Are All 5-HT₃ Receptor Antagonists the Same?

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Key Words

Ondansetron, granisetron, dolasetron, palonosetron, nausea, vomiting, chemotherapy

Abstract

The 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists have become the cornerstone for preventing and treating chemotherapy-induced nausea and vomiting. Four 5-HT₃ antagonists are commercially available in the United States, and numerous reports have been published comparing 2 or more agents. The studies ranged from randomized, double-blinded to open-label or retrospective trials; included chemotherapy-naïve and –non-naïve patients; and covered a range of doses and routes of administration with and without concomitant steroids, for preventing and treating nausea and vomiting after highly and moderately high emetogenic chemotherapy. With few exceptions, the studies uniformly show an equivalent efficacy rate and side effect profile among the various agents at equivalent doses. This article reviews the pharmacology of the class for insight into minor differences among the agents that could possibly influence drug selection for certain patients, and considers data on the absorption, half-life, metabolism, and receptor activity. Clinical trials support the claim of various guidelines that the 5-HT₃ receptor antagonists are therapeutically similar in safety and efficacy, particularly because the current best practice for preventing nausea and vomiting after highly and moderately high emetogenic chemotherapy is a combination of a 5-HT₃ antagonist, steroids, and aprepitant. (*JNCCN* 2007;5:35–43)

In 1991, the U.S. Food and Drug Administration (FDA) approved ondansetron, the first commercially available serotonin receptor antagonist for the prevention and treatment of chemotherapy-induced nausea and vomiting

(CINV). In less than 2 decades, the serotonin receptor (or 5-hydroxytryptamine type 3; 5-HT₃) antagonists have become the cornerstone for the prevention of CINV. In the United States, four 5-HT₃ antagonists are available: ondansetron, granisetron, dolasetron (a prodrug for hydrodolasetron), and a second-generation 5-HT₃ antagonist, palonosetron.

The National Comprehensive Cancer Network (NCCN) guidelines,¹ American Society of Clinical Oncology (ASCO) guidelines,² and Cancer Care Ontario practice guidelines³ currently describe these agents as equivalent in efficacy and lack of toxicity and therapeutically interchangeable after equipotent dosing. The literature supporting this conclusion is extensive and involves more than 49 reports comparing 2 or more agents directly in the clinical setting. The most reliable end point for evaluating studies of antiemetic regimens is the incidence of emesis. Nausea tends to occur at a higher incidence than vomiting, and vomiting does not usually occur without nausea. Nausea is a symptom that can be gauged only by the patient but may be indirectly quantified using questionnaires and visual reporting tools. The reported perceptions of nausea correlate well with the data from the combination of emesis incidence and use of rescue medications. By defining a complete response as no emetic episodes and no use of rescue medications after the administration of chemotherapy, data can be measured reliably with a high degree of accuracy.

Table 1 summarizes the clinical trials of 5-HT₃ antagonists for CINV. Most trials compare ondansetron and granisetron, and a range of doses using both the oral and intravenous routes were studied. Corticosteroid steroid use was another variable across the different trials. Prophylaxis was used prior to administration of moderately high and highly emetogenic regimens. Some trials also investigated antiemetic therapies for preparatory regimens for bone marrow transplant. Single-day chemotherapy

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and multiday chemotherapy were studied. Study designs included large trials that were randomized and double-blinded; randomized, open label; open label; crossover; and retrospective reports. Reports with small numbers of patients were included in Table 1.

Table 1 also includes the history of chemotherapy administration because it can substantially influence the results of an antiemetic trial. Populations were consistent within studies in terms of patient gender, alcohol use, or exclusion criteria such as complaints of nausea or vomiting in the immediate period before chemotherapy was administered. Table 1 lists the number of patients included in each treatment arm.

Response rates in the table reflect complete responses, that is, no emetic episodes and no use of rescue medications. If a drug was reported to be statistically better, then it is noted in the column after complete response rates.

