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Physical and Chemical Stability of Palonosetron Hydrochloride with Glycopyrrolate and Neostigmine During Simulated Y-Site Administration

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ABSTRACT

The objective of this study was to evaluate the physical and chemical stability of undiluted palonosetron hydrochloride 50 mcg/mL when mixed with undiluted glycopyrrolate 0.2 mg/mL and neostigmine methylsulfate 0.5 mg/mL during simulated Y-site administration. Duplicate test samples were prepared by admixing 7.5 mL of palonosetron hydrochloride with 7.5 mL of glycopyrrolate and neostigmine methylsulfate injections. Physical stability was assessed by using a multi-step evaluation procedure that included both turbidimetric and particulate measurements and visual inspection. Chemical stability was assessed by using stability-indicating high-performance liquid chromatography 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 turbidity remained unchanged and particulate content was low and exhibited little change. High-performance liquid chromatography analysis found palonosetron hydrochloride and both glycopyrrolate and neostigmine methylsulfate remained stable throughout the 4-hour test with no drug loss. Palonosetron hydrochloride is physically compatible and chemically stable with glycopyrrolate and neostigmine methylsulfate 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 and has recently completed Phase 3 trials 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] and it may be administered with many other drugs, including glycopyrrolate and neostigmine methylsulfate, 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 undiluted glycopyrrolate 0.2 mg/mL and with undiluted neostigmine methylsulfate 0.5 mg/mL injections.

MATERIALS AND METHODS

Materials

Palonosetron HCl injection (Lot HPA109; MGI PHARMA, Inc., Bloomington, Minnesota) was supplied by the manufacturer. Glycopyrrolate injection (Lot 45135; Baxter Healthcare, Deerfield, Illinois) and neostigmine methylsulfate injection (Lot

TABLE 1. High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron, Glycopyrrolate, and Neostigmine.

	Palonosetron[a]	Glycopyrrolate[b]	Neostigmine[c]
Mobile phase	720 mL Water 280 mL Acetonitrile 0.67 mL Trifluoroacetic acid	1.0 g Sodium sulfate 0.2 g Pentanesulfonic acid sodium salt 615 mL Water 235 mL Acetonitrile 3 mL 1 N Sulfuric acid 150 mL Methanol	Mobile Phase A: 20 mM Monobasic Potassium phosphate Phosphoric acid to pH 2.5 Water Mobile Phase B: Acetonitrile Time (min) % Mobile Phase B 0 0 9.99 40 10.0 40 15.0 40 15.01 0
Column	Zorbax SB-C8[d] (250 × 4.6 mm, 5 mcm)	Waters C18 Reversed Phase[e] (300 × 3.9 mm, 5 mcm)	Phenomenex C18[f] (150 × 4.6 mm, 5 mcm)
Flow rate	1.0 mL/minute	2.0 mL/minute	1.0 mL/minute
Detection	254 nm	200 nm	265 nm
Sample Injection volume	50 mcL	40 mcL	50 mcL
Retention times			
Palonosetron	9.4 minutes	4.2 minutes	8.0 minutes
Glycopyrrolate	14.5 minutes	5.5 minutes	Not detected
Neostigmine	3.6 minutes	Not detected	5.4 minutes
Decomposition products and other components	Multiple 2.3 to 2.5, 3.1, 3.3 minutes, and 5.7minutes	Multiple 1.4 to 2.3 minutes, 3.0, 4.1, 4.5, 14.7 minutes	2.1, 2.7, 3.4, 4.0, 6.1, 6.9, 8.1, 9.4, 10.5, 11.8, 12.6 minutes

[a]Precision: Mean ± standard deviation (SD) (n = 9) diluted in mobile phase to a nominal concentration of 25 mcg/mL; percent relative standard deviation (RSD) was 0.08%. Standard curve range was 6.25 to 31.25 mcg/mL. The correlation coefficient was >0.9999.
[b]Precision: Mean ± SD (n = 9) diluted in mobile phase to a nominal concentration of 100 mcg/mL; percent RSD was 0.15%. Standard curve range was 25 to 125 mcg/mL. The correlation coefficient was >0.99975.
[c]Precision: Mean ± SD (n = 9) diluted in mobile phase A to a nominal concentration of 250 mcg/mL; percent RSD was 0.06%. Standard curve range was 62.5 to 312.5 mcg/mL. The correlation coefficient was >0.99998.
[d]Supplied by Agilent (Palo Alto, California).
[e]Supplied by Waters Corporation (Milford, Massachusetts).
[f]Supplied by Phenomenex (Torrance California).

