Pharmacy Benefits Management and Medical Advisory Panel
Drug Class Review
5-Hydroxytryptamine Receptor Antagonists

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OBJECTIVES

1. To review the efficacy, safety, and administration of the currently available 5-hydroxytryptamine (5-HT3) receptor antagonists.

Generic Name	Brand Name (®)	Manufacturer
Dolasetron	Anzemet	Hoechst Marion Roussel
Granisetron	Kytril	SmithKline Beecham
Ondansetron	Zofran	Glaxo Wellcome

2. To present criteria for determining the formulary status of 5-HT3 receptor antagonists for the Veterans Health Administration National Drug Formulary.

I. FDA INDICATIONS

		Treatment PONV[a]	Prevention PONV	Prevention CINV[b]-highly emetogenic	Prevention CINV-mod[c] emetogenic	RINV[d]
Dolasetron	oral		X		X	
	parenteral	X	X	X	X	
Granisetron	oral			X	X	X
	parenteral			X	X	
Ondansetron	oral	X	X		X	X
	parenteral	X	X	X	X	

[a]PONV- postoperative nausea and vomiting
[b]CINV- chemotherapy induced nausea and vomiting
[c] mod-moderately
[d]RINV- radiotherapy induced nausea and vomiting

The 5-HT3 receptor antagonists are **not** indicated by the FDA to treat delayed chemotherapy-induced nausea and vomiting, anticipatory nausea and vomiting from chemotherapy, nor breakthrough vomiting from chemotherapy.

The 5-HT3 receptor antagonists have also been investigated in the management of anxiety, psychosis, drug and alcohol abuse, eating disorders, depression, cognition, pain and irritable bowel syndrome. Unfortunately, studies in these areas have **not** supported these indications. Currently, the 5-HT3 receptor antagonists do **not** have FDA-approval for any of these therapeutic areas.

II. PHARMACOLOGY [1-3]

The 5-HT3 receptor antagonists are highly selective agents which competitively inhibit the binding of serotonin to 5-HT3 receptors. Their antiemetic effects result from peripheral blockade of 5-HT3 receptors on vagal nerve terminals and central blockade in the area postrema and nucleus tractus solitarius. This equates with chemoreceptor trigger zone (CTZ) blockade. The 5-HT3 receptor antagonists have essentially no affinity for alpha adrenergic, dopaminergic, or histamine receptors. This characteristic eliminates the undesirable side effects of sedation, hypotension and extrapyramidal reactions that occur when using other nonselective antiemetic agents.

III. PHARMACOKINETICS [4-6]

Following oral administration, these agents are well absorbed and undergo limited first-pass metabolism. The clearance of ondansetron has been shown to be slower in women and the elderly. However, the clinical significance of this is not known and it is considered unnecessary to vary ondansetron dosage according to age or gender.

Measure	Hydrodolasetron[a]	Granisetron	Ondansetron
Bioavailability (% absorbed)	75	60	60
Protein binding (%)	69-77	60	70-76
Metabolism	Hepatic-cytochrome P450	Hepatic – cytochrome P450	Hepatic – cytochrome P450
Half-life (hours)	7.0	6.2	3.0
Excretion	Renal (50%)	Renal (11% unchanged)	Renal (5% unchanged)

[a] dolasetron undergoes rapid and near complete metabolism to this active metabolite in $\leq$ 10 min

IV. CLINICAL EFFICACY

A. Prevention of Postoperative Nausea and Vomiting

Several factors influence the development of postoperative nausea and vomiting (PONV). Gender, age, type of surgery and anesthetic agent may predispose patients to the development of PONV. Since fewer than one third of patients will experience this side effect, prophylactic antiemetic use is relatively uncommon.

The 5-HT3 antagonists have been investigated for their efficacy in the prevention and treatment of PONV. Variables in these trials include route of administration, dosing pre-induction or pre-reversal of anesthesia and multiple versus single dose.

1. Dolasetron

Both oral and parenteral dolasetron have proven efficacious in the prevention of PONV.[7-10] In women undergoing gynecological surgery, intravenous dolasetron doses of 12.5-100 mg were significantly better than placebo.[7, 8] Response rates did not vary with the different dose levels, indicating there may be no benefit with doses above 12.5 mg. Oral doses of 25-200 mg have been investigated with all doses significantly more efficacious than placebo ($p< 0.05$).[9] In a smaller trial, response rates for lower doses were not reported but 100-200 mg of dolasetron was superior to placebo.[10,11] Headache and dizziness were the most commonly reported adverse effects.

