

Compatibility and Stability of Palonosetron Hydrochloride with Lactated Ringer's, Hetastarch in Lactated Electrolyte, and Mannitol Injections During Simulated Y-Site Administration

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INTRODUCTION

Palonosetron hydrochloride (HCl) injection (Aloxi; MGI PHARMA, Inc.) is a longer-acting, selective 5-HT₃ receptor antagonist that has been approved for the prevention of chemotherapy-induced nausea and vomiting;¹⁻⁴ Phase 3 trials of the drug for the prevention of postoperative nausea and vomiting have been completed recently. Palonosetron HCl injection has been evaluated for compatibility with a number of chemotherapy and supportive care drugs,⁵⁻²⁰ and the findings of these studies show that it may be administered with many other drugs and solutions, including anti-infective drugs, by simultaneous or sequential Y-site administration.

The purpose of this study was to evaluate the physical and chemical stability of undiluted palonosetron HCl 50 mcg/mL when mixed during simulated Y-site administration with Lactated Ringer's injection, 6% hetastarch in lactated electrolyte injection, or 15% mannitol injection.

ABSTRACT

Palonosetron hydrochloride is a longer-acting, selective 5-HT₃ receptor antagonist that has been approved for the prevention of chemotherapy-induced nausea and vomiting and is being evaluated for the prevention of postoperative nausea and vomiting. The objective of this study was to evaluate the physical and chemical stability of palonosetron hydrochloride 50 mcg/mL when mixed with Lactated Ringer's injection, 6% hetastarch in lactated electrolyte injection, or 15% mannitol injection during simulated Y-site administration. Duplicate samples of each admixture were tested. The samples were stored and evaluated for 4 hours at room temperature. Physical stability was assessed by turbidimetric and particulate measurements, and by visual inspection. Chemical stability was assessed by using high-performance liquid chromatography. All of the admixtures were clear and colorless when viewed in normal fluorescent room light and when viewed with a Tyndall beam. Measured turbidity and particulate content were low initially and remained low throughout the observation period. Palonosetron hydrochloride concentration was unchanged in any of the samples throughout the study period. Palonosetron hydrochloride is physically and chemically stable with Lactated Ringer's injection, 6% hetastarch in lactated electrolyte injection, or 15% mannitol injection during simulated Y-site administration over 4 hours at ambient room temperature.

MATERIALS AND METHODS

Materials

Palonosetron HCl injection (Lot HPA109; MGI PHARMA, Inc., Bloomington, Minnesota) was supplied by the manufacturer. Lactated Ringer's injection (Lot 18-963-FW; Abbott Laboratories, North Chicago, Illinois), 6% hetastarch in lactated electrolyte injection (Hexend, Lot 23-279-FJ; Hospira, Inc., Lake Forest, Illinois), and 15% mannitol injection (Lot 31-122-DK; Hospira, Inc) were obtained commercially. Palonosetron HCl reference standard (Lot H-0492; Helsinn Chemicals SA, Lugano, Switzerland) was supplied by MGI PHARMA, Inc., and was used without further purification. The acetonitrile and other mobile phase components were suit-

able for high-performance liquid chromatographic (HPLC) analysis. The water used was also HPL-C grade (Barnstead Nanopure, Dubuque, Iowa) and was prepared immediately before use.

Allen et al reported that the mixing of an intravenous fluid in an administration set with a secondary additive through a Y-injection site occurs in a 1:1 ratio.²¹ To simulate this inline mixing, duplicate samples were prepared by combining 7.5-mL aliquots of undiluted palonosetron HCl 50 mcg/mL with 7.5-mL volumes of Lactated Ringer's injection, 6% hetastarch in lactated electrolyte injection, or 15% mannitol injection in colorless 15-mL borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described

elsewhere.²² The individual solutions were filtered through appropriate 0.22- μm filters (Millex-GS; Millipore Corporation, Bedford, Massachusetts) into the culture tubes. All manipulations were carried out in a Class 100 biological safety cabinet.

Physical Stability

The physical stability of the admixtures was assessed by visual examination and by measuring turbidity and particle size and content.²²⁻²⁴ The sample tubes had been previously triple-washed in HPLC-grade water and dried. To minimize the effects of scratches and imperfections in the glass, a thin layer of silicone oil was applied to the exterior of each tube. Visual examinations were performed in normal diffuse fluorescent room light with the unaided eye and by using a high-intensity monodirectional light (Tyndall beam; Dolan-Jenner Industries, Woburn, Massachusetts).

The turbidity of each sample was measured by using a color-correcting turbidimeter (Model 2100AN; Hach Company, Loveland, Colorado). Triplicate determinations were made on each of the samples. A light obscuration particle sizer/counter (Model 9703; Hiac-Royco, Grants Pass, Oregon) was used to determine particle content in the 2.04- μm to 112- μm range (the validated detection limits of the particle sizer/counter) and to verify the absence of unacceptable amounts of microparticulates 4 hours after mixing. Particulate determinations also were made in triplicate. Physical instability was defined as the presence of visible particulate matter, haze, or color change, or a change (increase or decrease) in measured turbidity of 0.5 nephelometric turbidity unit (NTU) or more.

