Compatibility and Stability of 5-HT_3 Receptor Antagonists: A Pharmacology Review

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Purpose/Objectives: To compare stability and compatibility among the 5-HT_3 antiemetics in multidrug cytotoxic regimens.

Data Sources: Published articles, product-prescribing information, and direct communication with manufacturers.

Data Synthesis: Stability and compatibility of ondansetron and granisetron with a variety of other agents used in the oncology setting generally are similar. Granisetron is compatible with all tested Y-site drugs; ondansetron is not compatible with amsacrine or fluorouracil. Information for dolasetron is not as readily available; therefore, comparisons are difficult to make.

Conclusion: Although 5-HT_3 receptor antagonists have made a significant impact in decreasing severe emesis, administration of complex regimens can be confusing at best for nurses because of the lack of compatibility data. By partnering with pharmacists, nurses can develop administration guidelines to minimize complications and improve outcomes.

Implications for Nursing: To maximize patients' outcomes, oncology nurses must be knowledgeable about stability and compatibility of complex multidrug regimens that include the commonly used 5-HT_3 receptor antagonist antiemetics.

Chemotherapy is one of the most common causes of iatrogenic nausea and vomiting in patients with cancer. Highly emetogenic agents, such as cisplatin, induce nausea and vomiting in 90% or more of patients (Craig & Powell, 1987; Love, Leventhal, Easterling, & Nerenz, 1989; Nightengale & Mauch, 1998; Rakel, 1999). Prior to the 1990s, standard therapy for chemotherapy-induced nausea and vomiting mainly consisted of dopaminergic-blocking agents (e.g., metoclopramide, phenothiazines) combined with dexamethasone and lorazepam (Johnson, Moroney, & Gay, 1997; San Angel, 1993). However, the dopaminergic agents often caused distressing side effects, including extrapyramidal symptoms, dystonia, diarrhea, and sedation. The introduction of the 5-HT_3 receptor antagonists in the early 1990s increased effective emetic control in chemotherapy recipients.

Key Points . . .

- Oncology nurses must be aware of the incompatibilities of 5-HT_3 receptor antagonists to safely manage complex multidrug regimens.
- Physical and chemical incompatibility information often is difficult to evaluate and incorporate into clinical practice.
- Review of drug compatibilities and stabilities with commonly used 5-HT_3 receptor antagonists will prevent administration complications.
- Nurses' knowledge of compatibilities can minimize the need for multiple venous access sites.

Goal for CE Enrollees:

To further enhance nurses' knowledge regarding compatibility and stability of 5-HT_3 receptor antagonists.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Discuss the stability and compatibility of 5-HT_3 receptor antagonist antiemetics in polyvinyl chloride containers.
2. Discuss the stability and compatibility of 5-HT_3 receptor antagonist antiemetics at Y-sites.
3. Discuss the nursing implications in the administration of multidrug regimens including the 5-HT_3 receptor antagonists.

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In addition, these new antiemetics did not cause extrapyramidal side effects, dystonia, and sedation.

Three 5-HT_3 receptor antagonists, ondansetron hydrochloride (Zofran®, GlaxoSmithKline, Research Triangle Park, NC), granisetron hydrochloride (Kytril®, Roche Pharmaceuticals, Nutley, NJ), and dolasetron (Anzemet®, Aventis Pharmaceuticals, Kansas City, MO), have been approved in the United States for prophylaxis of acute nausea and vomiting in patients receiving emetogenic chemotherapy. All three agents are available as oral and IV formulations.

Patients with cancer often receive highly emetogenic multidrug therapy. Nurses may coadminister IV 5-HT_3 receptor antagonists with a variety of other IV preparations, including antineoplastic agents, anti-infectives, immunosuppressants, narcotics, and other antiemetics. Frequently, this is accomplished using the Y-injection site of a multiport infusion set. The 5-HT_3 receptor antagonists also may be administered in combination with IV dexamethasone or methylprednisolone to produce greater antiemetic effect. In some centers, solutions of IV 5-HT_3 receptor antagonists, alone or in combination with corticosteroids or antineoplastic agents, are mixed in advance in glass or plastic containers and then stored frozen, refrigerated, or at room temperature until needed. Thus, the drugs may come into contact with one another in IV administration sets or storage containers, which can create potential problems relating to instability and drug incompatibilities.

Traditionally, issues related to stability and compatibility have been the concern of pharmacists. However, oncology nurses increasingly are being called on to manage complex multidrug regimens, including those that utilize 5-HT_3 receptor antagonists. To safely and effectively manage the use of these regimens, nurses must have a broad knowledge and understanding of 5-HT_3 receptor antagonists, including their storage and administration under various conditions and compatibilities and incompatibilities when mixed with other drugs commonly administered to patients with cancer.

This article reviews some fundamentals of drug stability and compatibility and presents a brief overview of information available about 5-HT_3 receptor antagonist stability and compatibility issues.

Drug Incompatibility and Instability

Most simply, drug incompatibility occurs when an IV drug, upon being mixed with an infusion solution or another drug, produces a product unsuitable for administration to patients (Bergman, 1977; Trissel, 1998). Drug instability is a reduction in drug potency or formation of a toxic decomposition product through a chemical or physical reaction (Stella, 1986). Drug incompatibility generally is categorized as physical or chemical even though all incompatibilities have a chemical basis (Trissel, 1998) and encompasses drug instability (Newton, 1978).