None of the randomized, double-blinded trials found a statistical difference in efficacy rates between granisetron and ondansetron. The studies with a less-rigid design also showed equivalency between the 2 agents, with a few exceptions. Yalcin et al.²⁸ reported an advantage to using granisetron, 3 mg intravenously, over ondansetron, 8 mg intravenously, for moderately emetogenic chemotherapy. Study size was small at 18 or 19 patients per study arm. In a retrospective review of antiemetic therapy, Dempsey et al.³⁸ found that ondansetron, 8 mg intravenously, was inferior to granisetron, 10 mcg/kg per dose. The study arms differed in that the ondansetron group was exposed to radiation more often, and corticosteroid use was less frequent in the ondansetron arm. Equivalent efficacy was also mostly reported in the setting of bone marrow transplants. The trial by Spitzer et al.¹⁶ showed a numerical superiority of granisetron over ondansetron, but the study arms were too small for statistical analysis. Lacerda et al.²⁰ observed that ondansetron, 24 mg/d, was superior to granisetron, but that 16 mg/d of ondansetron was equivalent. Only 16 and 24 patients were included in the study arms for ondansetron, 16 mg and 24 mg, respectively.

For delayed emesis, efficacy was also similar among the first-generation 5-HT₃ antagonists. A single dose of granisetron was reported by Stewart et al.¹¹ to be less effective against delayed nausea than a multi-day regimen of ondansetron. An argument can be made that these were not equivalent doses. The period

greater than 24 hours almost always showed less efficacy than the acute period.

In a meta-analysis of 14 studies and 6467 patients comparing ondansetron with granisetron in the prophylaxis of acute or delayed nausea and vomiting in the setting of highly emetogenic or moderately emetogenic chemotherapy, del Giglio et al.⁴⁸ showed an apparent equivalency between the 2 agents. Likewise, no significant differences in adverse effects occurred, except that patients receiving 32 mg of ondansetron intravenously experienced blurred vision and dizziness more often.⁸ The more common side effects were headache, constipation, and diarrhea.

Dolasetron and ondansetron were compared in a trial for moderately emetogenic agents by Fauser et al.⁴⁰ Dolasetron, 200 mg orally, was equivalent to multiple doses of ondansetron, 8 mg. Audhuy et al.⁴² published a report showing intravenous granisetron and intravenous dolasetron to be equivalent in managing acute nausea and vomiting after treatment with highly emetogenic agents.

Palonosetron is a second-generation 5-HT₃ antagonist. Three randomized, placebo-controlled, non-inferiority trials compared this newer agent with first-generation 5-HT₃ antagonists. Gralla et al.⁴⁵ compared 2 dose levels of palonosetron with a single dose of ondansetron, 32 mg intravenously, in the management of nausea and vomiting after treatment with moderately emetogenic chemotherapy in chemotherapy-naïve and –non-naïve patients not treated with steroids. Palonosetron, 0.25 mg intravenously, was statistically better than ondansetron in both complete control of acute nausea and vomiting and delaying nausea and vomiting.

Palonosetron, 0.75 mg, was found to have no statistical difference from ondansetron. Aapro et al.⁴⁶ studied palonosetron, 0.25 mg intravenously and 0.75 mg intravenously, against ondansetron, 32 mg intravenously, in both chemotherapy-naïve and –non-naïve patients with and without steroids undergoing highly emetogenic regimens. The 2 drugs showed no statistical difference either during the acute or the delayed phases.

Eisenberg et al.⁴⁷ compared dolasetron, 100 mg intravenously, with palonosetron, 0.25 mg intravenously and 0.75 mg intravenously, after moderately emetogenic chemotherapy in chemotherapy-naïve and –non-naïve patients. A small percentage of patients

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5-HT₃ Receptor AntagonistsTable 1 Comparative Clinical Trials of 5-HT₃ Receptor Antagonists

