Antiemetics Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
NK_1 receptor antagonist		
aprepitant (Emend®)[1]	Merck	In combination with other antiemetic agents for: ♦ Prevention of acute and delayed nausea and vomiting (N/V) associated with highly emetogenic cancer chemotherapy ♦ Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Prevention of post-operative N/V
5-HT_3 antagonists		
dolasetron (Anzemet®)[2]	Sanofi-Aventis	Prevention of N/V associated with moderately emetogenic cancer chemotherapy; including initial and repeat courses Prevention of postoperative N/V
granisetron (Kytril®)[3]	generic	Prevention of N/V associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin Prevention of N/V associated with radiation, including total body irradiation and fractionated abdominal radiation
granisetron transdermal (Sancuso®)[4]	ProStrakan	Prevention of N/V in patients receiving moderately or highly emetogenic chemotherapy regimens of up to five consecutive days duration
ondansetron (Zofran®)[5]	generic	Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2 Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Prevention of nausea and vomiting associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
palonosetron (Aloxi®)[6]	Helsinn Healthcare SA	Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
Cannabinoids		
dronabinol (Marinol®)[7]	Unimed	Treatment of N/V associated with cancer chemotherapy who have failed to respond adequately to conventional antiemetic treatments Anorexia associated with weight loss in patients with AIDS
nabilone (Cesamet®)[8]	Valeant	Treatment of N/V associated with cancer chemotherapy who have failed to respond adequately to conventional antiemetic treatments

Overview

The goal of antiemetic therapy is to prevent nausea and vomiting (N/V) completely. As a result of research over the last 20 years, this goal is achieved for many patients receiving chemotherapy or radiation therapy. Research has increased understanding of the pathophysiology of these symptoms and has resulted in therapy that is more effective and safer than in the past. With currently available agents, complete control of emesis (i.e., no vomiting) is achievable in the majority of patients in the first 24 hours and in approximately 45 percent of patients during the first week of chemotherapy.[9,10] Complete control correlates highly with patient perception of emesis and with patient satisfaction with their emetic control.

Nausea, the perception that emesis may occur, can be judged only by the patient. Nausea is quantified by the use of various questionnaires, such as visual analog scales (VAS).[11,12,13] The incidence of nausea correlates well with the incidence of vomiting, although chemotherapy-induced nausea occurs at a greater frequency.[14,15] Total control (no nausea or vomiting) is ideal, but lesser control rates such as major control (fewer than three emetic episodes) or minor control (three to five emetic episodes) may still have some value in difficult emetic situations. The American Society of Clinical Oncologists (ASCO) advises the use of complete control rates for the evaluation of emetic situations.

The prevention of delayed emesis and anticipatory emesis is equal in importance to the need to prevent acute (within first 24 hours) chemotherapy- and radiation-induced emesis. Risk factors for emesis include patient characteristics (age, sex, history of N/V, etc.) and emetogenicity of chemotherapy or radiotherapy. Consideration of these factors is critical in selection of the most appropriate antiemetic regimen for a particular patient.

Newer antiemetic regimens are more convenient for patients to receive and for healthcare professionals to administer. As antiemetic usage has grown, the classes of agents for treatment, the agents available, and their indications have increased in number, as well. The prevention and treatment of cancer chemotherapy- and radiotherapy-related N/V have come to be based largely on the use of type-3 serotonin (5-HT_3) receptor antagonists.[16] Aprepitant (Emend), a neurokinin-1 (NK_1) receptor antagonist, is used in combination with either dexamethasone or a 5-HT_3 receptor antagonist when treating chemotherapy-induced N/V. The cannabinoids are synthetic delta-9 THC (tetrahydrocannabinol) products and include two products, dronabinol (Marinol) and the newly re-introduced, nabilone (Cesamet).

