use in the US, tropisetron is available for use in Europe and other countries for the control of chemotherapy-induced nausea and vomiting. Studies comparing this drug with both granisetron and ondansetron have been conducted. In a study of 231 patients, Marty et al.[30] showed that tropisetron was as effective as ondansetron in controlling emetic episodes in patients receiving ≥50mg/m^2 of cisplatin (54 *vs* 65%, respectively). Jantunen et al.[31] compared tropisetron with ondansetron in a nonblinded, crossover study in 39 patients receiving cyclophosphamide-based regimens. Patients in both study arms also received intravenous doses of dexamethasone 20mg before chemotherapy. Ondansetron was statistically more effective in controlling acute vomiting (97%) than tropisetron (82%). Patients on the ondansetron arm were given the drug 3 times in the first 24 hours, compared with only once for tropisetron arm.

A study by Campora et al.[32] showed that tropisetron 5mg given daily over 4 days was equivalent to ondansetron 24mg over 4 days in women given moderately emetogenic chemotherapy for the treatment of breast cancer. Some of these studies comparing ondansetron with tropisetron have potential flaws that might bias results, such as small numbers of patients and unblinded, non-crossover study designs.[31-34]

Another study with a similar design by Jantunen et al.[35] compared intravenous ondansetron, granisetron and tropisetron, but the dose of ondansetron (8mg) was lower. In this study, most of the patients were female and had received prior chemotherapy. Granisetron was shown to be statistically superior to ondansetron, but not to tropisetron, for complete control of emetic episodes. The low control rate for ondansetron compared with the previous studies may be due to: (a) the use of a single low dose of ondansetron; (b) the lack of use of dexamethasone; and (c) the possibility that additional doses within the first 24 hours provide greater 24-hour efficacy for a regimen containing cyclophosphamide. None of these studies comparing the three 5-HT$_3$ antagonists was blinded, and testing for carry-over effects of the crossover design was not reported.

Dolasetron is the newest of the 5-HT$_3$ antagonists to be approved for use in the prevention of chemotherapy-induced nausea and vomiting. To date, there have been 4 studies published that compare dolasetron with either ondansetron or granisetron.

A comparison of 2 doses (1.8 and 2.4 mg/kg) of intravenous dolasetron against a single dose of intravenous ondansetron 32mg in patients receiving ≥70mg/m^2 of cisplatin has been published by Hesketh et al.[36] The majority of the 609 patients in this study were female and had not received prior chemotherapy. There was no difference in emetic response rate among the 3 groups. A subset analysis of patients who received ≥91mg/m^2 of cisplatin also showed no difference in response among the 3 groups; however, as expected, the response rates were significantly lower than those seen in the lower cisplatin dose group (≥70 to ≤90mg/m^2). Nausea was evaluated on a visual analogue scale and also showed no difference between the dolasetron and ondansetron groups. Nausea was less well controlled in the group of patients receiving the 2.4 mg/kg dose of dolasetron compared with the 1.8 mg/kg dose. Headache was the most frequently reported adverse effect and was also equal among all 3 groups.

A similarly designed study was performed by Audhuy et al.[37] Dolasetron was administered in the same manner as that reported in the study above, but was compared with a single intravenous dose of granisetron 3mg. All patients in this study received cisplatin ≥80mg/m^2, but not all were chemotherapy naïve. No differences among response rates were reported in this trial for either nausea or vomiting. There was also no difference in type or severity of adverse effects.

A comparison of dolasetron with ondansetron in combination with dexamethasone was reported as an abstract by Lofters and Zee.[38] Patients received either dolasetron or ondansetron intravenously on day 1 with or without orally administered dexamethasone. This was followed by an oral regimen of the 5-HT_3 receptor antagonist, again with or without dexamethasone, for 6 days, for a total of 7 days of treatment. In patients who did not receive dexamethasone, complete protection was significantly better in the group receiving ondansetron (65%) than in the dolasetron group (56%). Patients who received dexamethasone in combination with the 5-HT_3 antagonist also had a superior complete protection rate (66% with dexamethasone and 54% without).