Report	Drug	Regimen	Steroids	Type of Chemo-therapy	Study Design	Chemo therapy-Naïve	N	CR, Acute	Result	CR, Delayed	Result	Comment
Forni et al. ⁴ 2000	Gra	2 mg/m ² /d × 3 IV	No	High, MD	RN, DB	100%	30	62.90%	NS			
	Ond	5.3 mg/m ² /d × 3 IV	No	High, MD		100%	30	58.30%				
Barrajon and de las Penas ⁵ 2000	Gra	3 mg IV	Yes	High	RN, DB, C	47%	40	43%	NS			
	Ond	24 mg IV	Yes	High		61%	40	50%				
Gralla et al. ⁶ 1998	Gra	2 mg PO	58.80%	High	RN, DB	100%	534	54.70%	NS			
	Ond	32 mg IV	61.50%	High			520	58.30%				
Poon and Chow ⁷ 1998	Gra		No	Mod	RN, DB, C	No	20	37%	NS	28%	NS	
	Ond		No	Mod		No	20	35%				
Perez et al. ⁸ 1998	Gra	10 mcg/kg IV	82.30%	Mod	RN, DB, C	100%	311	58.6%	NS	27%	NS	Ond: more vision Sx
	Ond	32 mg IV	79.80%	Mod		100%	312	62.7%				
Perez et al. ⁹ 1998	Gra	2 mg PO	81.40%	Mod	RN, DB	100%	542	59.4%	NS	47%	NS	Ond: more vision Sx
	Ond	32 mg IV	81.60%	Mod		100%	543	58.0%				
Italian Group ¹⁰ 1995	Gra	3 mg IV	Yes	High	RN, DB	100%	483	72%	NS	50%	NS	
	Ond	8 mg IV	Yes	High		100%	483	72.0%				
Stewart et al. ¹¹ 1995	Gra	3 mg IV × 1	No	Mod	RN, DB	No	166	54%	NS	25%	Ond	
	Ond	8 mg IV + 8 mg PO bid × 8	No	Mod		No	167	51.0%				
	Ond	8 mg PO bid × 9	No	Mod		No	155	55				
Navari et al. ¹² 1995	Gra	10 mcg/kg IV	No	High	RN, DB	100%	328	38%	NS			
	Gra	40 mcg/kg IV					328	41%				
	Ond	0.15 mg/kg q4h × 3 IV					331	39%				
Huc et al. ¹³ 1998	Gra	1 mg PO bid	As chemo-therapy	Mod	RN, O, C	100%	188	> 50%	NS			
	Ond	8 mg PO bid						> 50%				
Jantunen et al. ¹⁴ 1993	Gra	3 mg IV	As chemo-therapy	Mod	RN, O, C	No	92	80%	NS			
	Ond	8 mg IV						69%				
Fox-Geiman et al. ¹⁵ 2001	Gra	1 mg PO q12h	Yes	High, MD	RN, DB	No	34	90%	NS	47%	NS	BMT
	Ond	32 mg IV qd	Yes	High, MD		No	34	90%				
	Ond	8 mg PO q8h	Yes	High, MD		No	34	95%				
Spitzer et al. ¹⁶ 2000	Gra	2mg PO qd	No	TBI	RN, DB	No	18	44.4%		27.8%		BMT
	Ond	8 mg PO q8h					16	26.7%				
Orchard et al. ¹⁷ 1999	Gra	7.5–10 mcg/kg q12h IV	Yes	TBI/High, MD	RN, DB	No	90		NS	0.73 /day*		BMT
	Ond	8 mg LD, 1 mg/h IV				Pediatric/Adults	97					
Slaby et al. ¹⁸ 2000	Gra	3 mg IV qd × 6		High, MD	RN, O	No	15	87%	NS			BMT
	Ond	8 mg IV bid × 6 days		High, MD		No	15	67%				

