Physical and Chemical Stability of Palonosetron with Metoclopramide and Promethazine During Simulated Y-Site Administration

Abstract

The objective of this study was to evaluate the physical and chemical stability of mixtures of undiluted palonosetron hydrochloride 50 µg/mL with undiluted metoclopramide hydrochloride 5 mg/mL and with promethazine hydrochloride 2 mg/mL diluted in 5% dextrose injection during simulated Y-site administration.

Triplicate test samples were prepared by admixing 7.5 mL of palonosetron hydrochloride with 7.5 mL of the undiluted metoclopramide hydrochloride and, separately, with the promethazine hydrochloride dilution. Physical stability was assessed using a multistep evaluation procedure that included both turbidimetric and particulate measurement as well as visual inspection. Chemical stability was assessed by using stability-indicating high-performance liquid chromatographic analytical techniques based on the determination of drug concentrations. Evaluations were performed initially upon mixing and 1 and 4 hours after mixing.

The samples were clear and colorless when viewed in normal fluorescent room light and when viewed with a Tyndall beam. Measured turbidities remained unchanged; particulate contents were low and exhibited little change. High-performance liquid chromatographic analysis revealed that palonosetron hydrochloride and both metoclopramide hydrochloride and promethazine hydrochloride remained stable throughout the 4-hour test with no drug loss.

Palonosetron hydrochloride is physically compatible and chemically stable with undiluted metoclopramide hydrochloride and also with promethazine hydrochloride diluted in 5% dextrose injection during simulated Y-site administration.

Introduction

Palonosetron hydrochloride (HCl) (Aloxi) is a selective 5-HT_3 receptor antagonist approved for use in the prevention of chemotherapy-induced nausea and vomiting and is currently being evaluated for the prevention of post-operative nausea and vomiting.[1-4] Palonosetron HCl injection has been evaluated for compatibility with a number of chemotherapy and supportive care drugs.[5-15] However, palonosetron hydrochloride may be administered with many additional drugs by simultaneous or sequential Y-site administration, including metoclopramide HCl and promethazine HCl.

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The purpose of this study was to evaluate the physical and chemical stability of undiluted palonosetron HCl 50 µg/mL when mixed with undiluted metoclopramide HCl 5 mg/mL and with promethazine HCl 2 mg/mL diluted in 5% dextrose injection, during simulated Y-site administration.

Methods

Materials

Palonosetron HCl injection (Aloxi; Lot HPA109, MGI PHARMA, Inc., Bloomington, Minnesota) was supplied by the manufacturer. Metoclopramide HCl injection (Lot 015024; Baxter Healthcare, Deerfield, Illinois) and promethazine HCl injection (Lot 05B030A; Paddock Laboratories, Minneapolis, Minnesota) were obtained commercially. The infusion solution, 5% dextrose injection (Lot C647339; Baxter Healthcare) in polyvinylchloride bags, was also 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. Reference standards for metoclopramide (Lot UC 0694; Spectrum Chemical, Gardena, California) and promethazine HCl (Lot SA 0495; Spectrum Chemical) were obtained commercially. The acetonitrile and other mobile phase components were suitable for high-performance liquid chromatographic (HPLC) grade analysis. The water used was also HPLC grade (Barnstead Nanopure, Dubuque, Iowa) and was prepared immediately before use.

Allen et al[16] 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. To simulate this inline mixing,

Table 1. High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron, Metoclopramide, and Promethazine.