2. Ondansetron

Parenteral doses of ondansetron have been shown to be safe and effective for PONV in ambulatory and inpatient settings. [12-14] Overall, the studies have shown a 4 mg IV effective dose, with an 8 mg IV dose adding benefit in patients with a previous history of PONV. Adverse events were similar in all studies with primary side effects of dizziness, headache, and shivers. Oral ondansetron was investigated in two multicenter studies. In the first study, the 8 mg and 16 mg ondansetron groups had a significantly lower incidence of PONV in the 24-hour period following surgery than the placebo group. There appeared to be no additional clinical benefit with the 16 mg dose. In the second study, ondansetron given 8 mg three times daily was also significantly better than placebo.[15,16]

3. Granisetron

Postoperative nausea and vomiting is not included in the FDA-approved labeling for parenteral granisetron. However, the effectiveness of this agent in the prevention of PONV was evaluated in four dose-ranging studies.[17-19.] Single IV doses administered were 20 mcg/kg , 40 mcg/kg, 1 mg, or 3 mg. In general, IV granisetron was determined to be effective in the prevention of PONV, however, the optimal dosage and timing of administration was not clear. Side effects most commonly encountered were dizziness, headache, fatigue, and constipation.

4. Comparative Trials

Two studies have compared parenteral ondansetron with granisetron or the newly marketed agent, dolasetron.[20,21] The results of the trials are summarized in Table 1. No differences in the incidence of PONV could be demonstrated among the 5-HT3 receptor antagonists.

B. Treatment of Postoperative Nausea and Vomiting

Both dolasetron and ondansetron have been compared to placebo in the treatment of PONV. Although low response rates were found, they were significantly better than placebo.

Dolasetron in doses of 12.5-100 mg IV were found significantly better than placebo, with no apparent benefit gained by increasing the dose above 12.5 mg.[22,23] Additionally, ondansetron in single doses of 1 mg IV, 4 mg IV, or 8 mg IV were investigated. Mean nausea scores were significantly lower for all doses of ondansetron compared to placebo. The optimal dose of ondansetron for the treatment of PONV was found to be 4 mg IV. Similar results were found in two additional studies of similar design.[24,25] The investigators concluded that ondansetron in doses less than or equal to 8 mg IV, is safe and effective in the treatment of PONV, with a single dose of 4 mg IV appearing to be optimal. A separate trial evaluating the pharmacokinetics of ondansetron 4 mg IV or intramuscularly (IM) was undertaken in healthy male volunteers.[25] Systemic bioavailability was equivalent between both routes. The IM formulation provides an alternative dosage form for ondansetron in the treatment of PONV.

C. Acute Chemotherapy-Induced Nausea and Vomiting

1. Highly Emetogenic Chemotherapy

High-dose cisplatin has been used as the gold standard for antiemetic clinical trials because of its high emetogenicity and well-defined pattern of emesis. Table 2 summarizes results from studies comparing the safety and efficacy of dolasetron, granisetron and ondansetron in the prevention of nausea and vomiting(NV) with cisplatin regimens. There appears to be no significant difference between the agents. Direct comparisons of dolasetron to ondansetron showed no difference in control of emesis or nausea. The results of direct comparisons between granisetron and ondansetron suggest that a single IV dose of granisetron controls NV similarly to single or multiple doses of ondansetron.[26-33] Advantages of granisetron in these trials were demonstrated as increased patient compliance and acceptance. Oral granisetron has proven to be highly effective in the control of emesis induced by high-dose cisplatin. The response rates were comparable to those obtained with parenteral ondansetron.[34] These findings suggest single IV doses or oral dosing of granisetron are as efficacious as initial dosing strategies.