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Table 1 Continued

Walsh et al. ¹⁹ 2004	Gra Ond	10 mcg/kg/ d IV 0.15 mg/kg q8h IV	Yes Yes	High, MD High, MD	RN, DB	No No	46 50	83% 90%	NS	54% 56%	NS	BMT
Lacerda et al. ²⁰ 2000	Gra Ond Ond	3 mg IV qd 16 mg IV qd 24 mg IV qd	Yes Yes Yes	High, MD	RN, O	No No No	36 16 24	28% 31% 63%	O24 NS			8-day period BMT
Bonnetterre and Hecquet ²¹ 1995	Gra Ond	3 mg IV 8 mg IV + 8 mg PO × 8	No No	Mod Mod	RN, O, C	100% 100%	77 73	71% 66%	NS	57% 50%	NS	
Martoni et al. ²² 1996	Gra Ond	3 mg IV 8 mg IV q8h × 3 + 8 mg PO × 2	No No	High High	RN, O, C	100% 100%	66 58	62% 59%	NS			
Park et al. ²³ 1997	Gra Ond	3 mg IV 8 mg IV q8h + 8 mg po bid × 10	No No	Mod Mod	RN, O	No NO	48 49	77% 72.9%	NS	51% 54%	NS	
Mantovani et al. ²⁴ 1996	Gra Ond	3 mg IV 24 mg IV	No No	High High	RN, O	100% 100%	48 49	72% 73.3%	NS			Multiple cycle
Chiou et al. ²⁵ 2000	Gra Ond	1 mg PO bid 8 mg IV q8h	Yes Yes	High High	RN, O	No No	26 25	85% 84%	NS	16% 19%	NS	
Chua et al. ²⁶ 2000	Gra Ond	3 mg IV 8 mg IV + 8 mg PO bid	Yes Yes	High High	RN, O, C	100% 100%	30 30	81% 74%	NS			
Oge et al. ²⁷ 2000	Gra Ond	3 mg IV 8 mg IV	No No	High High	RN, O	100% 100%	36 35	66% 51%	NS			
Yalcin et al. ²⁸ 1999	Gra Ond	3 mg IV 8 mg IV	No No	Mod Mod	RN, O	100% 100%	19 18	74% 39%	Gra			
Gibbs and Cassoni ²⁹ 1996	Gra Ond	IV PO bid	No No	TBI TBI	RN, O	100% 100%	12 13	67% 77.0%	NS			BMT
Kalaycio et al. ³⁰ 1998	Gra Ond	0.5 mg, 0.04 mg/h IV 8 mg, 1 mg/h IV	Yes	High, MD	RN	No	22 23	15.8 15.8			NS	BMT
Gebbia et al. ³¹ 1994	Gra Ond Gra Ond	3 mg IV 16 mg IV 3 mg IV qd 24 mg IV + 8 mg PO bid	No No No No	Mod Mod High High	RN, O RN, O	No No No No	80 78 84 82	67% 52%	NS NS	37% 31% 39%	NS	
Ruff et al. ³² 1994	Gra Ond Ond	3 mg IV 8 mg IV 32 mg IV	No No	High High	RN, DB	No No	169 165 162	56% 59% 51%	NS			
Noble et al. ³³ 1994	Gra Ond	3 mg IV qd × 5 24 mg IV qd × 5	No No	High, MD High, MD	RN, DB, C	No No	169 165	44% 39.8%	NS			
Jaing et al. ³⁴ 2004	Gra Ond	10 mcg/kg 0.15 mg/kg q4h × 3	No No	Mod Mod	RN, O, C Pediatric	No No	33 33	60.6% 45.5%	NS			