The 2006 ASCO guidelines state that “at equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably.”[17] This position is confirmed in the 2008 Multinational Association of Supportive Care in Cancer (MASCC) guidelines.[18] The American Society of Health-System Pharmacists (ASHP) agrees with this assessment.[19] The National Comprehensive Cancer Network, in partnership with the American Cancer Society, states that the choice of antiemetic should be based on emetic risk of the chemotherapy as well as patient factors while noting that no one 5-HT_3 antagonist is more effective than another according to the 2007 update to their treatment guidelines.[20] In addition, nabilone has been added to the 2007 treatment guidelines update of recommended breakthrough treatments for CINV (chemotherapy induced nausea and vomiting).

The 2006 ASCO guidelines have incorporated aprepitant into first-line therapy for patients on chemotherapy of high emetic risk (with a 5-HT_3 antagonist and dexamethasone), patients receiving an anthracycline and cyclophosphamide (with a 5-HT_3 antagonist and dexamethasone), and the prevention of delayed emesis with agents of high emetic risk (with dexamethasone).[21]

Pharmacology

NK_1 receptor antagonist – aprepitant (Emend)[22]

Aprepitant exerts its main antiemetic action by occupying brain substance P-NK_1 receptors. This receptor pathway regulates the behavioral responses to a range of noxious and stressful stimuli. Expression in the brainstem emetic nuclei has implicated substance P in the control of vomiting.[23] Aprepitant has little or no affinity for 5-HT_3, D_2, or corticosteroid receptors.

5-HT_3 antagonists [dolasetron (Anzemet), granisetron (Kytril), granisetron transdermal (Sancuso), ondansetron (Zofran), palonosetron (Aloxi)][24,25,26,27,

Dolasetron, granisetron, ondansetron, and palonosetron selectively block 5-HT_3 receptors. While the mechanism of action of these drugs has not been fully elucidated, they are not D_2 receptor antagonists. Serotonin receptors of the 5-HT_3 type are found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines. It has not been determined whether the antiemetic action of the 5-HT_3 antagonists is mediated centrally, peripherally, or a combination of both sites. N/V during chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. The released serotonin may stimulate vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

Cannabinoids [dronabinol (Marinol), nabilone (Cesamet)][28,29]

Dronabinol and nabilone act on the cannabinoid receptors (CB1 and CB2) in the brain. These receptors are believed to regulate nausea and vomiting. Like most cannabinoids, these agents have complex effects on the central nervous system (CNS) and may even exert central sympathomimetic activity.

Pharmacokinetics

Drug	Bioavailability (%)	$t_{1/2}$ (h)	Metabolites	Excretion (%)
NK_1 receptor antagonist				
aprepitant (Emend)[30]	60-65	9-13	7, inactive	urine: 50 feces: 50
5-HT_3 antagonists				
dolasetron (Anzemet)[31]	75	8.1	hydrodolasetron, active	urine: 61 feces: 39
granisetron (Kytril)[32]	--	6.2	yes, activity questionable	urine: 59 feces: 38
granisetron transdermal (Sancuso)[33]	--	N/A; drug is released from patch continuously	yes	urine: 61 feces: 34
ondansetron (Zofran)[34]	56	3.1-6.2	yes, none significant	urine: 5
palonosetron (Aloxi)[35]	97	37±12	yes, none significant	urine: 85-93 feces: 5-8
Cannabinoids				
dronabinol (Marinol)[36]	10-20	25-36	yes, one active	urine: 15 feces: 50
nabilone (Cesamet)[37]	5-20	2-35	yes, active and inactive	urine: 22 feces: 67

Granisetron transdermal patch (Sancuso) delivers 66 percent of active ingredient following application for seven days.

Contraindications/Warnings[38,39,40,41,42,43,44]

5-HT_3 receptor antagonists are contraindicated in patients with known hypersensitivity to the drug or any of its components.

Granisetron and ondansetron do not stimulate gastric or intestinal peristalsis. They should not be used instead of nasogastric suction. Their use in patients following abdominal surgery or in chemotherapy-induced N/V may mask a progressive ileus and/or gastric distention.