2. Moderately Emetogenic Chemotherapy

Most antiemetic studies utilize cyclophosphamide-based regimens as the model for moderately emetogenic chemotherapy. Cyclophosphamide induced NV may occur 6-12 hours following infusion and continue for another 48-72 hours. Despite extensive investigation of corticosteroids, metoclopramide, and phenothiazines, either alone or in combination, none of these agents has emerged as the treatment of choice. However, data from these studies provide a basis for comparison of newer antiemetic agents such as the 5-HT_3 receptor antagonists. Table 3 provides a summary of data from patients receiving moderately emetogenic chemotherapy, including cyclophosphamide, 5-fluorouracil, methotrexate, carboplatin and doxorubicin based chemotherapy. No significant differences were seen between dolasetron, granisetron and ondansetron antiemetic therapy.[35-40]

Scientific data supports the use of oral 5-HT3 receptor antagonists for the prevention of acute chemotherapy induced emesis (CIE) due to moderately emetogenic chemotherapy.[38-43] Indeed, single dose oral dolasetron was proven equally efficacious to multiple dose oral ondansetron. Similar response rates are seen with oral granisetron and ondansetron when compared to their corresponding parenteral formulations .[39] One clinical trial suggested a role for a single 1 mg dose of oral granisetron in patients receiving moderately emetogenic chemotherapy.[44] Recently, it was shown that a single 2 mg dose of oral granisetron taken 1 hour prior to chemotherapy offered 24-hour protection against moderately emetogenic CIE.[39] Data are also available for alternative oral ondansetron where twice-daily dosing has been shown to be as effective as thrice-daily dosing in patients receiving cyclophosphamide-based therapies.[45]

D. Delayed Chemotherapy-Induced Nausea and Vomiting

Delayed NV induced by chemotherapy may be protracted and severe. Currently there are few treatment options available. The 5-HT3 receptor antagonists have not been uniformly effective in preventing delayed NV.[46] The mechanism of delayed emesis may not involve serotonin receptors as a primary mechanism but instead may involve other neurotransmitters. Therefore, these agents would be less likely to be effective in delayed NV. A trend toward better control of NV from cisplatin chemotherapy has been shown for the combination of ondansetron and dexamethasone. However, differences were significant only in the control of nausea during the third cycle.[47] The optimal approach to controlling delayed emesis remains controversial. Overall, the efficacy of 5-HT3 receptor antagonists for the prevention of delayed NV appears limited.[48] Numerous studies comparing these agents against placebo, combinations with other antiemetic agents, or combinations of each other have shown little or no difference.[46] Poor control of acute NV is the most important predictor for the development of delayed NV. Therefore, good control of acute NV will have a major impact on the prevention of delayed CIE.

E. Breakthrough Vomiting from Chemotherapy

Despite the recent advances in the management of CIE, patients still have severe breakthrough nausea and/or vomiting requiring rescue treatment. The optimal approach to breakthrough emesis management in these patients has not been confirmed with controlled, comparative studies. Therefore, the choice of agent may be based on adverse event profiles and cost. Results from several noncomparative trials demonstrate that episodes of breakthrough vomiting can be controlled by intervention with a 5-HT3 receptor antagonist.[49-51] Optimal management of breakthrough vomiting should include providing scheduled doses of antiemetics as opposed to intermittent or as needed doses given after nausea is experienced. Parenteral antiemetics should be used in patients that are actively vomiting.

F. Radiotherapy-Induced Nausea and Vomiting (RINV)

Although the risk of radiation-induced emesis may not be as high as CIE, a subgroup of patients receiving radiation therapy may experience significant consequences. Situations in which emesis is more likely to occur are radiotherapy application to the upper abdomen, large field size such as total body irradiation which presents the greatest emetic challenge, single high doses of radiotherapy, and increasing dose per fraction.[52,53] It is recommended that patients receiving total or upper hemi-body irradiation, or therapy to the upper abdomen should receive preventive therapy for NV each day of radiotherapy. Several studies are available supporting the efficacy of dolasetron, granisetron or ondansetron in the prevention of RINV.[54] Complete response rates with the 5-HT3 receptor antagonists have been in the range of 53% to 96%. In general, investigators suggest using a 5-HT3 receptor antagonist for each day of radiotherapy with oral administration being the preferred route.

Table 1. Comparative trials of 5-HT3 receptor antagonists versus other 5-HT3 receptor antagonists for preventing postoperative nausea and vomiting.