A number of common practices and situations can result in drug incompatibilities in an oncology setting (Eisenberg, 1997), including

- Failure of nurses to fully consider incompatibilities when administering urgently needed IV drugs to patients already receiving IV medication.
- Concurrent administration of commonly used yet incompatible drugs (e.g., dexamethasone and midazolam) in the same IV tube or cannula, which results in the formation of a precipitate (Trissel & Martinez, 1995; Trissel, Tramonte, & Grilley, 1991; Wong, Law, Walker, & Bowles, 2000).
- The need for prolonged IV therapy, which can increase the potential for combining two incompatible drugs, especially in patients with limited venous access (Vyas, Baptista, Mitrano, & Sesin, 1987).
- Use of a gravity-fed piggyback system for administering drugs, which can lead to incompatibility reactions subsequent to inline mixing of primary and secondary solutions or incomplete flushing of the tube or catheter (Leissing, Story, & Zaske, 1989).
- Trapping successively administered but incompatible drugs in an IV Y-site injection port where they precipitate.

Physical Incompatibility

Physical incompatibilities in most instances are characterized by visible changes in a mixture of two or more drugs. Typically, these changes involve the formation of a precipitate, gas bubbles, an unexpected color change, or development of turbidity or cloudiness. Physical incompatibilities may be related to changes in pH, formation of insoluble salts, presence of additives (e.g., buffers, cosolvents), storage temperature, sorption, or method of delivery (Eisenberg, 1997; Salamone & Muller, 1990). Of these, a shift in pH as a result of admixing is the most common cause of incompatibility between two drugs (Stella, 1986).

A drug may be lost from solution by adsorption onto the surface or absorption into the matrix of glass or plastic containers or administration sets (Stella, 1986; Trissel, 1998). This problem often is overlooked because any visible change is seldom indicative of a reaction. Absorption is likely to occur when lipid-soluble drugs are stored in polyvinyl chloride (PVC) containers or administration sets. PVC is a rigid polymer that is flexible because of the addition of phthalate plasticizers. Lipid-soluble drugs have a high affinity for plasticizers and sometimes diffuse into the plasticizer core of PVC containers. The opposite reaction (i.e., leaching) also can occur. In this case, phthalate plasticizers are extracted from PVC containers and tubing by surfactant solutions or solutions containing large amounts of cosolvents, with resultant contamination of the solutions with particulate matter (Stella; Trissel, 1998). Some commonly used drugs and biologics known to exhibit sorption include cyclosporine, carmustine, paclitaxel, tacrolimus, nitroglycerin, lorazepam, diazepam, warfarin, and insulin (Eisenberg, 1997; Trissel, 1998).

Chemical Incompatibility

Chemical incompatibilities (i.e., interactions resulting in inactivation or toxic degradation of a drug) occur at the molecular level, often as a result of hydrolysis or oxidation-reduction reactions (Eisenberg, 1997; Stella, 1986; Trissel, 1998). Concentration, pH, acid-base character, and photolysis also may be involved in chemical incompatibilities (Newton, 1978). In clinical practice, decomposition or degradation of more than 10% of one or more components of a drug solution is considered significant (Newton).

In contrast to physical incompatibilities, chemical incompatibilities are seldom visibly evident and, therefore, they are not easily detected by nurses. In fact, in some cases, a decrease in therapeutic benefit is the only indication that a

Table 1. Compatibility of Ondansetron and Granisetron With IV Fluids and Drugs Stored in Polyvinyl Chloride Bags

Ondansetron Studies						
Author	**Ondansetron Concentration (mg/ml)**	**Dexamethasone Sodium Phosphate Concentration (mg/ml)**	**Other Drug Concentrations (mg/ml)**	**Diluent(s)**	**Container and Conditions**	**Results**
McGuire et al., 1993	0.110	0.303	–	5% dextrose injection	50 ml polyvinyl chloride (PVC) bags stored for up to 24 hours at 23°C	Ondansetron and dexamethasone sodium phosphate were physically compatible and chemically stable in all admixtures, with < 6% change in concentration. Lorazepam-containing solutions in 0.9% sodium chloride injection became cloudy starting three hours after mixing but did not do so in 5% dextrose injection. Lorazepam concentrations in both 5% dextrose and 0.9% sodium chloride injection fell below 90% within four hours.
	0.382	0.262	–	5% dextrose injection		
	0.126	0.300	–	0.9% sodium chloride injection		
	0.388	0.261	–	0.9% sodium chloride injection		
	0.362	0.233	Lorazepam 0.024	5% dextrose injection		
	0.382	0.252	Lorazepam 0.025	0.9% sodium chloride injection		
Hagan et al., 1996	0.10, 0.20, 0.40, 0.64	0.2 and 0.4 with each ondansetron concentration	–	0.9% sodium chloride injection	50 ml PVC bags stored for up to 30 days at 2°C–6°C then 48 hours at 22°C–23°C	Solutions remained clear and were free of visible particulates. Changes in pH generally were < 0.1; < 10% change in ondansetron and dexamethasone sodium phosphate concentrations was noted.
Stewart et al., 1996	0.03 or 0.30	–	Cytarabine 0.2 and 40, dacarbazine 1 and 3, doxorubicin 0.1 and 2, etoposide 0.1 and 0.4, methotrexate 0.5 and 6, with each ondansetron concentration	5% dextrose injection	50 ml PVC bags stored for 21.8°C and 23%–48% relative humidity for up to 48 hours	No visible precipitation, change in color or clarity, or change in pH $\geq$ 0.5 in any admixture over the 48-hour observation period. Ondansetron, cytarabine, doxorubicin, etoposide, and methotrexate were stable alone and in the ondansetron or antineoplastic combination. Dacarbazine was slightly more stable with ondansetron than alone in solution and was unstable in all solutions at 48 hours, with concentrations reduced up to 25%.
Evrard et al., 1997	0.15	0.43	–	0.9% sodium chloride injection or 5% dextrose injection	50 ml PVC bags stored at 2°C–8°C and 15°C–25°C for up to 28 days	No color change or turbidity was found. The change in pH generally was $\leq$ 0.2. Greatest stability was observed with ondansetron 0.15 mg/ml plus dexamethasone sodium phosphate 0.43 mg/ml in 0.9% sodium chloride injection or 5% dextrose injection
	0.14	0.40	–		50 ml PVC bags stored at 2°C–8°C and 15°C–25°C for up to 28 days	
	0.76	0.23	–		100 ml PVC bags stored at	