Oral dolasetron has also been tested against oral ondansetron for efficacy in moderately emetogenic chemotherapy. Fauser et al.[39] performed a dose-ranging study of oral dolasetron administered before chemotherapy compared with oral ondansetron 8mg before chemotherapy and every 8 hours for 3 doses. The dolasetron 200mg dose was significantly better than the 25, 50 and 100mg doses in controlling emesis. Ondansetron was significantly better than the 25 and 50mg doses of dolasetron, but not the 100 and 200mg doses. In addition, dolasetron 200mg orally was statistically significantly better than ondansetron in controlling nausea, based on a visual analogue scale assessment.

4.2 Summary of Comparative Studies

Despite the shortcomings of some of the study designs, the studies discussed above provide useful information on the comparative clinical efficacy of 5-HT_3 antagonists. Although statistically significant differences in efficacy are reported in some trials,[31,34,35,38] the overall preponderance of the studies shows equal efficacy among all of the 5-HT_3 antagonists in the prevention of chemotherapy-induced nausea and vomiting, especially for moderately emetogenic chemotherapy regimens.

The report by Jantunen et al.[35] reveals that intravenous ondansetron 8mg is inferior to intravenous granisetron 3mg (69 *vs* 80%; p = 0.034). The difference in efficacy may be attributed to the low dose of ondansetron used in this trial; however, the Italian Group for Antiemetic Research reported equal efficacy when these same doses were used in combination with dexamethasone.[29] Another study by Jantunen and colleagues demonstrated that intravenous-plus-oral ondansetron 24mg is superior to intravenous tropisetron 5mg, both in combination with dexamethasone in moderately emetogenic chemotherapy.[31] Another study demonstrates that ondansetron 24mg is effective even in highly emetogenic chemotherapy.[26] Despite numerous trials that demonstrate efficacy, the dose and regimen of ondansetron has not been clearly defined.

It has been demonstrated from these studies that intravenous granisetron 3mg is as effective as other 5-HT_3 antagonists; however, the dose approved for use in the US for granisetron is 10 μg/kg intravenously, which is somewhat lower than that approved in Europe where many of the comparative trials with granisetron have been performed. Only one of these comparative studies used the dose approved in the US;[23] however, this large, well designed study did demonstrate that the 10 μg/kg dose has equivalent efficacy to the 40 μg/kg (approximately 3mg) dose.

Tropisetron was found to be inferior to ondansetron and granisetron in one study[34] in which patient numbers were small, but the differences (44 *vs* 65 and 72% complete response, respectively) were large in patients receiving highly emetogenic chemotherapy. Both granisetron and ondansetron were superior to tropisetron (p<0.001 and p<0.004, respectively). In another small study, tropisetron was statistically inferior to ondansetron (82 *vs* 97% complete response, respectively).[31] More comparative studies of tropisetron would be useful in determining its comparative efficacy in the treatment of nausea and vomiting with highly emetogenic chemotherapy.

In the 4 studies comparing dolasetron and ondansetron, only one showed a statistically significant difference in favour of the latter.[38] In 3 studies of highly emetogenic chemotherapy, dolasetron was as effective in controlling acute nausea and vomiting as granisetron and ondansetron.[36,37,39] Dolasetron has been less well studied than the other 3 available compounds and has only recently been approved for use, but these comparative studies show excellent efficacy and this agent promises to be another useful alternative to the $5\text{-}HT_3$ antagonists already available.

4.3 Comparison of Adverse Effects of $5\text{-}HT_3$ Antagonists

It is clear from all of these studies that the safety profile of each of the $5\text{-}HT_3$ antagonists is superb. None of the studies, with hundreds of patients enrolled, has demonstrated any adverse effects that are significant or severe. This is especially true in comparison with the adverse effect profile of other antiemetic agents. It is also clear that the adverse effect profiles of the $5\text{-}HT_3$ antagonists are not different despite some pharmacological and pharmacokinetic differences. All of these agents are safe, well tolerated and, in terms of adverse effect profiles, no different.