Clinical Trial	Time of administration	24 – hour Response	Results Based on Intravenous 5-HT3 Dosage Regimen (% of patients w/ emesis or nausea)	Comments
Naguib [20] RDB[a], placebo controlled Adult males and females; inpatient laparoscopic cholecystec-tomy	Immediately before induction of anesthesia	PONV[b]	ondansetron 4 mg IV (N = 29)[c] 34.5% granisetron 3 mg IV (N = 25) 48% tropisetron 5 mg IV (N = 25) 52% metoclopramide 10 mg IV (N = 24) 71% placebo (N = 29) 72%	-employed standardized, balanced anesthetic technique and standardized postoperative analgesic regimen -rescue antiemetic allowed (metoclopramide 10 mg IV prn); recovery to first rescue antiemetic times were longer in the 5-HT3 receptor antagonist groups -no major adverse effects were observed in the study groups -conclusions: O[b] reduced the incidence of PONV significantly more than metoclopramide or placebo; no differences in the incidence of PONV could be demonstrated among the 5-HT3 receptor antagonists
Korttila [21] RDB,placebo controlled multicenter Adult males and females; inpatient gynecological or laparoscopic surgery, or thyroidectomy	Fifteen minutes prior to induction of anesthesia	Complete response[d] Total response[d] Nausea incidence	ondansetron 4 mg IV (N = 130)[e] 64% dolasetron 25 mg (N = 127) 51% dolasetron 50 mg (N = 129)[f] 71% placebo (N = 128) 49% ondansetron 4 mg IV (N = 130)[g] 54% dolasetron 25 mg (N = 127) 43% dolasetron 50 mg (N = 129)[h] 50% placebo (N = 128) 36% ondansetron 4 mg IV (N = 130)[i] 38% dolasetron 25 mg IV (N = 127) 43% dolasetron 50 mg IV (N = 129)[j] 29% placebo (N = 128) 56%	-employed standardized, balanced anesthetic technique -stratified according to gender, race, previous surgery, aspirin, physical status, history of PONV, history of motion sickness, and surgical technique; patients with a history of PONV, anesthesia > 1.66 hours, undergoing laparoscopic or gynecologic surgery had significantly lower complete response rates -most frequently reported adverse effects were bradycardia and headache, with no difference in these among groups -conclusions: D[b] 50 mg IV is equivalent to O[b] 4 mg IV and superior to D 25 mg IV and P[b] for the prevention of PONV

[a]RDB= randomized double-blind

[b] PONV = postoperative nausea and vomiting; O = ondansetron; D = dolasetron; P = placebo.

[c] Ondansetron significantly different from metoclopramide and placebo, p = 0.02

[d] Complete response was defined as zero emetic episodes and no rescue medication during study period; total response was defined as complete response plus no nausea up to 6 hours postrecovery.

[e] Ondansetron significantly different from dolasetron 25 mg, p = 0.027. No significant difference between ondansetron and dolasetron 50 mg.

[f] Dolasetron 50 mg significantly different from dolasetron 25 mg, p = 0.001 and placebo, p < 0.001.

[g] Ondansetron significantly different from placebo, p < 0.05. No significant difference between ondansetron and dolasetron 25 mg or dolasetron 50 mg.

[h] Dolasetron 50 mg significantly different from dolasetron 25 mg, p = 0.005 and placebo, p = 0.0001.

[i] Ondansetron approached statistical significance compared with dolasetron 50 mg, p = 0.069. No significant difference between ondansetron and dolasetron, p = 0.378.

[j] Dolasetron 50 mg significantly different from dolasetron 25 mg, p = 0.008 and placebo, p < 0.001.

Table 2. Prevention of acute chemotherapy-induced nausea and vomiting in cisplatin regimens by 5-HT3 receptor antagonists