(Continued on next page)

PFS–preservative-free formulation; RDF–readily dissolvable formulation

Table 1. Compatibility of Ondansetron and Granisetron With IV Fluids and Drugs Stored in Polyvinyl Chloride Bags *(Continued)*

Ondansetron Studies

Author	Ondansetron Concentration (mg/ml)	Dexamethasone Sodium Phosphate Concentration (mg/ml)	Other Drug Concentrations (mg/ml)	Diluent(s)	Container and Conditions	Results
					2°C–8°C and 15°C–25°C for up to 28 days	and with ondansetron 0.14 mg/ml plus dexamethasone sodium phosphate 0.4 mg/ml in 0.9% sodium chloride at either 2°C–8°C or 15°C–25°C in 50 ml PVC bags.
	0.740	0.22	–		100 ml PVC bags stored at 2°C–8°C and 15°C–25°C for up to 28 days	
Stewart et al., 1997	0.640	–	Dacarbazine 8 + doxorubicin PFS or RDF 0.8	5% dextrose injection	50 ml PVC bags for 24 hours at 30°C or up to seven days at 4°C, then 24 hours at 30°C	No visible precipitate, change in color or clarity, or change in pH > 0.7 in any admixture. All admixtures were stable except dacarbazine 8 mg/ml plus ondansetron and doxorubicin, which after removal from refrigeration, showed concentration decreases of 10.3% at eight hours and up to 14.3% at 24 hours at 30°C.
	0.640	–	Dacarbazine 20 + doxorubicin PFS 1.5	5% dextrose injection	50 ml PVC bags for 24 hours at 30°C or up to seven days at 4°C, then 24 hours at 30°C	
	0.903	–	Doxorubicin RDF 0.724 + vincristine 0.028	0.9% sodium chloride injection	50 ml PVC bags for 24 hours at 4°C, then five days at 30°C	
	0.994	–	Doxorubicin RDF 0.772 + vincristine 0.031	0.9% sodium chloride injection	50 ml PVC bags for 24 hours at 4°C, then five days at 30°C	

Granisetron Studies

Author	Granisetron Concentration (mg/ml)	Dexamethasone Sodium Phosphate Concentration (mg/ml)	Other Drug Concentrations (mg/ml)	Diluent(s)	Container and Conditions	Results
Pinguet et al., 1995	0.05	–	–	5% dextrose injection	50 ml PVC bags stored three days at 20°C, seven days at 4°C + three days at 20°C, and 30 days at –20°C + seven days at 4°C + three days at 22°C	All admixtures were clear with no color change; pH was stable over the study period. Less than 5% change in the concentration of granisetron, dexamethasone, or methylprednisolone under any study condition
		–	–	0.9% sodium chloride injection	50 ml PVC bags stored three days at 20°C, seven days at 4°C + three days	

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PFS–preservative-free formulation; RDF–readily dissolvable formulation

Table 1. Compatibility of Ondansetron and Granisetron With IV Fluids and Drugs Stored in Polyvinyl Chloride Bags *(Continued)*

Granisetron Studies						
Author	**Granisetron Concentration (mg/ml)**	**Dexamethasone Sodium Phosphate Concentration (mg/ml)**	**Other Drug Concentrations (mg/ml)**	**Diluent(s)**	**Container and Conditions**	**Results**
					at 20°C, and 30 days at –20°C + seven days at 4°C + three days at 22°C	
		0.07	–	5% dextrose injection	Three days at 20°C	
		0.35	–	5% dextrose injection	Three days at 20°C	
		–	Methylprednisolone hemisuccinate 2.26	5% dextrose injection	Three days at 20°C	
		0.07	–	0.9% sodium chloride injection	Three days at 20°C	
		0.35	–	0.9% sodium chloride injection	Three days at 20°C	
		–	Methylprednisolone hemisuccinate 2.26	0.9% sodium chloride injection	Three days at 20°C	
Mayron & Gennaro, 1996	1	–	–	5% dextrose injection (50 ml)	Stored in PVC bag at 20°C for 24 hours	For all infusion fluids, solutions remained clear, colorless, and without a Tyndall cone throughout the 24-hour observation period; changes in pH were ≤ 0.13 units. Remaining concentrations were ≥ 96% of original. In the granisetron and dexamethasone sodium phosphate combination, no evidence of incompatibility was found (no Tyndall cone or change in color or clarity), and pH was virtually unchanged (–0.03 unit). Granisetron retained 100% and dexamethasone retained 99% of original concentration.
		–	–	5% dextrose injection + 0.9% sodium chloride injection (50 ml)	Stored in 50 ml PVC bag at 20°C for 24 hours	
		–	–	0.9% sodium chloride injection (50 ml)	Stored in PVC bag at 20°C for 24 hours	
		–	–	5% dextrose injection + 0.45% sodium chloride injection (50 ml)	Stored in 50 ml PVC bag at 20°C for 24 hours	
		0.50 ml	–	0.9% sodium chloride injection (50 ml)	Stored in PVC bag for one hour	

PFS–preservative-free formulation; RDF–readily dissolvable formulation

chemical incompatibility has occurred, which is a potentially serious problem for patients (Eisenberg, 1997).

Finding physical compatibility does not rule out the possibility of chemical instability. Similarly, the determination of chemical stability does not rule out the possibility of the presence of unacceptable levels of particulate matter or turbidity in a solution. Therefore, nurses always must be aware of the possibility of incompatibility when managing concomitant administration of IV drugs for which both physical and chemical compatibility information are unavailable.