The adverse effects of $5\text{-}HT_3$ antagonists have been reviewed[49] and are listed in table VI. They are usually mild to moderate and transient, rarely requiring drug discontinuation. Headache is the most commonly reported adverse effect, but is usually rated as mild to moderate and is relieved by non-narcotic analgesics. This is the only adverse effect of the antagonists that is reported to occur more frequently in patients receiving those drugs than in those receiving a comparator (other non-$5HT_3$ receptor antagonists such as antiemetics) or placebo. Fatigue and sedation are also usually reported as mild. Extrapyramidal adverse effects are not reported with the $5\text{-}HT_3$ antagonists, but occur at a high frequency in patients receiving high dose metoclopramide. There have been significant elevations in hepatic transaminases in patients receiving $5\text{-}HT_3$ receptor antagonists, but these same elevations were not observed in healthy volunteers, which suggests that chemotherapy is responsible for hepatic toxicity, not $5\text{-}HT_3$ antagonists. Electrocardiographic (ECG) changes have also been observed with all of these agents, but were not clinically significant, and their relationship to the $5\text{-}HT_3$ antagonists is unclear.[36,37,50-52]

Table VI. Adverse effects of $5\text{-}HT_3$ antagonists

Headache
Lightheadedness or dizziness
Abdominal pain or cramping
Constipation
Sedation and fatigue
Elevations in hepatic transaminases and/or bilirubin
Electrocardiographic changes

Abbreviation: 5-HT = 5-Hydroxytryptamine (serotonin).

4.4 Is Statistically Significant Clinically Meaningful?

Despite the report of some statistically significant differences among the $5\text{-}HT_3$ antagonists, it is difficult to know if these differences translate into clinically meaningful differences, especially when the majority of comparative studies show no differences in efficacy. The largest statistically significant percentage difference between treatment groups was 15% in a study of only 39 patients[31] and, in all of the other studies, differences in control rates were less than this. In addition, a similarly designed trial of approximately the same number of patients shows no statistically significant difference between the same 2 treatments.

Patient preference for granisetron was observed in 3 of 4 studies where it was assessed, and there was no significant difference in the fourth. This outcome is difficult to interpret, since only patients who expressed a preference were included in the evaluation and there were no differences in efficacy or adverse events to explain the difference in preference. For these reasons, it is not clear that this is a meaningful difference between granisetron and the other $5\text{-}HT_3$ antagonists, but it is an area that deserves further research.

5. Comparative Efficacy of 5-HT$_3$ Antagonists in Delayed Nausea and Vomiting

Less is known about the efficacy of 5-HT$_3$ antagonists for the prevention of delayed nausea and vomiting. This can be a serious complication for patients. It can be protracted and severe, and there are very few good treatment options for its prevention. Kris et al.[53] have reported the incidence to be 93% in patients receiving high dose cisplatin.

The 5-HT$_3$ antagonists have not been uniformly effective in preventing delayed nausea and vomiting. Urinary excretion of the serotonin metabolite, 5-HIAA, peaks at 6 hours after cisplatin chemotherapy and declines steadily thereafter to pretreatment levels by 24 hours.[54] This provides evidence that delayed nausea and vomiting is not associated with serotonin release and that other neurotransmitters must be involved.

Ondansetron has not been shown to be consistently more effective than other treatments or placebo for preventing delayed nausea and vomiting.[55-60] Gandara et al.[55] studied 31 patients who had undergone chemotherapy with high dose cisplatin. After standard antiemetic therapy for the first 24 hours, patients were randomised 2 : 1 to receive ondansetron 16mg 3 times daily for 4 days or a matching placebo. Over the 4-day period, there was no difference between groups in the number of patients who experienced nausea or vomiting.

De Mulder et al.[56] compared ondansetron with high dose metoclopramide for the management of acute and delayed emesis following cisplatin chemotherapy in a randomised, double-blind, crossover study. Before the first course of cisplatin, patients were randomised to receive one of the two following regimens. Group 1 patients received intravenous ondansetron 8mg before chemotherapy, then 1 mg/h for 24 hours; followed by oral ondansetron 8mg administered 3 times daily for 5 days. Group 2 patients received intravenous metoclopramide 3 mg/kg before chemotherapy, then 4 mg/kg infused over 8 hours and normal saline intravenously for the next 16 hours to maintain blinding, followed by oral metoclopramide 20mg given three times daily for 5 days. Vomiting was controlled in only 24% of patients receiving ondansetron and 27% of those receiving metoclopramide. Nausea was significantly better controlled with metoclopramide than with ondansetron.