Clinical Trial	Chemotherapy Regimen	Antiemetic Drug/Dose in First 24 hours	Results
Gebbia [26] RP[a], open label N=182	cisplatin > 70 mg/m^2	granisetron 3 mg IV ondansetron 24 mg IV	complete emesis control 49% G[b], 52% O[b] ; nausea 79% G and 74% O NS[c]
Mantovani[27] R[a], open label, crossover N=86	cisplatin > 80 mg/m^2	granisetron 3 mg IV ondansetron 24 mg IV tropisetron 5 mg IV	Both G and O significant over T[b] Best compliance with G Complete emesis control 79% G and O
Noble[28] RDB[a], crossover N=309	cisplatin 5-day fractionated	granisetron 3 mg IV/day X 5 days ondansetron 8 mg IV tid X 5 days	Complete emesis control 79% both G and O Significant patient preference with G
Ruff[29] RDB, parallel N=496	cisplatin ≥ 50 mg/m^2	granisetron 3 mg IV ondansetron 8 mg IV ondansetron 32 mg IV	complete emesis control 56% G, 59% O 8mg, 51% O 32 mg NS Nausea control 56% G and O 8mg, 48% O 32 mg Headache equal among groups
Italian Group for Antiemetic Research [30] RDB, parallel N=966	cisplatin ≥ 50 mg/m^2	granisetron 3 mg IV + dexamethasone 20 mg IV ondansetron 8 mg IV + dexamethasone 20 mg IV	Both regimens emesis control 79%, nausea control 72% Mild adverse effects no significant difference
Navari[31] RDB, parallel N=987	cisplatin ≥ 60 mg/m^2	granisetron 10mcg/kg IV granisetron 40mcg/kg IV ondansetron 0.15 mg/kg X 3 doses	Emesis control 79% both G regimens, 51% O Not significant Nausea control 39% G 10mcg, 42% G 40mcg, 40% O
Gralla[32] DB[a], parallel N=1054	cisplatin≥60mg/m^2	granisetron 2 mg PO ondansetron 32 mg IV	emesis and nausea control 55% G, 58 % for O NS, Equivalent side effects
Hesketh [33] RDB, parallel N=609	cisplatin ≥91 mg/m^2 or ≥ 70 mg/m^2	dolasetron 1.8 mg/kg IV dolasetron 2.4 mg/kg IV ondansetron 32 mg IV	Emesis control 44%, 40%,43% respectivelyNS Nausea control 92%,86%,84% respectivelyNS No significant difference with side effects

[a] RDB=randomized double-blind, RP=randomized placebo, DB=double-blind, R=randomized
[b] D=dolasetron, G=granisetron, O=ondansetron, T=tropisetron
[c] NS-not significant

Table 3. Prevention of nausea and vomiting in moderately emetogenic chemotherapy regimens by 5-HT3 receptor antagonists

Clinical Trial	Chemotherapy Regimen	Antiemetic Drug/Dose in First 24 hours	Results
Bonneterre [35] R[a], open-label, crossover N=150	cyclophosphamide	Granisetron 3 mg IV Ondansetron 8 mg IV + 8 mg PO q 8 hrs X 3 doses	Emesis control 72% G[b], 77% O[b], nausea control 54% G, 47% O. NS[c]
Jantunen [36] R, open-label, crossover Multiple cycle N=130	cyclophosphamide 5-flurouracil methotrexate	Granisetron 3 mg IV Ondansetron 8 mg IV Tropisetron 5 mg IV	Emesis control 80% G, 69% O, 75%T[b]. NS Adverse effects similar
Massidda[37] Parallel N=122	cyclophosphamide	Granisetron 3 mg IV Ondansetron 16 mg IV + 8 mg PO X 2 doses + 8 mg PO X 2 doses X 4 days Tropisetron 5 mg IV + 5 mg PO X 4 days	NS differences in emesis and nausea control. No apparent benefit with multiple doses
Stewart [38] RDB[a], double-dummy Parallel N=488	cyclophosphamide	Granisetron 3 mg IV Ondansetron 8 mg IV + 8 mg PO bid X 4 days ondansetron 8 mg PO bid X 4 days	NS differences in emesis control for day 1. Significant difference on day 2-5 with higher rescue and withdrawal with G
Perez[39] DB[a] parallel N=1085	cyclophosphamide carboplatin	granisetron 2 mg PO ondansetron 32 mg IV	NS difference with emesis and nausea (71%G vs73%O, 60%G vs 58%O respectively); significantly more reports of dizziness and abnormal vision with O
Fauser [40] RDB N=399	cyclophosphamide doxorubicin	dolasetron 25 mg PO dolasetron 50 mg PO dolasetron 100 mg PO dolasetron 200 mg PO ondansetron 8 mg X 3 or 4 doses PO	D[b] 200mg significantly better than other D doses. Single D dose of 200 mg = to O dosing. No significant side effects

[a] RDB=randomized double-blind, DB=double-blind, R=randomized
[b] D=dolasetron, G=granisetron, O=ondansetron, T=tropisetron
[c] NS-not significant

V. ADVERSE EFFECTS[46,55-57]

Clinical studies have proven the safety profile of the 5-HT3 receptor antagonists to be acceptable. In comparison to the adverse effect profile of other antiemetic agents, 5-HT3 receptor antagonists demonstrated no clinically significant or severe events.[1,46] Although there are pharmacological and pharmacokinetic differences between the 5-HT3 receptor antagonists, their adverse effect profiles are equivalent. In general, the 5-HT3 receptor antagonists are safe and well tolerated.