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Table 1 Continued

Zeidman et al. ³⁵ 1998	Gra Ond	3 mg IV 8 mg IV + 4 mg PO q6h × 2	No		Mod/High RN	100% 100%	30 28	93% 75%					
Herrington et al. ³⁶ 2000	Gra Ond	1 mg PO 16 mg PO	Yes Yes		Mod RN, O	100% 100%	28 33	46% 45%	NS				
Farley et al. ³⁷ 1997	Gra Ond	1 mg IV or 2 mg PO 24 mg IV or 20 mg PO	74% 74%		Mod/high O Mod/high	14.30% 17.80%	74 45			60% 56.7%	NS		
Dempsey et al. ³⁸ 2004	Gra Ond Ond	10 mcg/kg IV 8 mg IV 32 mg IV	64% 41% 96%		Mod Mod Mod	Retro- spective	100% 100% 100%	80 68 76	75% 50% 74%		9% 6% 9%		
de Wit et al. ³⁹ 2001	Gra Ond	3 mg IV 8 mg IV	Yes		High RN, DB, C	Ond Failure	19 21	47.4% 4.8%	Gra				
Fauser et al. ⁴⁰ 1996	Ond Dol Dol	3 or 4 × 8 mg PO 100 mg PO 200 mg PO	No		Mod RN, DB	No	83 80 76	72.3% 60.5% 76.3%		Ond NS			
Tan et al. ⁴¹ 2004	Gra Dol	2 mg PO 100 mg PO	Yes		High/Mod O	No	13 13	69.2% 23.1%	Gra				
Audhuy et al. ⁴² 1996	Gra Dol Dol	3 mg IV 1.8 mg/kg IV 2.4 mg/kg IV	No		High RN, DB	60% 61% 59%	150 163 161	48% 54% 47%	NS				
Hesketh et al. ⁴³ 1996	Ond Dol Dol	32 mg IV 1.8 mg/kg IV 2.4 mg/kg IV	No		High RN, DB	92% 92% 91%	206 198 205	43% 44% 40%	NS				
Lofters et al. ⁴⁴ 1997	Ond Ond Dol	32 mg IV 32 mg IV 2.4 mg/kg IV 2.4 mg/kg IV 2.4 mg/kg IV	Yes No Yes Yes No		Mod RN, DB	Yes	198 149 198 145	67% 57%	Ond	39% 36%	NS	Steroid group Better	
Gralla et al. ⁴⁵ 2003	Pal Pal Ond	0.25 mg IV 0.75 mg IV 32 mg IV	No No No		Mod Mod Mod	RN, DB	40.20% 42.30% 42.20%	189 189 185	81% 73.50% 68.60%	Pal NS	74.10% 64.60% 55.10%	Pal NS	
Aapro et al. ⁴⁶ 2006	Pal Pal Ond	0.25 mg IV 0.75 mg IV 32 mg IV	67% 67% 66.50%		High High High	RN, DB	59.60% 57.80% 59.30%	223 223 221	59% 65.50% 57.00%	NS NS	45.30% 48% 38.90%	NS NS	
Eisenberg et al. ⁴⁷ 2003	Pal Pal Dol	0.25 mg IV 0.75 mg IV 100 mg IV	6% 6% 4.20%		Mod Mod Mod	RN, DB	65.60% 69.30% 65.40%	189 189 191	63% 57.10% 52.90%	Pal = Dol Pal = Dol	54% 56.60% 38.70%	Pal Pal	

Abbreviations: *, number of episodes vomiting per day; bid, twice a day; BMT, bone marrow transplant; C, crossover design; CR, no episode of vomiting, no rescue medicine for nausea; DB, double-blinded; Dol, dolasetron; Gra, granisetron; High, highly emetogenic chemotherapy; IV, intravenous; MD, multiday regimen; Mod, moderately emetogenic chemotherapy; NS, not significant; O, open; Ond, ondansetron; Pal, palonosetron; PO, by mouth; q, every; RN, randomized; Sx, symptoms; TBI, total body irradiation.

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were treated with steroids. For the acute control of nausea and vomiting, palonosetron was not found to be inferior to dolasetron. For delayed nausea and

vomiting, palonosetron was superior to dolasetron in preventing symptoms.

Data are emerging on multiday use of palonosetron. Hunt et al.⁴⁹ reported on the safety of 3-day therapy

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with palonosetron in normal subjects. Brames et al.⁵⁰ used dexamethasone daily and palonosetron on days 1, 3, and 5 of fractionated cisplatin therapy (bleomycin and etoposide or etoposide alone) for testicular cancer and found the therapy to be at least as effective and safe as historical controls involving ondansetron.

Palonosetron is at least as effective as first-generation 5-HT3 antagonists against acute nausea and vomiting. The primary goal of the above trials was to prove noninferiority of palonosetron to the first-generation 5-HT3 antagonists, and that goal was achieved. No trials have been designed to prove the superiority of palonosetron over other agents in its class. The comparative efficacy of palonosetron against delayed nausea and vomiting cannot be fully determined until trials have been conducted with other agents dosed appropriately to provide a pharmacologic effect throughout the study period, including the acute and delayed phases.

Steroids and aprepitant have emerged as the favored agents to prevent nausea and vomiting in the delayed phase after highly emetogenic chemotherapy. The current recommended antiemetic treatment strategies for moderately and highly emetogenic chemotherapy use combinations of 5-HT3 antagonists, steroids, and aprepitant.^{1,2} As the 2006 ASCO guidelines² point out, “The superiority question has now evolved to whether or not palonosetron is better than other 5-HT3 antagonists when they are combined with both dexamethasone and aprepitant.”

At equivalent doses, the 5-HT3 antagonists may be judged as similar in efficacy and safety, and other factors, such as cost or convenience, can be considered in choosing between them. These agents have pharmacologic differences in terms of absorption, half-life, receptor-binding affinity, selectivity of binding sites, and metabolism (Table 2). Bioavailability for the first-

generation 5-HT3 antagonists allows for oral administration. Palonosetron is unlikely to be available orally because of extensive first-pass effect. As the results of the clinical trials indicate, oral administration of the other agents has similar efficacy.