5-HT_3 receptor antagonists should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QT_c.

Patients with phenylketonuria should be informed that ondansetron orally disintegrating tablets contain <0.03 mg phenylalanine in both the 4 mg and 8 mg tablets.

Adverse psychiatric effects can persist for 48 to 72 hours following discontinuation of nabilone (Cesamet). Cautious use of both cannabinoids [dronabinol (Marinol) and nabilone] in patients with current or previous psychiatric disorders (e.g. manic depression, depression and schizophrenia) is recommended.

Cautious use of the cannabinoids (dronabinol and nabilone) is recommended also in patients with a history of substance abuse and dependence.

Proteinuria has been reported in 6.8 percent of patients receiving aprepitant (Emend) in clinical trials.

Drug Interactions

aprepitant (Emend)[45]

Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents, which are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant 80 or 125 mg could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than its effect on the pharmacokinetics of intravenous (IV) CYP3A4 substrates. Coadministration of aprepitant with drugs that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, diltiazem, clarithromycin) may result in increased plasma concentrations of aprepitant. CYP2C9 metabolism may be induced by aprepitant. Weak inhibition of CYP enzymes by 40 mg doses of aprepitant is not expected to affect concentration of other drugs to a significant degree.

Coadministration of aprepitant with warfarin may result in a clinically significant decrease in INR. In patients on warfarin, INR should be closely monitored at seven to 10 days following initiation of the three-day regimen of aprepitant with each chemotherapy cycle.

The efficacy of oral contraceptives during administration of aprepitant may be reduced.

Because administration of aprepitant with dexamethasone or methylprednisolone approximately doubles the area-under-the-curve (AUC) of the corticosteroid, doses of the coadministered corticosteroid should be reduced by 50 percent when coadministered with aprepitant.[46]

5-HT_3 receptor antagonists[47,48,49,50]

Dolasetron (Anzemet), granisetron (Kytril, Sancuso), ondansetron (Zofran) and palonosetron (Aloxi) are metabolized by various CYP450 enzymes; however, due to the variety of enzymes involved, no clinically significant drug interactions have been identified at this time.

Blood levels of hydrodolasetron increased 24 percent when dolasetron was coadministered with cimetidine (nonselective inhibitor of CYP450) for seven days, and decreased 28 percent with coadministration of rifampin (potent inducer of CYP450) for seven days.

In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

Cannabinoids[51,52]

Both of the cannabinoids, dronabinol (Marinol) and nabilone (Cesamet), are highly protein bound and may displace other highly protein bound drugs. Examples include tricyclic antidepressants, amphetamines, barbiturates, benzodiazepines, fluoxetine, theophylline, and others. A change in dosage of the concomitant drug may be necessary. Consult prescribing information for dosages recommendations.

Adverse Effects

Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
NK1 receptor antagonist								
aprepitant (Emend)[53]	6	nr	5-16.4	nr	0.5-3	5.5-10.3	17.8-21.9	7.1-12.7
5-HT3 antagonists								
dolasetron (Anzemet)[54]	<1	2.2-3	7-22.9	nr	5.3	2.1-5.3	2.6-5.7	nr
granisetron (Kytril)[55]	5-6	nr	14-21	nr	<1	4-9	nr	nr
granisetron transdermal (Sancuso)[56]	nr	nr	<1	nr	nr	nr*	nr	nr
ondansetron (Zofran)[57]	1-2	reported	11-27	nr	5	3-7	9-13	nr
palonosetron (Aloxi)[58]	< 1	< 1	3.7-5.6	nr	nr	nr	1	< 1
Cannabinoids								
dronabinol (Marinol)[59]	<1	>1	<1	3-10	0.3-1	0.3-1	nr	3-10
nabilone (Cesamet)[60]	nr	reported	6	11	8	reported	nr	4

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

*Constipation is the predominant adverse effect associated with granisetron transdermal (Sancuso), occurring at a rate of 5.4 percent.