Stability and Compatibility Studies of 5-HT_3 Receptor Antagonists

Several studies reported in the literature have examined the stability and compatibility of IV solutions of ondansetron and granisetron under simulated conditions of storage in PVC bags and Y-site administration with drugs commonly used to treat patients with cancer (see Table 1). A MEDLINE® literature search revealed no published reports on the stability or compatibility of dolasetron; however, explicit manufacturers' information on compatibility and stability exists on file for dolasetron and the other 5-HT_3 receptor antagonists can be obtained by written request to the respective manufacturers. When managing multidrug IV regimens, compatibility and stability information from manufacturers, published studies, or standard textbooks on injectable drugs may be valid for drugs as tested under the conditions described but may not be applicable if the drugs are administered under other conditions (e.g., in other diluents, at different concentrations) or if a different brand is used.

Ondansetron

Storage in PVC bags: Three studies assessed the stability and compatibility of ondansetron and dexamethasone sodium phosphate in commonly used storage containers, including PVC bags (Evrard, Ceccato, Gaspard, Delattre, & Delporte, 1997; Hagan, Mallett, & Fox, 1996; McGuire, Narducci, & Fox, 1993). In all three studies, admixtures of ondansetron (the concentration range across studies was 0.1–0.76 mg/ml) and dexamethasone sodium phosphate (the concentration range across studies was 0.2–0.43 mg/ml), which were mixed in 0.9% sodium chloride injection or 5% dextrose injection, were physically compatible and, in most cases, chemically stable when stored in 50 ml PVC bags for 1–32 days under refrigeration or at room temperature. In Evrard et al.'s study, ondansetron and dexamethasone were stored in 50 ml and 100 ml PVC bags; dexamethasone was stable under all conditions, but ondansetron, as indicated by concentrations of remaining ondansetron less than 95%, was unstable under several conditions, most commonly when stored in 100 ml bags containing about 0.7 mg/ml ondansetron. The loss of ondansetron may have been the result of adsorption to the PVC bags, which would be consistent with the greater surface area available for adsorption in the 100 ml bags compared with 50 ml bags. McGuire et al. assessed the stability of lorazepam in solution with ondansetron and dexamethasone sodium phosphate admixed with both 0.9% sodium chloride and 5% dextrose injection. In that study, ondansetron and dexamethasone were physically compatible and chemically stable in all admixtures. However, lorazepam showed evidence of physical incompatibility in 0.9% sodium chloride injection and chemical instability in both 5% dextrose and 0.9% sodium chloride injection, suggesting that lorazepam should not be admixed in either IV fluid or PVC bags.

Ondansetron injection (as a hydrochloride salt) was mixed with 5% dextrose injection and either cytarabine, dacarbazine, etoposide, doxorubicin hydrochloride, or methotrexate sodium in a 50 ml PVC bag in a study conducted by Stewart, Warren, King, and Fox (1996). All antineoplastic drugs were tested at concentrations commonly used in clinical practice. In their study, ondansetron and each antineoplastic drug proved physically and chemically stable alone and in all admixtures with one exception: Dacarbazine 1 mg/ml was unstable alone and with ondansetron 0.3 mg/ml at 24 hours, and both concentrations of dacarbazine were unstable alone and in all solutions at 48 hours.

Stewart et al. (1997) investigated the stability of ondansetron, doxorubicin, and dacarbazine or vincristine sulfate in PVC bags. These combinations were of particular interest because of their potential for use in the home setting: doxorubicin and dacarbazine for the treatment of sarcomas and Hodgkin's disease and doxorubicin and vincristine for the treatment of hematologic cancers and Kaposi's sarcoma. In their study, ondansetron, dacarbazine, and doxorubicin (preservative-free formulation or readily dissolvable formulation [RDF]) were mixed in 50 ml PVC bags of 5% dextrose injection, whereas ondansetron, doxorubicin hydrochloride RDF, and vincristine sulfate were mixed in 0.9% sodium chloride in 50 ml PVC bags. At the concentrations and storage times used, all of the admixtures studied were physically compatible and virtually all were chemically stable in PVC bags stored at 4°C and then at 30°C. The single exception was dacarbazine 8 mg/ml, which was stable in admixtures for only four to eight hours in PVC bags.

Y-site compatibility: The visual compatibility of ondansetron with 79 selected drugs was evaluated during simulated Y-site injection. In their study, Trissel et al. (1991) prepared a solution of ondansetron at a concentration of 1 mg/ml in 0.9% sodium chloride injection (or 5% dextrose if indicated) in PVC containers. A 2 ml sample of the ondansetron solution then was mixed with a 2 ml sample of each of the secondary additives that previously had been placed in PVC bags containing 5% dextrose injection (or 0.9% sodium chloride, if indicated). The samples were stored in glass vials at room temperature (~22°C) for up to four hours under constant fluorescent light.

Trissel et al. (1991) found that 65 mixtures were compatible over the four-hour study period (see Tables 2–4). However, evidence of incompatibility, generally seen as formation of a precipitate or turbidity, was noted for 14 mixtures. The investigators believed that differences in pH may have been involved in at least some of the incompatibilities. Precipitation previously had been observed in solutions of ondansetron with a pH greater than 5.7 and, therefore, finding incompatibilities between ondansetron and drugs such as 5-fluorouracil, acyclovir sodium, ganciclovir sodium, alkaline antibiotics, aminophylline, and furosemide, which have alkaline pH values, and amphotericin B and methylprednisolone sodium succinate, which are sensitive to differences in pH, was not surprising. Precipitation of ondansetron in a sodium bicarbonate solution (pH = 8.6) used to alkalinize urine also has been reported (Jarosinski & Hirschfeld,

Table 2. Y-Site Injection Compatibility of Ondansetron, Granisetron, and Dolasetron With Antineoplastic Drugs