	Palonosetron[a]	*Metoclopramide*[b]	*Promethazine*[c]
Mobile phase	720 mL water 280 mL acetonitrile 0.67 mL trifluoroacetic acid	9.24 g ammonium acetate 800 mL water 200 mL acetonitrile	1.2 g pentanesulfonic acid sodium salt 600 mL water 6 mL glacial acetic acid 400 mL acetonitrile
Column	Zorbax SB-C8[d] (250 × 4.6 mm, 5 µm)	Phenomenex Gemini-C18[e] (150 × 4.6 mm, 5 µm)	Phenomenex Gemini-C18[e] (150 × 4.6 mm, 5 µm)
Flow Rate	1.0 mL/min	1.5 mL/min	1.5 mL/min
Detection	254 nm	268 nm	254 nm
Sample injection volume	50 µL	10 µL	10 µL
Retention times			
Palonosetron	9.6 min	15.4 min	1.6 min
Metoclopramide	4.4 min	4.5 min	Not applicable
Promethazine	8.9 min	Not applicable	2.7 min
Decomposition products and other components	Multiple 2.3 to 2.5, 3.1, 3.3 min, and 5.7min	1.3 min	Multiple1.2 to 1.6, 2.2, and 4.8 min

[a]Precision: Mean ± SD (n = 9) diluted in mobile phase to a nominal concentration of 25 µ/mL; percent relative standard deviation was 0.08%. Standard curve range was 6.25 to 31.25 µg/mL. The correlation coefficient was >0.9999.
[b]Precision: Mean ± SD (n = 9) diluted in a diluent composed of 200 mL water and 800 mL methanol with 0.132 mL phosphoric acid to a nominal concentration of 100 µg/mL; percent relative standard deviation was 0.29%. Standard curve range was 25 to 125 µg/mL. The correlation coefficient was >0.99997.
[c]Precision: Mean ± SD (n = 9) diluted in methanol to a nominal concentration of 100 µg/mL; percent relative standard deviation was 0.2%. Standard curve range was 25 to 125 µg/mL. The correlation coefficient was >0.99999.
[d]Agilent, Palo Alto, California
[e]Phenomenex, Torrance, California

triplicate samples were prepared by mixing 7.5-mL samples of undiluted palonosetron HCl 50 µg/mL with 7.5-mL samples of undiluted metoclopramide HCl 5 mg/mL and with promethazine HCl 2 mg/mL in 5% dextrose injection individually in colorless 15-mL borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described elsewhere.[17] The individual drug solutions were filtered through appropriate 0.22-µm filters (Millex-GS; Millipore Corporation, Bedford, Massachusetts) into the culture tubes.

Physical Stability

The physical stability of the admixtures was assessed by visual examination and by measuring turbidity and particle size and content.[17-19] 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 using a color-correcting turbidimeter (Model 2100AN, Hach Company, Loveland, Colorado). Triplicate determinations were made on each of the samples. After 4 hours, a light obscuration particle sizer/counter (Model 9703; Hiack-Royco, Division of Pacific Scientific Company, Grants Pass, Oregon) was used to quantify particles in the samples 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. Triplicate determinations were made on these samples. Physical instability was defined as visible particulate matter, haze, color change, or a change (increase or decrease) in measured turbidity of 0.5 nephelometric turbidity unit (NTU) or more.[17-19]

High-Performance Liquid Chromatographic Analysis

The drug concentrations were determined by using stability-indicating HPLC assay methods. The details of the analytical methods used in this study are cited in Table 1. The palonosetron HCl analytical method was provided by the drug manufacturer.[20] The analytical methods for metoclopramide HCl and promethazine HCl were adapted from previously published methods.[21,22] All of the methods were validated in our laboratory to verify their suitability for this testing. Two high-performance liquid chromatographs, a Hewlett-Packard Series 1050 (Agilent Technologies, Palo Alto, California) and a Hewlett-Packard

Table 2. Stability of Palonosetron Hydrochloride and Metoclopramide Hydrochloride During Simulated Y-site Administration.

	Percentage of Initial Concentration Remaining[a]			
	Palonosetron Hydrochloride[b]		*Metoclopramide Hydrochloride*[c]	
Time (Hours)	*#1*	*#2*	*#1*	*#2*
1	99.96 ± 0.01	100.07 ± 0.04	99.91 ± 0	99.80 ± 0.01
4	100.08 ± 0.01	99.96 ± 0.02	99.86 ± 0.01	100.4 ± 0

[a]Mean ± SD for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 25.0 and 25.6 µg/mL.
[c]Initial concentrations of the duplicate samples were 2.59 and 2.53 mg/mL.