Special Populations

Pediatrics

Little information is available about dosage in pediatric patients four years of age or younger. There is no experience with the use of ondansetron 24 mg dosage in pediatric patients. There is no experience with the use of oral ondansetron in the prevention of radiation-induced or postoperative nausea and vomiting in pediatric patients.[61] Although not FDA-approved, there are data that also support using ondansetron in patients six months and older for post-operative N/V. Prescribing information states that ondansetron (Zofran) can be used for patients over four years old.

Dolasetron (Anzemet) is indicated for use in patients over two years old in the prevention of post-operative N/V and the prevention of chemotherapy-induced N/V.

Safety and efficacy of granisetron (Kytril) and granisetron transdermal (Sancuso) have not been established for pediatric patients.[62] Granisetron (Kytril) may be effective in patients older than four years old, according to limited randomized, controlled trials for post-operative N/V.[63,64,65] There is no experience with oral granisetron in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Aprepitant (Emend) and palonosetron (Aloxi) have not been studied in patients under 18 years old. Neither dronabinol (Marinol) nor nabilone (Cesamet) have been studied in children. Caution is recommended in prescribing dronabinol or nabilone for children because of the psychoactive effects.

dolasetron (Anzemet) and ondansetron (Zofran)

In a randomized, placebo-controlled, double-blind trial, oral dolasetron and ondansetron were compared in preventing post-operative N/V in 150 children after various surgical operations.[66] Children were assigned randomly to one of three groups to receive dolasetron 1.8 mg/kg, ondansetron 0.15 mg/kg, or a placebo. All children received methylene blue capsules orally as an indicator before the induction of anesthesia. Post-operative contamination of the mouth and the endotracheal tube by methylene blue, and post-operative N/V were recorded for 24 hours. In the one-hour period after the operation, there were no differences between the groups. During the period one to 24 hours after surgery, dolasetron was significantly better than placebo (16 versus 48 percent for nausea and vomiting, respectively). Over the entire 24 hours, both dolasetron and ondansetron were significantly better than placebo (32 versus 48 versus 78 percent, respectively, for nausea and vomiting). There were no significant differences between dolasetron and ondansetron, and no important adverse events were reported.

Pregnancy[67,68,69,70,71,72,73]

The NK-1 receptor antagonist, aprepitant, is Pregnancy Category B. The 5-HT_3 antagonists, ondansetron, granisetron, dolasetron, and palonosetron, are Pregnancy Category B. The cannabinoids, dronabinol and nabilone, are Pregnancy Category C.

Dosages

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK_1 receptor antagonist						
aprepitant (Emend)	125 mg before chemotherapy, then 80 mg once daily for two days as part of regimen including corticosteroid and a 5-HT_3 antagonist	--	--	40 mg up to three hours prior to induction of anesthesia	--	capsules: 40, 80, 125 mg tri-fold pack: one 125 mg capsule and two 80 mg capsules
5-HT_3 antagonists						
dolasetron (Anzemet)	100 mg orally within one hour before chemotherapy	2-16 years: 1.8 mg/kg (up to 100 mg) orally within one hour before chemotherapy	--	100 mg within two hours before surgery	2-16 years: 1.2 mg/kg (up to 100 mg) given within two hours before surgery	tablets: 50, 100 mg
granisetron (Kytril)	2 mg up to 1 hour before chemotherapy for one dose OR 1 mg up to 1 hour before chemotherapy followed by 1 mg 12 hours after the first dose	--	2 mg once daily taken within 1 hour of radiation	--	--	tablets: 1 mg oral solution: 1 mg/5 mL
granisetron transdermal (Sancuso)	Apply single patch to upper outer arm 24 hours prior to chemotherapy. Remove 24 hours after completion of chemotherapy. The patch can be worn for up to seven days.	--	--	--	--	transdermal patch containing 34.3 mg granisetron that releases 3.1 mg over 24 hours for seven days