Despite the shorter half-life seen with ondansetron, all of the first-generation 5-HT3 antagonists seem to be able to be administered daily with similar efficacy, suggesting a dissociation of duration of action from half-life. Ondansetron has displayed activity at various receptors other than 5-HT3 receptors. These include 5-HT1A, 5-HT1B, α 1-adrenergic, and μ -opioid receptors. Palonosetron also binds to 5-HT α 1A, 5-HT1A, 5-HT1D, 5-HT2A, 5-HT2C, muscarinic M₂, and κ - and δ -opioid receptors. Obvious differences in the incidence of adverse effect related to these additional binding sites have not been reported consistently in the clinical trials.

The primary metabolic pathway for ondansetron is hydroxylation on the indole ring followed by glucuronide or sulfate conjugation, with some nonconjugated active metabolites. Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation. Some metabolites may also have 5-HT3 receptor antagonist activity.

Dolasetron is reduced to hydrodolasetron by a ubiquitous enzyme, carbonyl reductase. CYP2D6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron and both CYP3A and flavin monooxygenase are responsible for N-oxidation of hydrodolasetron. Palonosetron is metabolized to N-oxide-palonosetron and 6-S-hydroxy-palonosetron. Metabolites have very weak antagonist activity. CYP2D6 and, to a lesser extent, CYP3A and CYP1A2 are involved in metabolizing palonosetron. Kinetic parameters of palonosetron are not significantly different between poor and extensive metabolizers of

Table 2 Pharmacologic Properties of 5-HT3 Antagonists

Drug	Oral Bioavailability	Half-life (h)	Receptor Binding Affinity	Enzymes Involved in Metabolism
Dolasetron (hydrodolasetron)	75%	7.3	9.8 (PA ₂)	Carbonyl reductase, CYP2D6*, CYP3A, flavin monooxygenase
Granisetron	65%	4.91–8.95	8.42 pK _i	CYP3A
Ondansetron	56%	3.5–5.5	8.07 pK _i	CYP2D6, CYP3A4*, CYP1A2, CYP2E1
Palonosetron	9% (monkey)	40	10.4 pK _i	CYP2D6*, CYP3A, CYP1A1

*Dominant role

Abbreviations: PA₂, comparative index of antagonism for 5-HT3 receptor; pK_i, measure of the binding affinity of the test compound to the receptors present in the cell homogenate; CYP, human cytochrome P450.

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CYP2D6 substrates. The enzymes involved in metabolizing the 5-HT₃ antagonists are listed in Table 2.

Metabolism does not appear to have a major influence on the results seen in clinical trials.

Ultrarapid metabolizers have been reported in association with CYP2D6. Kaiser et al.⁵¹ reported on CYP2D6 genotypes influencing emetic control after ondansetron use, showing that patients experiencing failed treatment with 5-HT₃ antagonists may benefit from treatment with an agent not metabolized by CYP2D6. The incidence of ultra metabolizers is variable across different populations: Saudis 21%, Ethiopians 18%, Sephardic Jews 13%, Italians 8%, and Caucasians 1% to 8%.⁵¹ de Wit et al.³⁹ rescued patients experiencing ondansetron failures who were undergoing highly emetogenic chemotherapy. In a randomized, double-blind study, either granisetron, 3 mg intravenously with dexamethasone, or ondansetron, 8 mg intravenously with dexamethasone, was given on the second cycle. Compared with only 5% of the ondansetron group, 47% of the granisetron group experienced complete protection. de Wit et al.³⁹ concluded that the presence of no cross-tolerance among 5-HT₃ antagonists and the changing of medications within the class have significant potential to provide antiemetic efficacy. Whether differences in enzyme metabolism can fully explain a lack of cross tolerance is unknown.

Summary

Clinical trials support a policy of considering the 5-HT₃ antagonists therapeutically similar in efficacy and safety. The minor differences in half-life, receptor binding, and metabolism may influence adaptations to a treatment plan but do not play a major role in the initial selection of a 5-HT₃ antagonist.

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