	Ondansetron				Granisetron				Dolasetron	
Drug	Drug Concentration[a] (mg/ml)	Ondansetron Concentration[b] (mg/ml)	Compatibility	Author	Drug Concentration (mg/ml)	Granisetron Concentration	Compatibility	Author	Compatibility	Author
Amsacrine	1	1[a]	Incompatible	Trissel et al., 1991	1	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Bleomycin sulfate	1[b, c]	1	Compatible	Trissel et al., 1991	1[b, c]	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Carboplatin	5	1	Compatible	Trissel et al., 1991	0.5[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	Compatible	dof
Carmustine	1.5	1	Compatible	Trissel et al., 1991	1.5	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	Incompatible	dof
Cisplatin	1[d]	1	Compatible Compatible	Trissel et al., 1991	0.5[d] 0.025[b]	0.5 mg/ml 0.5 mg/ml	Compatible Compatible	Mayron & Gennaro, 1996	Compatible	dof
Cladribine	0.015[b] 0.5[e]	1	Compatible	Trissel et al., 1996	0.015[b] 0.5[e]	0.05 mg/ml[b]	Compatible	Trissel et al., 1996	–	N/A
Cyclophosphamide	10	1	Compatible	Trissel et al., 1991	1[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	Compatible	dof
Cytarabine	50[d]	1	Compatible	Trissel et al., 1991	50[d] 1[b]	50 mcg/ml[a] 0.5 mg/ml	Compatible Compatible	Trissel et al., 1997b Mayron & Gennaro, 1996	– –	N/A
Dacarbazine	4	1	Compatible	Trissel et al., 1991	0.85[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	Compatible	dof
Dactinomycin	0.01	1	Compatible	Trissel et al., 1991	0.01	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Daunorubicin	2	1	Compatible	Trissel et al., 1991	1	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Doxorubicin	2[d]	1	Compatible	Trissel et al., 1991	0.1[b]	0.5 mg/ml	Compatible[f]	Mayron & Gennaro, 1996	Compatible[g]	dof
Doxorubicin liposome	0.4	1[a]	Compatible	Trissel et al., 1997a	0.4	0.05 mg/ml[a]	Compatible	Trissel et al., 1997a	–	N/A
Etoposide	0.4	1	Compatible	Trissel et al., 1991	0.4 0.2[b]	50 mcg/ml[a] 0.5 mg/ml	Compatible Compatible	Trissel et al., 1997b Mayron & Gennaro, 1996	Compatible	dof
Floxuridine	3	1	Compatible	Trissel et al., 1991	3	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Fludarabine phosphate	1[h]	0.5[h]	Compatible	Trissel, 1998	1	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Fluorouracil	16	1	Incompatible	Trissel et al., 1991	16 16	50 mcg/ml[a] 50 mcg/ml[a]	Compatible Compatible	Trissel et al., 1997b Trissel & Martinez, 1995	Incompatible	dof

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[a] Tested in 5% dextrose injection United States Pharmacopeia (USP) or 5% dextrose injection (unless otherwise specified); [b] Tested in 0.9% sodium chloride injection USP or 0.9% sodium chloride injection (unless otherwise specified); [c] Units/ml; [d] Tested as an undiluted solution; [e] Tested with bacteriostatic sodium chloride 0.9% preserved with benzyl alcohol 0.9%; [f] Slight Tyndall effect at three hours but considered compatible; [g] Hydrochloride (doxorubicin) or sulfate (vincristine) not specified; [h] Tested in dextrose 5% in water; [i] Tested in sodium chloride 0.9%; dof–data on file with manufacturer; N/A–no published information available

Table 2. Y-Site Injection Compatibility of Ondansetron, Granisetron, and Dolasetron With Antineoplastic Drugs *(Continued)*

	Ondansetron				Granisetron				Dolasetron	
Drug	Drug Concentration[a] (mg/ml)	Ondansetron Concentration[b] (mg/ml)	Compatibility	Author	Drug Concentration (mg/ml)	Granisetron Concentration	Compatibility	Author	Compatibility	Author
					1[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996		
Idarubicin	–	–	–	N/A	0.5	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Ifosfamide	25	1	Compatible	Trissel et al., 1991	2[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	Compatible	dof
Mechlorethamine	1[d]	1	Compatible	Trissel et al., 1991	0.25[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	–	N/A
Melphalan	0.1[i]	1[i]	Compatible	Trissel, 1998	0.1[b]	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Methotrexate sodium	15	1	Compatible	Trissel et al., 1991	6.25[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	–	N/A
Mitomycin	0.5[d]	1	Compatible	Trissel et al., 1991	0.5[d]	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Mitoxantrone	0.5	1	Compatible	Trissel et al., 1991	0.5	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Paclitaxel	0.03 and 1.2[h]	0.03 and 0.3[h]	Compatible	Trissel, 1998	1.2	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
					0.145[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996		
Pentostatin	0.4[b]	1	Compatible	Trissel et al., 1991	–	–	–	N/A	–	N/A
Plicamycin	–	–	N/A	Trissel et al., 1991	0.01	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Streptozocin	30	1	Compatible	Trissel et al., 1991	4.55[b]	0.5 mg/ml	Compatible	Mayron & Gennaro, 1996	–	N/A
Teniposide	0.1	1	Compatible	Trissel et al., 1991	0.1	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Thiotepa	1[h]	1[h]	Compatible	Trissel, 1998	1	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Vinblastine sulfate	0.12	1	Compatible	Trissel et al., 1991	0.12	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A
Vincristine sulfate	0.05	1	Compatible	Trissel et al., 1991	0.005[b] 0.17[b]	0.5 mg/ml 0.5 mg/ml	Compatible Compatible	Mayron & Gennaro, 1996	Compatible[g]	dof
Vinorelbine tartrate	1[i]	1[i]	Compatible	Trissel, 1998	1	50 mcg/ml[a]	Compatible	Trissel et al., 1997b	–	N/A