Dosages (Continued)

Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
ondansetron (Zofran)	**High emetogenicity**: 24 mg 30 minutes before start of chemotherapy; **Moderate emetogenicity**: 8 mg 30 minutes before start with a subsequent dose 8 hours after the first dose, 8mg should then be given every 12 hours for 1-2 days following completion of chemotherapy.	High emetogenicity: No experience with 24 mg dosage Moderate emetogenicity: 4-11 years: 4 mg 30 minutes before chemotherapy with subsequent doses 4 and 8 hours after the 1st dose. 4mg should be given every 8 hours for 1-2 days after completion of chemotherapy. ≥12 years: same as adult	8 mg up to two hours before radiation and up to three times daily for one to two days	16 mg one hour before induction of anesthesia	--	tablets: 4, 8, 24 mg oral solution: 4 mg/5 mL tablets, orally disintegrating (ODT): 4, 8 mg
palonosetron (Aloxi)	0.5 mg approximately one hour prior to the start of chemotherapy	--	--	--	--	capsules: 0.5 mg
Cannabinoids						
dronabinol (Marinol)	Initial dose of 5 mg/m^2 given one to three hours prior to chemotherapy, then every two to four hours after for a total of four to six doses per day. The initial starting dose may be adjusted in increments of 2.5 mg/m^2 if necessary up to a maximum of 15 mg/m^2.	--	--	--	--	capsules: 2.5, 5, 10 mg
nabilone (Cesamet)	Usual adult dose is 1 to 2 mg twice daily. 1 or 2 mg may be given the night prior to chemotherapy or one to three hours before initial chemotherapy. Maximum daily dose of 6 mg in divided doses.	--	--	--	--	capsules: 1 mg

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

aprepitant (Emend) versus ondansetron (Zofran)

Patients receiving cisplatin were blindly assigned to receive one of the following three regimens: (1) aprepitant 375 mg one hour before cisplatin on Day 1 and aprepitant 250 mg on Days 2-5 (n=35); (2) aprepitant 125 mg before cisplatin and aprepitant 80 mg on Days 2-5 (n=81); or (3) placebo before cisplatin on Days 2-5 (n=86).[74] All groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin, and dexamethasone 8 mg on Days 2-5. The primary endpoint was complete response (no emesis and no rescue therapy) over five days following cisplatin in up to six cycles. The aprepitant 375/250 mg regimen was discontinued early in light of new pharmacokinetic data. In the first cycle, 64 percent of patients in the aprepitant group and 49 percent in the standard therapy group had a complete response ($p<0.05$). Thereafter, complete response rates for the aprepitant group were still 59 percent by Cycle 6, but decreased to 34 percent by Cycle 6 for the standard therapy group ($p<0.05$).

dolasetron (Anzemet) versus ondansetron (Zofran)

A multicenter, randomized, double-blind study was designed to compare the antiemetic efficacy and safety of single oral doses of dolasetron with a multiple-dose regimen of oral ondansetron in 399 cancer patients receiving moderately emetogenic chemotherapy.[75] Single oral doses of 25, 50, 100, or 200 mg of dolasetron were administered one hour prior to the initiation of chemotherapy. Ondansetron 8 mg, or matching placebo for patients randomized to dolasetron, was given 1.5 hours before and 6.5, 14.5, and 22.5 hours after the start of chemotherapy. A statistically significant ($p<0.001$) linear dose-response relationship was observed over the entire dolasetron dosage range for all efficacy parameters. Complete response rates were 45, 49.4, 60.5, and 76.3 percent for 25, 50, 100, and 200 mg dolasetron, respectively, and 72.3 percent for ondansetron patients. Overall, there were no significant differences in the incidence of adverse events between any of the dolasetron doses, or between dolasetron and ondansetron; headache was most frequently reported (approximately 15 percent for each drug). In the study, a single oral 200 mg dolasetron dose was therapeutically equivalent to multiple-dose ondansetron in the prevention of N/V following moderately emetogenic chemotherapy.