During healthy volunteer trials with dolasetron, some patients experienced electrocardiograph (ECG) changes. As a class, 5-HT3 receptor antagonists may demonstrate cardiac effects due to their ability to alter sodium and potassium channels.[58] Dolasetron, compared to granisetron and ondansetron, has been the most extensively studied for changes seen in ECG and heart rate. [33,58-60] Prolongation of the QT_c interval and increased heart rate were seen with dolasetron.[61] In contrast, granisetron and ondansetron decrease heart rate and increase QT and JT intervals.[59,62] The alterations in ECG and heart rates seen in these clinical trials were asymptomatic and clinically insignificant. Care should still be taken with any conditions or therapies that could augment the cardiac effects of dolasetron.

Common adverse effects of 5-HT3 receptor antagonists are listed in **Table 4**. These are usually mild to moderate, transient and rarely require drug discontinuation. The most commonly reported adverse effect is headache. Patients rate it as being mild to moderate, with relief obtained from non-narcotic analgesics. It is the only adverse effect reported to occur more frequently in patients receiving 5-HT3 receptor antagonists then placebo. Mild fatigue and sedation may also occur. Extrapyramidal symptoms were not reported with the 5-HT3 receptor antagonists. Significant elevations in hepatic transaminases have been reported in patients receiving the agents, but not in healthy volunteers. This suggests that chemotherapy itself is responsible for hepatic toxicity rather than the 5-HT3 receptor antagonists.

Table 4. Adverse effects of 5-HT$_3$ receptor antagonists.[55-57]

Adverse Effects	**Percent Incidence from Clinical Trial Experience (%)**
Cardiovascular:	
Hypertension	2
Central Nervous System:	
Dizziness	3 – 12
Headache	14 – 24
EPS[a]	Rare
Other (agitation, anxiety, CNS[b] stimulation, insomnia)	<2
Gastrointestinal:	
Abdominal pain	6
Constipation	3
Diarrhea	4 – 12
Hepatic:	
ALT elevation (transient)	2
AST elevation (transient)	9
Hypersensitivity:	
Anaphylactoid reaction	Rare
Pruritus	2
Miscellaneous:	
Fever	3
Taste disorder	2

[a] extrapyramidal symptoms
[b] central nervous system

VI. CLINICALLY SIGNIFICANT DRUG INTERACTIONS[55-57]

Dolasetron, granisetron and ondansetron do not induce or inhibit the cytochrome P-450 enzyme system. Inducers or inhibitors of these P-450 enzymes may alter the clearance or half-life of the 5-HT3 receptor antagonists. There have been no major drug-drug interaction studies to examine pharmacokinetic or pharmacodynamic interactions with other drugs. However, 5-HT3 receptor antagonists have been safely administered with benzodiazepines, neuroleptics, and anti-ulcer medications commonly prescribed with chemotherapy regimens.

Dolasetron should be administered with caution in patients receiving anti-arrhythmics, drugs that can prolong the QT_c interval, diuretics which can induce electrolyte disturbances and cumulative high dose anthracycline therapy.

VII. DOSING AND ADMINISTRATION [55-57]

The 5-HT3 receptor antagonists are available in oral and parenteral formulations. Ondansetron is the only agent with an oral solution available. Information is available on the extemporaneous compounding of an oral dolasetron solution. In addition, ondansetron suppositories have been compounded from oral tablets.[1] FDA-approved dosages are listed in **Table 5**.