[a] Tested in 5% dextrose injection United States Pharmacopeia (USP) or 5% dextrose injection (unless otherwise specified); [b] Tested in 0.9% sodium chloride injection USP or 0.9% sodium chloride injection (unless otherwise specified); [c] Units/ml; [d] Tested as an undiluted solution; [e] Tested with bacteriostatic sodium chloride 0.9% preserved with benzyl alcohol 0.9%; [f] Slight Tyndall effect at three hours but considered compatible; [g] Hydrochloride (doxorubicin) or sulfate (vincristine) not specified; [h] Tested in dextrose 5% in water; [i] Tested in sodium chloride 0.9%; dof–data on file with manufacturer; N/A–no published information available

Table 3. Y-Site Injection Compatibility of Ondansetron, Granisetron, and Dolasetron With Supportive Drugs

Drug	Ondansetron	Granisetron	Dolasetron
Allopurinol sodium	Incompatible[a]	Compatible[b]	N/A
Amifostine	Compatible[a]	Compatible[b]	N/A
Aminophylline	Incompatible[c]	Compatible[b]	Incompatible[d]
Bumetanide	N/A	Compatible[b]	N/A
Buprenorphine	N/A	Compatible[b]	N/A
Butorphanol tartrate	N/A	Compatible[b]	N/A
Calcium gluconate	N/A	Compatible[b]	Compatible[d]
Chlorpromazine	Compatible[c]	Compatible[b]	N/A
Cimetidine	Compatible[c]	Compatible[e]	N/A
Dexamethasone sodium phosphate	Compatible[c]	Compatible[e]	N/A
Diphenhydramine	Compatible[c]	Compatible[b]	Compatible[d]
Dobutamine	N/A	Compatible[b]	N/A
Dopamine	Compatible[a]	Compatible[b]	Compatible[d]
Droperidol	Compatible[c]	Compatible[b]	Compatible[d]
Enalaprilat	N/A	Compatible[b]	N/A
Famotidine	Compatible[c]	Compatible[b]	N/A
Filgrastim	Compatible[a]	Compatible[b]	N/A
Furosemide	Incompatible[c]	Compatible[e]	N/A
Gallium nitrate	Compatible[a]	Compatible[b]	N/A
Haloperidol lactate	Compatible[c]	Compatible[b]	N/A
Heparin sodium	Compatible[c]	Compatible[b]	Incompatible[d]
Hydrocortisone sodium phosphate	Compatible[c]	Compatible[b]	N/A
Hydrocortisone sodium succinate	Compatible[c]	Compatible[b]	Compatible[d]
Hydromorphone	Compatible[c]	Compatible[b]	N/A
Hydroxyzine	Compatible[c]	Compatible[b]	N/A
Leucovorin calcium	N/A	Compatible[b]	N/A
Levoleucovorin calcium	N/A	Compatible[b]	N/A
Lorazepam	Incompatible[c]	Compatible[b]	N/A
Magnesium sulfate	Compatible[c]	Compatible[b]	Compatible[d]
Mannitol	Compatible[c]	N/A	N/A
Meperidine	Compatible[c]	Compatible[b]	Compatible[d]
Mesna	Compatible[c]	Compatible[e]	N/A
Methylpresnisolone sodium succinate	Incompatible[c]	Compatible[b]	Incompatible[d]
Metoclopramide	Compatible[c]	Compatible[b]	Compatible[d]
Morphine sulfate	Compatible[c]	Compatible[b]	Compatible[d]
Nalbuphine	N/A	Compatible[b]	N/A
Potassium chloride	Compatible[c]	Compatible[e]	Compatible[d]
Prochlorperazine edisylate	Compatible[c]	Compatible[b]	Compatible[d]
Promethazine	Compatible[c]	Compatible[b]	Compatible[d]
Ranitidine	Compatible[c]	Compatible[b]	N/A
Sargramostim	Incompatible[a]	Compatible[b]	N/A
Sodium bicarbonate	Incompatible[a]	Compatible[b]	Incompatible[d]

[a] Trissel, 1998; [b] Trissel et al., 1997b; [c] Trissel et al., 1991; [d] Data on file with manufacturer; [e] Mayron & Gennaro, 1996; N/A—no published information available

1991), again reflecting the incompatibility of ondansetron with drugs that have alkaline pH values.

Ondansetron has been investigated in screening studies of the Y-site compatibility of cladribine (Trissel, Martinez, & Gilbert, 1996), doxorubicin liposome injection (Trissel, Gilbert, & Martinez, 1997a), and gatifloxacin (Trissel, Gilbert, & Williams, 1999), as well as three-in-one parenteral nutrition admixtures (Trissel, Gilbert, Martinez, et al., 1999). Ondansetron proved compatible with cladribine, doxorubicin liposome injection, and gatifloxacin (see Tables 2–4). However, in a study with nine different three-in-one parenteral nutrition admixtures, ondansetron was found to be physically incompatible with all nine admixtures, as evidenced by emulsion disruption with immediate oiling out (i.e., formation of a layer of free oil on the top of a disrupted fat emulsion layer) (Trissel, Gilbert, Martinez, et al.).

Granisetron

Storage in PVC bags: Pinguet et al. (1995) demonstrated that a granisetron solution of 0.05 mg/ml was stable in both 5% dextrose and 0.9% sodium chloride injection fluids stored frozen (–20°C) for up to 30 days, refrigerated (4°C) for up to seven days, and at room temperature (22°C) for up to three days in PVC bags. Granisetron 0.05 mg/ml also was stable when mixed with dexamethasone sodium phosphate or methylprednisolone hemisuccinate in PVC bags containing 5% dextrose or 0.9% sodium chloride and stored for three days at 20°C.