Table 3. Stability of Palonosetron Hydrochloride and Promethazine Hydrochloride During Simulated Y-site Administration.

	Percentage of Initial Concentration Remaining[a]			
	Palonosetron Hydrochloride[b]		*Promethazine Hydrochloride*[c]	
Time (Hours)	*#1*	*#2*	*#1*	*#2*
1	100.05 ± 0.06	100.49 ± 0.04	99.27 ± 0	99.94 ± 0
4	100.23 ± 0.03	100.65 ± 0.02	99.65 ± 0	99.33 ± 0

[a]Mean ± SD for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 26.05 and 25.06 µg/mL.
[c]Initial concentrations of the duplicate samples were 1.052 and 1.087 mg/mL.

Series 1100 (Agilent Technologies) were used for analysis of palonosetron HCl and the other drugs. Each HPLC consisted of a multisolvent 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 methods for each of the drugs were demonstrated to be stability-indicating by accelerated degradation by using the following four decomposition enhancing techniques. The sample solutions were mixed with 1 N hydrochloric acid, 1 N sodium hydroxide, 3% hydrogen peroxide, and were subjected to heating. Loss of the intact drugs was observed, and the degradation product peaks or other drug peaks did not interfere with the peak of the intact subject drug.

The initial concentrations of palonosetron HCl, metoclopramide HCl, and promethazine HCl were defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration. Stability of the drugs was defined as not less than 90% of the initial drug concentration remaining in the admixtures.

Results and Discussion

All of the samples of palonosetron HCl with metoclopramide HCl, and promethazine HCl were initially clear and colorless in normal fluorescent room light and when viewed with a Tyndall beam. In addition, the samples were essentially without haze, having measured turbidities of less than 0.11 NTU. Changes in turbidity for the samples were minor throughout the study, generally less than 0.01 NTU. Measured particulates of 10 µm or larger were few in number in all samples and remained so throughout the observation period. The admixtures remained colorless throughout the study.

The results of the HPLC analysis for each of the test drugs are shown in Tables 2 and 3. No loss of concentration of palonosetron HCl occurred with either of the drugs over 4 hours. Similarly, little or no loss of concentration of metoclopramide HCl and palonosetron HCl occurred in 4 hours. Therefore, palonosetron HCl is compatible and stable with both of these drugs tested during simultaneous or sequential Y-site administration.

Conclusion

Palonosetron HCl is physically and chemically stable when mixed with metoclopramide HCl and with promethazine HCl during simulated Y-site administration.

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STATEMENT OF THE JOINT COMMISSION ON ACCREDITATION OF HEALTHCARE ORGANIZATIONS

At the December 2005 Midyear Clinical Meeting of the American Society of Health-System Pharmacists, Darryl Rich, PharmD., a surveyor for the Joint Commission on Accreditation of Healthcare Organizations ("Joint Commission"), gave a presentation on updates to the Joint Commission standards. At the conclusion of his prepared remarks, Dr. Rich was asked a question about USP 797. Although the question was outside the scope of Dr. Rich's remarks, and indeed, his area of expertise, he answered the question based upon information he received outside of the Joint Commission on USP 797 and its impact on barrier isolators. Unfortunately, Dr. Rich's statements were inaccurate and his response misleading, and he sincerely regrets any confusion it has caused to health system pharmacists and others, including manufacturers of barrier isolators that meet the ISO Class 5 air quality standards.

The sole responsible entity for USP 797 and its interpretation is United States Pharmacopeia ("USP"). According to Susan de Mars, USP's Chief Legal Counsel, USP 797 (2004) does not require a positive pressure barrier isolator that provides at least ISO Class 5 quality of air to be operated within a clean room.

Darryl Rich, PharmD, is a valued employee of the Joint Commission. One function the Joint Commission provides is to disseminate accurate information on healthcare issues. The Joint Commission believes that Dr. Rich has always attempted to satisfy this function.

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