granisetron (Kytril) versus ondansetron (Zofran)

A double-blind study was conducted to determine the efficacy of oral ondansetron, oral granisetron, and IV ondansetron for the prevention/control of N/V associated with high-dose chemotherapy or radiotherapy prior to hematopoietic stem cell transplantation.[76] In addition to dexamethasone 10 mg IV, 102 patients were randomized to receive either ondansetron 8 mg orally every eight hours, granisetron 1 mg orally every 12 hours, or ondansetron 32 mg IV every 24 hours, each given on days one and two. Overall complete response rates were 48 percent for oral ondansetron, 47 percent for oral granisetron, and 49 percent for IV ondansetron; this difference is not statistically significant (p=NS). Overall major efficacy rates were 82 percent for oral ondansetron, 84 percent for oral granisetron, and 81 percent for IV ondansetron (p=NS). Mean VAS nausea scores were 32 for oral ondansetron, 32 for oral granisetron, and 27 for IV ondansetron (p=NS).

A double-blind, randomized, crossover study comparing granisetron 3 mg/day and ondansetron 24 mg/day enrolled 309 patients receiving two cycles of identical chemotherapy over five days.[77] Primary efficacy variables were prospectively defined as complete response (no vomiting and mild or absent nausea) over five days and patient preference. Both agents achieved good control of emetic symptoms with five-day complete response rates of 44 percent on granisetron and 39.8 percent on ondansetron (p=NS). Complete response rates were very similar in patients receiving either cisplatin or ifosfamide. There was a statistically significant difference in patient preference in favor of granisetron (p=0.048).

A randomized, cross-over pilot study of post-operative nausea and vomiting (PONV) was conducted in 250 female patients who received prophylactic ondansetron 4 mg at the end of a surgical procedure requiring general anesthesia.[78] Women were then followed post-operatively for four hours. Eighty-eight of the women developed PONV and were randomly assigned to receive one of the following: a repeat dose of ondansetron 4 mg (n=30), granisetron 1 mg (n=30) or granisetron 0.1 mg (n=28). They were followed for 24 hours. Patients who received the repeat dose of ondansetron had a complete response of 57 percent, those receiving granisetron 1 mg or 0.1 mg had complete responses of 60 percent and 68 percent, respectively. This difference was not statistically significant (p=0.773).

The efficacy of oral granisetron and oral ondansetron was compared for preemptive antiemesis in women undergoing modified radical mastectomy.[79] A randomized, double-blind, controlled study assigned 90 women, aged 18 to 65 years old, scheduled to receive radical mastectomies to receive orally granisetron 2 mg, ondansetron 4 mg, or placebo (30 women in each group) one hour before induction of anesthesia. Post-operative N/V was assessed until 24 hours post surgery. A complete response in zero to two hours after anesthesia was found in 43 percent, 63 percent, and 90 percent of patients who had received placebo, granisetron, or ondansetron, respectively; and of these, the percentages of patients requiring rescue antiemetics were 40 percent, 17 percent, and seven percent. The presence of N/V was less than 23 percent after two hours in all three groups. Also, after two hours, N/V scores and need for antiemetics were similar in all three groups. Oral ondansetron 4 mg provided better preemptive antiemesis than oral granisetron 2 mg and placebo in the two hours following surgery with general anesthesia.

granisetron (Kytril) versus granisetron transdermal (Sancuso)

A Phase III, randomized, parallel-group, double-dummy, double-blind trial was conducted in 641 patients who receive multi-day chemotherapy to compare the efficacy, tolerability, and safety of granisetron transdermal to oral granisetron 2 mg once daily in the prevention of N/V.[80] The

primary endpoint was proportion of patients achieving no vomiting and/or retching, no more than mild nausea, and without use of a rescue medication from the first administration until 24 hours after start of the last day's administration of multi-day chemotherapy. The effect of granisetron transdermal was established in 60.2 percent of patients and in 64.8 percent of the patient taking granisetron orally (p=NS).