High-Performance Liquid Chromatographic Analysis

The drug concentrations in each admixture were determined by using a stability-indicating HPLC assay method. The details of the analytical method used in this study are cited in Table 1. The palonosetron HCl analytical method was provided by the drug manufacturer.²⁵ The analytical method was validated in our laboratory to verify its suitability for this testing. Two high-performance liquid chromatographs, a Hewlett-Packard Series 1050 and a Hewlett-Packard Series 1100 (Agilent Technologies, Palo Alto, California), were used for analysis of palonosetron HCl. Each high-performance liquid chromatograph consisted of a multisolute delivery pump, autosampler, and photodiode array detector. The systems were controlled and integrated by a personal computer with chromatography management software (HPLC ChemStation Version A.09.03; Agilent Technologies). Triplicate HPLC determinations were performed on duplicate samples of each test admixture.

The analytical method for palonosetron HCl was demonstrated to be stability-indicating by accelerated degradation using the following four decomposition enhancing techniques. The sample solutions were mixed with 1 N hydrochloric acid, 1 N sodium hydroxide, or 3% hydrogen peroxide, or were subjected to heating, and loss of intact drug was observed. The degradation product peaks did not interfere with the peak of the intact subject drug.

The initial concentrations of palonosetron HCl were defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration. Drug stability was defined as not less than 90% of the initial drug concentration remaining in the admixture.

TABLE 1. High-Performance Liquid Chromatographic Analytical Method Used for Palonosetron Hydrochloride.

	<i>Palonosetron Hydrochloride^a</i>
Mobile phase	720 mL Water 280 mL Acetonitrile 0.67 mL Trifluoroacetic acid
Diluent	Mobile phase
Column	Zorbax SB-C8 ^b (250 × 4.6 mm, 5 μm)
Flow rate	1.0 mL/minute
Detection	254 nm
Sample	
Injection volume	50 μL
Retention times	
Palonosetron	9.3 min
Lactated Ringer's	Nothing detected
Hextend	Nothing detected
Mannitol	Nothing detected
Decomposition products	Multiple 2.3 to 2.5, 3.1, and 3.3 minutes

^aPrecision: Mean \pm standard deviation ($n = 9$) diluted in mobile phase to a nominal concentration of 25 $\mu\text{g}/\text{mL}$; percent relative standard deviation was 0.08%. Standard curve range was 6.25 to 31.25 $\mu\text{g}/\text{mL}$. The correlation coefficient was >0.9999 .

^bSupplied by Agilent Technologies (Palo Alto, California).

RESULTS AND DISCUSSION

All of the admixtures of palonosetron HCl with the three injections were initially clear and colorless in normal fluorescent room light. When viewed with a Tyndall beam, the palonosetron HCl mixtures with Lactated Ringer's and 15% mannitol injections were clear, but the Hextend injection had a normal inherent haze that extended to the mixtures with palonosetron HCl. The mixtures of palonosetron HCl with Lactated Ringer's injection and with 15% mannitol were essentially without haze, having measured turbidities of less than 0.2 NTU. Changes in turbidity of the mixtures were minor throughout the study. The palonosetron HCl samples in Hextend had a measured haze near 2.8 NTU, which is normal for this polymeric plasma volume expander. The haze did not exhibit substantial change throughout the study period. Measured particulates of 10 μm or larger were few in number in all samples and remained so throughout the observation period. All samples remained colorless throughout the study.

The results of the HPLC analysis for palonosetron HCl are shown in Table 2. No loss of palonosetron HCl occurred with any of the test injections over 4 hours. Therefore, palonosetron HCl is compatible and stable with the three large-volume injections tested during simultaneous or sequential Y-site administration.

The previous stability and compatibility tests of palonosetron HCl during simulated Y-site administration with a variety of parenteral medications have demonstrated that palonosetron HCl is a very stable drug.⁵⁻²⁰ None of the previous studies have found any loss of palonosetron HCl during the testing. Similarly, in this series of tests of simulated Y-site administration with three large-volume injections, palonosetron HCl once again demonstrated stability.

TABLE 2. Stability of Mixtures of Palonosetron Hydrochloride with Three Large-Volume Injections During Simulated Y-site Administration.

Time (Hours)	Percentage of Initial Palonosetron Hydrochloride Concentration Remaining ^a					
	with Lactated Ringer's Injection ^b		with Hextend Injection ^c		with Mannitol Injection ^d	
	#1	#2	#1	#2	#1	#2
1	100.11 ± 0.32	99.97 ± 0.18	100.35 ± 0.50	99.09 ± 0.99	99.86 ± 0.21	98.24 ± 0.06
4	100.14 ± 0.11	100.06 ± 0	98.24 ± 1.50	99.22 ± 1.89	99.67 ± 0.06	99.49 ± 0.04

^aMean ± standard deviation for triplicate determinations of duplicate samples.

^bInitial palonosetron concentrations of the duplicate samples were 26.48 and 27.23 mcg/mL.

^cInitial palonosetron concentrations of the duplicate samples were 24.11 and 24.83 mg/mL.

^dInitial palonosetron concentrations of the duplicate samples were 26.53 and 27.43 mg/mL.

The previous studies reported that most of the tested drugs were also stable and compatible in the presence of palonosetron HCl. An exception is methylprednisolone sodium succinate, which, when combined with palonosetron, formed a precipitate of free methylprednisolone,¹² most likely due to the acidic pH (pH 4.5 to 5.5) of the palonosetron HCl injection.¹ While all of the other previously tested drugs were stable and compatible with palonosetron HCl, it is useful to keep in mind that drugs that demonstrate pH-dependent incompatibility, like methylprednisolone sodium succinate, may present compatibility problems if combined with or administered simultaneously with acidic drug solutions such as palonosetron HCl.

CONCLUSION

Palonosetron HCl is physically and chemically stable when mixed with Lactated Ringer's injection, 6% hetastarch in lactated electrolyte injection, or 15% mannitol injection during simulated Y-site administration.

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