Mayron and Gennaro (1996) found that granisetron 1 mg (as a hydrochloride salt) was stable for 24 hours at room temperature (20°C) in standard IV fluids, including 5% dextrose injection, 5% dextrose plus 0.9% sodium chloride injection,

Table 4. Summary: Y-Site Injection Compatibility of Ondansetron, Granisetron, and Dolasetron With Anti-Infective Drugs

Drug	Ondansetron	Granisetron	Dolasetron
Acyclovir sodium	Incompatible[a]	Compatible[b]	Incompatible[c]
Amikacin sulfate	Compatible[a]	Compatible[b]	N/A
Amphotericin B	Incompatible[a]	Incompatible[b]	Incompatible[c]
Ampicillin sodium	Incompatible[a]	Compatible[b]	Incompatible[c]
Ampicillin sodium-sulbactam sodium	Incompatible[a]	Compatible[b]	N/A
Aztreonam	Compatible[a]	Compatible[b]	N/A
Cefazolin sodium	Compatible[a]	Compatible[b]	Incompatible[c]
Cefepime	Incompatible[d]	Compatible[b]	N/A
Cefonicid sodium	N/A	Compatible[b]	N/A
Cefoperazone sodium	Incompatible[a]	Compatible[b]	N/A
Ceforanide	Compatible[a]	N/A	N/A
Cefotaxime sodium	Compatible[a]	Compatible[b]	N/A
Cefotetan sodium	N/A	Compatible[b]	N/A
Cefoxitin sodium	Compatible[a]	Compatible[b]	N/A
Ceftazidime (sodium carbonate)	Compatible[a]	Compatible[e, f]	N/A
Ceftazidime (arginine)	Compatible[a]	N/A	N/A
Ceftizoxime sodium	Compatible[a]	Compatible[b]	Compatible[c]
Ceftriaxone sodium	N/A	Compatible[b]	N/A
Cefuroxime sodium	Compatible[a]	Compatible[b]	N/A
Ciprofloxacin	N/A	Compatible[b]	N/A
Clindamycin phosphate	Compatible[a]	Compatible[b]	Incompatible[c]
Doxycycline hyclate	Compatible[a]	Compatible[b]	N/A
Fluconazole	Compatible[a]	Compatible[b]	N/A
Ganciclovir sodium	Incompatible[a]	Compatible[b]	N/A
Gatifloxacin	Compatible[g]	Compatible[g]	N/A
Gentamicin sulfate	Compatible[a]	Compatible[e]	Compatible[c]
Imipenem-cilastatin sodium	Compatible[a]	Compatible[b]	N/A
Metronidazole	N/A	Compatible[b]	Compatible[c]
Mezlocillin disodium	Incompatible[a]	Compatible[e]	N/A
Miconazole	Compatible[a]	Compatible[b]	N/A
Minocycline	N/A	Compatible[b]	N/A
Netilmicin sulfate	N/A	Compatible[b]	N/A
Ofloxacin	N/A	Compatible[b]	N/A
Piperacillin sodium	Incompatible[a]	Compatible[b]	N/A
Piperacillin sodium-tazobactam sodium	Compatible[d]	Compatible[b]	N/A
Tetracycline	Compatible[a]	N/A	N/A
Ticarcillin disodium	Compatible[a]	Compatible[b]	N/A
Ticarcillin disodium-clavulanate potassium	Compatible[a]	Compatible[b]	N/A
Tobramycin sulfate	N/A	Compatible[b]	Compatible[c]
Trimethoprim-sulfamethoxazole	N/A	Compatible[b]	Incompatible[c]
Vancomycin	Compatible[a]	Compatible[b]	Compatible[c]
Zidovudine	Compatible[a]	Compatible[b]	N/A

[a] Trissel et al., 1991; [b] Trissel et al., 1997b; [c] Data on file with manufacturer; [d] Trissel, 1998; [e] Mayron & Gennaro, 1996; [f] Ceftazidime; [g] Trissel, Gilbert, & Williams, 1999; N/A—no published information available

5% dextrose plus 0.45% sodium chloride injection, and 0.9% sodium chloride injection stored in PVC bags. Also, 1 ml of granisetron injection and dexamethasone sodium phosphate injection (0.5 ml) were stable and compatible when combined in 50 ml of 0.9% sodium chloride injection in a PVC bag and stored for one hour at room temperature (light-protected). However, Hourcade et al. (1997) reported variations (range = 82%–108%) in the concentration of granisetron over time when diluted in 5% glucose or 0.9% sodium chloride injection and stored in PVC bags. According to Hourcade et al., this suggests that granisetron should be stored undiluted and then diluted at the time of administration (as is recommended in the prescribing information [Roche Pharmaceuticals, 2002]).

Y-site compatibility: Two large studies examined the compatibility of granisetron with selected drugs during simulated Y-site administration. In the first study, 29 drugs were mixed in a 1:1 ratio with granisetron injection (1 mg/ml) in 0.9% sodium chloride and stored at room temperature (20°C–23°C) under fluorescent light (or light-protected, if indicated) for four hours (Mayron & Gennaro, 1996). In the second study, 5 ml of granisetron 50 mg/ml in 5% dextrose injection was combined with 5 ml each of 91 secondary additives in 5% dextrose injection or 0.9% sodium chloride injection and stored at room temperature (~23°C) under fluorescent light for four hours (Trissel et al., 1997b). All mixtures in the two studies were compatible over the four-hour study period, with the exception of the combination of granisetron and amphotericin B, which showed an unacceptable increase in turbidity (Trissel et al., 1997b). The granisetron-doxorubicin combination showed a very slight Tyndall effect (i.e., visible particles with monodirectional light) at three hours (Mayron &

Gennaro). However, the combination was considered compatible, although close examination of admixtures of granisetron and doxorubicin before use was recommended. Mayron and Gennaro, in the only study to evaluate drug stability, determined that the concentrations of both granisetron and the 29 secondary admixtures were greater than or equal to 96% of the initial concentration. One exception was demonstrated: A combination with sodium bicarbonate yielded only 92% of the initial concentration of granisetron. Granisetron, in contrast to ondansetron, did not precipitate when in contact with alkaline drugs, such as 5-fluorouracil, furosemide, lorazepam, and mezlocillin sodium.