dronabinol (Marinol), ondansetron (Zofran), combination therapy versus placebo

A five-day, double-blind, placebo-controlled study was conducted in 64 patients to compare the efficacy and tolerability of dronabinol, ondansetron, or the combination for delayed chemotherapy-induced nausea and vomiting (CINV).[81] Patients receiving moderately to highly emetogenic chemotherapy received dexamethasone 20 mg orally, ondansetron 16 mg IV, and either placebo or dronabinol 2.5 mg pre-chemotherapy on day one. Patients randomized to active treatment (dronabinol and/or ondansetron) also received dronabinol 2.5 mg after chemotherapy on day one. On day two, fixed doses of placebo, dronabinol 10 mg, ondansetron 16 mg, or combination therapy were administered. On days three to five, patients received placebo, flexible doses of dronabinol 10 to 20 mg, ondansetron 8 to 16 mg, or dronabinol 10 to 20 mg and ondansetron 8 to 16 mg. The primary outcome was a total response (TR) of nausea intensity < 5 mm on visual analog scale, no vomiting/retching and no use of rescue antiemetic. The TR was similar for the active treatments: dronabinol (54 percent), ondansetron (58 percent), and combination (47 percent) versus placebo (20 percent). Nausea absence was significantly greater for the active treatment groups versus placebo (15 percent): dronabinol (71 percent), ondansetron (64 percent), and combination (53 percent, p<0.05 for all). Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Dronabinol or ondansetron were similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. All active treatments were well tolerated. The population size is the greatest limitation of these data.

orally disintegrating ondansetron (Zofran ODT) versus conventional tablet formulation of ondansetron (Zofran)

Due to a lack of other available data, this study has been included. The efficacy of ondansetron ODT was compared to the conventional oral tablet of ondansetron in controlling N/V among breast cancer patients receiving high-dose epirubicin.[82] In a randomized trial, 134 patients received ondansetron ODT 8 mg twice daily or ondansetron tablet 8 mg twice daily, both for three days. Ondansetron tablet was significantly better at controlling emesis (72 percent versus 52 percent, respectively, p=0.020) and statistically insignificant when attempting to control nausea (66 percent versus 48 percent, respectively, p=0.054) compared to ondansetron ODT. However, when looking at major control of emesis (as having zero to two emetic episodes during the three days) between the conventional ondansetron tablet versus ondansetron ODT, there was no real difference (76 percent versus 70 percent, respectively, p=0.28). For control of major emesis and nausea, there are no major differences between the formulations.

Summary

The 5-HT_3 antagonists offer significant advantages in the prevention of N/V due to chemotherapy and radiotherapy. Based on available data, there appears to be little significant difference among the four drugs in this class. Most antiemesis guidelines reflect this stance. Granisetron transdermal (Sancuso) may offer benefit to select patients undergoing moderate to highly emetogenic chemotherapy regimens who cannot tolerate other formulations. The transdermal formulation did not demonstrate superior efficacy to the oral formulation of

granisetron.

Aprepitant (Emend) can be used in combination with either dexamethasone or a 5-HT_3 receptor antagonist when treating chemotherapy-induced N/V or for use as monotherapy in prevention of post-operative N/V, but its effectiveness has not been compared to other agents for these uses.

The synthetic cannabinoids are recommended as second-line therapy for chemotherapy induced nausea and vomiting when patients fail to respond adequately to conventional antiemetics. The significant risk for abuse and misuse, increased potential for drug interactions and increased risk for psychotomimetic reactions that has not been observed with other oral antiemetics suggest the cannabinoids should be monitored closely and reserved for specific use only.

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