Table 5. Dosing for the 5-HT3 receptor antagonists

		PONV		CIE-high emetogenic	CIE- mod emetogenic	RINV		
		Prevent	**Treat**			**TBI**	**Single dose**	**Daily fractionated**
Dolasetron	Oral	100 mg within 2 hr of surgery			100 mg 1hr prior to chemotherapy			
	Parenteral	12.5 mg IV 15 min prior to reversal	12.5 mg IV	1.8 mg/kg IV 30 min prior to chemotherapy				
Granisetron	Oral			1 mg BID first dose 1 hr prior to chemotherapy or 2 mg QD 1 hr prior to chemotherapy	1 mg BID first dose 1 hr prior to chemotherapy or 2 mg QD 1 hr prior to chemotherapy	2 mg within 1 hr of therapy		2 mg within 1 hr of fractionated radiotherapy to the abdominal region
	Parenteral			10 mcg/kg IV within 30 min prior to chemotherapy	10 mcg/kg IV within 30 min prior to chemotherapy			
Ondansetron	Oral	16 mg dose 1 hr prior to induction			8 mg BID first dose 1hr prior to chemotherapy	8 mg 1-2 hrs prior	8 mg 1-2 hrs prior with doses Q8H for 1-2 days post completion	8 mg 1-2 hrs prior with doses Q8H for each day of radiotherapy
	Parenteral	4 mg IV dose prior to induction	4 mg IV dose	Three 0.15 mg/kg IV doses infused over 15 min, 30 min prior and 4,8 hours post first dose or 32 mg IV single dose infused over 15 min 30 min prior	Three 0.15 mg/kg IV doses infused over 15 min, 30 min prior and 4,8 hours post first dose or 32 mg IV single dose infused over 15 min 30 min prior			

IV = intravenous; BID = twice daily; Q8H= every eight hours; QD= daily

VIII. SUMMARY

Few head-to-head comparative studies for the prevention of PONV exist with the 5-HT3 receptor antagonists. However, studies with the individual agents or in comparison to traditional antiemetics show similar response rates in the prevention of PONV. Treatment should be reserved for use in patients with high-risk factors such as obesity, preoperative anxiety, history of previous PONV or motion sickness, delayed gastric emptying, abdominal, gynecological or otolaryngologic surgical procedures, or long duration of surgery. The choice of agent should be based on patient-specific factors and cost. Oral ondansetron and dolasetron have been shown to be effective in the prevention of PONV when compared to placebo. Trials of parenteral granisetron have shown it to be effective but an optimal dose is unclear. There are no published studies with oral granisetron in the prevention of PONV. Parenteral ondansetron and dolasetron are safe and effective for the treatment of PONV due to general anesthesia or opioid-induced nausea and vomiting. Response rates were comparable to those seen with droperidol and metoclopramide. There are no published studies supporting the use of granisetron for treating PONV.

Dolasetron, ondansetron and granisetron are considered equally efficacious in preventing acute chemotherapy-induced nausea and vomiting from highly emetogenic chemotherapy. Both oral dolasetron and granisetron have proven highly effective in CIE from high-dose cisplatin. Response rates have equaled those obtained from the use of parenteral formulations. Similar response rates are seen with oral dolasetron, granisetron and ondansetron when used for prophylaxis of acute CIE from moderately emetogenic chemotherapy.

The 5-HT3 receptor antagonists have not been uniformly effective in preventing delayed NV from chemotherapy. Currently, the optimal approach to controlling delayed emesis remains controversial. Control of acute NV is essential. It is one of the most important predictors for the development of delayed NV and will have a major impact in its prevention. Control of anticipatory NV is through effective pharmacologic prophylaxis for acute and delayed emesis. There is no role for the 5-HT3 receptor antagonists in anticipatory NV. Round-the-clock dosing of a 5-HT3 receptor antagonist may be used in the management of breakthrough NV. The optimal management of breakthrough NV has not been confirmed. Therefore, the choice of agent should be based on adverse effects and cost. Several studies have supported the efficacy of dolasetron, granisetron or ondansetron in the prevention of RINV. When these agents are used for RINV, the drug should be given on each day of radiotherapy with oral administration being the preferred route.

The adverse event profile of the 5-HT3 receptor antagonists is limited to clinically insignificant effects, rarely requiring drug discontinuation. No significant drug interactions have been reported with the 5-HT3 receptor antagonists.

IX. RECOMMENDATIONS

Dolasetron, granisetron and ondansetron may be considered equally efficacious in the management of PONV and CINV. Their side effect profiles are similar and acceptable. One agent should be selected for the VA National Formulary based on cost. Clinical guidelines for use should follow after the selection of the particular agent with emphasis on specific indications for use and recommended dosage regimens.

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