Granisetron, like ondansetron, was investigated in screening studies of the Y-site compatibility of cladribine (Trissel et al., 1996), doxorubicin liposome injection (Trissel et al., 1997a), gatifloxacin (Trissel, Gilbert, & Williams, 1999), and three-in-one parenteral nutrition admixtures (Trissel, Gilbert, Martinez, et al., 1999). In these studies, granisetron was compatible with all of the agents evaluated, including the three-in-one parenteral nutrition admixtures.

Dolasetron

Although no published stability information on dolasetron mesylate in PVC bags seems to exist, limited information on the stability of this drug under recommended storage conditions and combined with standard IV fluids is provided in the dolasetron prescribing information (Aventis Pharmaceuticals, 2002). However, oncology nurses requiring further information on dolasetron compatibility can contact the manufacturers regarding the data on file that demonstrates the results of several studies evaluating the physical compatibility of dolasetron mesylate and other IV solutions and medications during Y-site administration. According to data on file with the manufacturer (R. Slavik, personal communication, April 6, 1999), physical incompatibilities following Y-site administration were observed in these studies between dolasetron mesylate and acyclovir sodium, aminophylline, amphotericin B, ampicillin sodium, carmustine, cefazolin sodium, chloramphenicol sodium succinate, clindamycin phosphate, 5-fluorouracil, heparin sodium, methylprednisolone sodium succinate, potassium phosphate, sodium bicarbonate, thiopental sodium, and trimethoprim or sulfamethoxazole. Also, incompatibilities were found between various combinations of dolasetron mesylate 100 mg or 200 mg plus dexamethasone sodium phosphate 10 mg or 20 mg diluted in 50 ml or 100 ml of either 0.9% sodium chloride or 5% dextrose and water. A precipitate was noted with the following combinations: (a) 100 mg dolasetron plus 10 mg or 20 mg dexamethasone, (b) 200 mg dolasetron plus 20 mg dexamethasone diluted in 50 ml or 100 ml 5% dextrose and water, and (c) 100 mg dolasetron plus 20 mg dexamethasone diluted in 50 ml 0.9% sodium chloride. A window of at least two hours in which solutions were visually clear was noted for additional combinations, including (a) 100 mg dolasetron plus 10 mg dexamethasone diluted in 50 ml or 100 ml 0.9% sodium chloride and (b) 100 mg dolasetron plus 20 mg dexamethasone diluted in 100 ml 0.9% sodium chloride. Nonvisual particles in these solutions, which were measured by a light-obscuration particle counter, were stable for up to two hours, and more than 90% of these particles were removed on filtration with a 0.22 micron filter. The clinical significance of the nonvisual particles is unknown.

Nursing Implications

When caring for patients with cancer, nurses should know the principal guidelines for the safe administration of IV admixtures containing 5-HT_3 receptor antagonists (Cohen et al., 1985; Eisenberg, 1997; Gordon, 1986; McKenry & Salerno, 1998; Trissel, 1993; Whitman, 1995). They should be familiar with the individual 5-HT_3 receptor antagonist being administered and read the prescribing information carefully for specific instructions when giving these drugs for the first time and periodically thereafter. In addition, before mixing a 5-HT_3 receptor antagonist with another drug, nurses should check a compatibility chart, if available, and discuss any questions about compatibility with a pharmacist. If the compatibility of the 5-HT_3 receptor antagonist and drug to be combined is unknown and no information is available, each drug should be administered alone and the line flushed with 10–15 ml of normal saline solution before and after administering each drug. After mixing the 5-HT_3 receptor antagonist and secondary drug, the solution in the container should be checked for any visible sign of incompatibility. Any drug that has changed color or consistency or formed visible particles when mixed with another drug should not be administered. The IV line should be observed carefully, both immediately after and periodically during administration. If an incompatibility is discovered, administration should be discontinued and the line removed; then, using an alternative IV line or a new line, nurses should alternate administration of the incompatible drugs or ask a physician if a compatible combination of drugs can be substituted. Administering nurses should remain with patients who are receiving their first dose of an IV medication for at least five minutes and monitor them closely for adverse effects (e.g., difficulty breathing, tachycardia, bradycardia, loss of consciousness, allergic reaction, nausea, confusion). If an adverse reaction occurs, medication should be stopped, patients reassured, appropriate therapy instituted or facilitated, and the adverse event documented. Recording the administration of each dose should be performed as soon as possible following administration. All medications administered should be recorded in one place to allow nurses to consider incompatibilities, interactions, or duplication of similar drugs. The name of the drug, dose, and time and route of administration should be noted on the medication container and on patients' medication records. Lastly, patients should be monitored for therapeutic benefit of the 5-HT_3 receptor antagonist. If the desired effect is not achieved (i.e., prevention or reduction of nausea and vomiting), the possible role of chemical instability or reaction with the drug container as a source of drug loss should be assessed.

Conclusion

The IV 5-HT_3 receptor antagonists often are administered in combination with a wide variety of other IV drugs to treat patients undergoing chemotherapy. This introduces the possibility of stability and compatibility problems, which can put patients at risk of serious untoward effects. Because of their role in managing patients' treatment, oncology nurses must be knowledgeable about the fundamentals of stability and compatibility problems, as well as how to safely and effectively administer often complex multidrug regimens, including those requiring the use of 5-HT_3 receptor antagonists. Such knowledge and appropriate intervention by

nurses, possibly in partnership with pharmacists, may produce better patient outcomes, both in terms of safety and therapeutic benefit.

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