Similar results were observed by Jones et al.[58] when they compared ondansetron and dexamethasone for both acute and delayed nausea and vomiting from cancer chemotherapy. No difference in delayed vomiting was demonstrated between the 2 groups, while dexamethasone was significantly better than ondansetron in controlling delayed nausea.

Navari et al.[59] designed a study to determine the efficacy and safety of oral ondansetron for the control of delayed emesis in patients who had not required rescue medication for acute emesis. Chemotherapy-naïve patients were randomised to receive ondansetron 8mg twice daily on days 2 and 3, 8mg twice daily on days 2 to 6, or placebo on days 2 to 6. Efficacy results for both ondansetron arms were combined. The percentage of patients achieving a complete response and major response with ondansetron on days 2 and 3 was 56%, compared with 37% with placebo. This is one of the few studies that show any benefit of 5-HT$_3$ antagonists in delayed nausea and vomiting and is not confirmed by other studies.

Tropisetron[61,62] and granisetron[63,64] have also been studied in the delayed nausea and vomiting setting. Complete responses have been reported to be between 12 and 60% for cisplatin-containing regimens and higher for non–cisplatin-containing ones (78%). Many of these studies are noncomparative and thus should be interpreted with caution, since it is not known whether the 5-HT$_3$ antagonist is superior to no treatment or placebo and may simply correspond to the proportion of patients who would not have developed delayed emesis.

Some of the comparative studies in table V also compared efficacy in delayed nausea and vomiting,[21,22,25,30,33] although none of these studies was designed specifically to evaluate this end-point. In moderately emetogenic chemotherapy regimens, analysis of efficacy over days 1 or 2 through to days 5 or 6 showed no difference between groups. In the study by Stewart et al.,[25] ondansetron given in the delayed phase was superior to the placebo administered in the patients who had received granisetron on day 1. Despite better control in the ondansetron arm, there was no difference in global satisfaction between the 2 arms. In general, control rates in the delayed phase were low compared with the acute phase control and were either low or no different from the control rates reported in the literature in comparison with other antiemetic regimens.

Overall, the efficacy of 5-HT_3 antagonists for the prevention of delayed nausea and vomiting appears to be limited. Numerous studies comparing these agents with placebo or against combinations with other antiemetic agents show little or no difference, and the response rates are low. Studies comparing the 5-HT_3 antagonists directly have also yielded disappointing results.[65] On the basis of the release and excretion of serotonin after highly emetogenic chemotherapy, there is also little theoretical evidence that would indicate that this class of compounds would be useful. Since control of acute nausea and vomiting is one of the most important predictors for the development of delayed nausea and vomiting, the efficacy of these agents in the acute setting may provide the most important impact on delayed nausea and vomiting.

6. Conclusions

The review of studies which have compared the efficacy of 5-HT_3 antagonists has yielded little in the way of important differences in clinical outcomes. Although all of these compounds have been reported to be efficacious in preventing chemotherapy-induced nausea and vomiting in the acute setting, none have shown impressive activity in the delayed setting. However, the adverse effects of 5-HT_3 antagonists are mild and when they occur are easily managed, especially in comparison with conventional antiemetic regimens.

The cost of the 5-HT_3 antagonists is one factor that should be considered when comparing these agents. Acquisition costs of 5-HT_3 antagonists can vary considerably, making the most financially attractive choice for one institution different from that of another. The route of administration and the total daily dose used must be considered when examining cost. Using lower doses of antiemetics to lower the cost of therapy must be balanced against the likelihood of failing to prevent nausea and vomiting. The decision as to which antiemetic is most cost effective can only be made once the optimal dose and schedule for the given drug in the target population is established. This will require further comparative studies using different doses, regimens and routes of administration for the 5-HT_3 antagonists.

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Correspondence and reprints: Professor *David S. Ettinger*, Department of Oncology and Medicine, Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21287, USA.
E-mail: ettinger@welchlink.welch.jhu.edu