05H129; Baxter Healthcare) 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. Reference standards for glycopyrrolate (Lot UL1212; Spectrum Chemical, Gardena, California) and neostigmine methylsulfate (Lot QC0152; Spectrum Chemical) were obtained commercially. The acetonitrile and other mobile phase components were suitable for high-performance liquid chromatographic (HPLC) analysis. The water used was also HPLC 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.[16] To simulate this inline mixing, duplicate samples were prepared by mixing 7.5-mL samples of undiluted palonosetron HCl 50 mcg/mL with 7.5-mL samples of undiluted glycopyrrolate 0.2 mg/mL and with neostigmine methylsulfate 0.5 mg/mL, individually, in colorless 15-mL borosilicate glass screw-cap culture

TABLE 2. Stability of Palonosetron Hydrochloride and Glycopyrrolate During Simulated Y-Site Administration.

	Percentage of Initial Concentration Remaining[a]			
Time	*Palonosetron Hydrochloride*[b]		*Glycopyrrolate*[c]	
(Hours)	*#1*	*#2*	*#1*	*#2*
1	99.79 ± 0.01	99.69 ± 0.04	99.83 ± 0	100.00 ± 0.11
4	99.73 ± 0.05	99.49 ± 0.09	99.69 ± 0.21	99.90 ± 0.28

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 26.94 and 26.06 mcg/mL.
[c]Initial concentrations of the duplicate samples were 97.8 and 101.3 mcg/mL.

TABLE 3. Stability of Palonosetron Hydrochloride and Neostigmine Methylsulfate During Simulated Y-Site Administration.

	Percentage of Initial Concentration Remaining[a]			
Time	*Palonosetron Hydrochloride*[b]		*Neostigmine Methylsulfate*[c]	
(Hours)	*#1*	*#2*	*#1*	*#2*
1	99.45 ± 0.26	99.57 ± 0.22	100.66 ± 0.23	99.21 ± 0.23
4	98.56 ± 0.14	100.12 ± 0.18	99.74 ± 0.23	98.69 ± 0.23

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 25.92 and 24.78 mcg/mL.
[c]Initial concentrations of the duplicate samples were 0.254 and 0.255 mg/mL.

tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described elsewhere.[17] The individual drug admixtures were filtered through appropriate 0.22-mcm 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 by a color-correcting turbidimeter (Model 2100AN, Hach Company, Loveland, Colorado). Triplicate determinations were made on each of the samples. In addition, a light obscuration particle sizer/counter (Model 9703; Hiac-Royco, Division of Pacific Scientific Company, Grants Pass, Oregon) was used to quantify particles in the samples in the 2.04-mcm to 112-mcm 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 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 in each admixture were determined 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 method for glycopyrrolate was adapted from a previously published method.[21] The analytical method for neostigmine was developed in our laboratory. 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 and a Hewlett-Packard Series 1100 (Agilent Technologies, Palo Alto, California) were used for analysis of palonosetron HCl and the other drugs. Each high-performance liquid chromatograph 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 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, glycopyrrolate, and neostigmine methylsulfate were defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial

concentration. Drug stability was defined as a concentration of not less than 90% of the initial drug concentration remaining in the admixtures.

RESULTS AND DISCUSSION

All of the samples of palonosetron HCl admixtures with glycopyrrolate and neostigmine methylsulfate were initially clear and colorless in normal fluorescent room light and when viewed with a Tyndall beam. The samples were essentially without haze, having measured turbidities of less than 0.12 NTU. Changes in turbidity for the samples were minor throughout the study, generally being less than 0.01 NTU. Measured particulates of 10 mcm 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 palonosetron HCl occurred in any of the drug admixtures over 4 hours. Similarly, little or no loss of glycopyrrolate and neostigmine methylsulfate occurred in 4 hours. Therefore, palonosetron HCl is compatible with and stable in admixtures with glycopyrrolate and neostigmine methylsulfate at the concentrations tested during simultaneous or sequential Y-site administration.

CONCLUSION

Palonosetron HCl is physically and chemically stable when mixed with glycopyrrolate and with neostigmine methylsulfate during simulated Y-site administration.

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