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Compatibility and Stability of Palonosetron Hydrochloride with Four Neuromuscular Blocking Agents During Simulated Y-Site Administration

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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 any of the neuromuscular blocking drugs cisatracurium besylate 0.5 mg/mL, rocuronium bromide 1 mg/mL, succinylcholine chloride 2 mg/mL, and vecuronium bromide 1 mg/mL during simulated Y-site administration. Triplicate samples of palonosetron hydrochloride with each of the neuromuscular blocking drugs were tested. Samples were stored and evaluated for up to 4 hours at room temperature. Physical stability was assessed by turbidimetric and particulate measurements and visual inspection. Chemical stability was assessed by 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 study. The drug concentration was unchanged in all of the samples tested. Palonosetron hydrochloride is physically and chemically stable with cisatracurium besylate, rocuronium bromide, succinylcholine chloride, or vecuronium bromide at the concentrations tested during simulated Y-site administration over 4 hours at ambient room temperature.

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 is currently being evaluated for use in postoperative nausea and vomiting.[1-4] Palonosetron HCl injection has been evaluated for compatibility with a number of chemotherapy and supportive care drugs.[5-16] However, palonosetron HCl may be administered with many other drugs by simultaneous or sequential Y-site administration, including neuromuscular blocking agents.

The purpose of this study was to evaluate the physical and chemical stability of undiluted palonosetron HCl 50 mcg/mL when mixed with cisatracurium besylate 0.5 mg/mL, rocuronium bromide 1 mg/mL, succinylcholine chloride 2 mg/mL, or vecuronium bromide 1 mg/mL diluted in dextrose 5% during simulated Y-site administration.

METHODS AND MATERIALS
Materials
Palonosetron HCl injection (Lot HPA 109; MGI PHARMA, Inc., Bloomington, Minnesota) was supplied by the manufacturer. Cisatracurium besylate (Lot 211953A; Abbott Laboratories, North Chicago, Illinois), rocuronium bromide (Lot 900116; Baxter Pharmaceutical, Deerfield, Illinois), succinylcholine chloride (Lot 124288; Sandoz Pharmaceuticals, Princeton, New Jersey), and vecuronium bromide (Lot 870569Z; Bedford Laboratories, Bedford, Ohio) injections were obtained commercially. The infusion solution 5% dextrose injection (Lot C647339; Baxter Healthcare, Deerfield, Illinois) in polyvinylchloride bags also was 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 succinylcholine (Lot UV0321; Spectrum Chemical, Gardena, California) and vecuronium (Lot FOC367; United States Pharmacopeia, Rockville, Maryland) were obtained commercially. Cisatracurium and rocuronium reference standards were commercially unavailable at the time this study was conducted, and therefore, the drug formulations served as reference materials for drug concentration comparison purposes. The acetonitrile and other mobile phase components used were suitable for high-performance liquid chromatographic (HPLC) analysis. The water used was 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.[17]

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 cisatracurium besylate 0.5 mg/mL, rocuronium bromide 1 mg/mL, succinylcholine chloride 2 mg/mL, or vecuronium bromide 1 mg/mL in colorless 15-mL borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described elsewhere.[18] The individual drug solutions were filtered through appropriate 0.22-mcm filters (Millex-GS, Millipore Corporation, Bedford, Massachusetts) into the 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.[18-20] The sample tubes had been triple-washed previously 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 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. 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.

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 summarized in Table 1. The palonosetron HCl analytical method was provided by the drug manufacturer.[21] The other analytical methods were adapted from a previously published method[22] or were 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 (both supplied by Agilent Technologies, Palo Alto, California) were used for analysis of palonosetron HCl and the neuromuscular blockers. 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. The sample solutions were mixed with 1 N hydrochloric acid, 1 N sodium hydroxide, or 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 and the neuromuscular blocking agents 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 admixtures.

RESULTS AND DISCUSSION

All of the samples of palonosetron HCl mixed with a neuromuscular blocking agent 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, 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 Table 2. No loss of concentration of palonosetron HCl occurred in any of the drug admixtures over 4 hours. Similarly, no loss of the neuromuscular blocking agents occurred in 4 hours. Therefore, palonosetron HCl is compatible with and stable in the presence of any of the four neuromuscular blocking agents at the concentrations tested during simultaneous or sequential Y-site administration.

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.[5-16] None of the previous studies have found any loss of palonosetron HCl during the testing. In this series of tests of simulated Y-site administration with four neuromuscular blocking agents, palonosetron HCl once again demonstrated stability. Most of the drugs tested in the published studies were stable and compatible in the presence of palonosetron HCl. When palonosetron was mixed with methylprednisolone sodium succinate, however, free methylprednisolone precipitated, most likely because of the acidic pH (4.5 to 5.5)[1] of the palonosetron HCl injection. While all of the neuromuscular blocking agents in the present study were stable and compatible in a palonosetron admixture, it is useful to keep in mind that drugs that demonstrate such pH-dependent incompatibility 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 cisatracurium besylate, rocuronium bromide, succinylcholine chloride, or vecuronium bromide during simulated Y-site administration.

TABLE 1. High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron and Neuromuscular Blockers.

	Palonosetron[a]	Cisatracurium[b]	Rocuronium[c]
Mobile phase	720 mL Water 280 mL Acetonitrile 0.67 mL Trifluoroacetic acid	20 g Ammonium formate 600 mL Water 200 mL Methanol 200 mL Acetonitrile 10 mL Formic acid	Mobile phase A 95% 25 mM monobasic sodium phosphate, 0.1 g heptanesulfonic acid sodium, phosphoric acid to pH 2.5 5% Methanol Mobile phase B 5% 25 mM monobasic sodium sodium phosphate, 0.1 g heptanesulfonic acid, phosphoric acid to pH 2.5 95% Methanol Time (minute) / % Mobile phase B 0 / 0 7.99 / 0 8.0 / 100 13.0 / 100 13.01 / 0
Column	Zorbax SB-C8[d] (250 × 4.6 mm, 5 mcm)	Phenomenex Jupiter-C18[e] (250 × 4.6 mm, 5 mcm)	Zorbax-C8[d] (250 × 4.6 mm, 5 mcm)
Flow rate	1.0 mL/minute	1.5 mL/minute	1.0 mL/minute
Detection	254 nm	280 nm	207 nm
Sample Injection volume	50 mcL	20 mcL	10 mcL
Retention times			
Palonosetron	9.3 minutes	5.0 minutes	12.0 minutes
Cisatracurium	2.8, 7.0, 7.5, 12.1 minutes[f]	8.0 minutes	Not detected
Rocuronium	Not detected	Not detected	2.8 minutes
Succinylcholine	4.8 minutes	Not detected	Not detected
Vecuronium	2.2 minutes	Not detected	Not detected
Decomposition products and other components	Multiple 2.3 to 2.5, 3.1, and 3.3 minutes	Multiple 2.4 to 2.9, 3.3, 3.9 minutes	4.8, 11.8 minutes

[a]Precision: Mean ± standard deviation (n = 9) diluted in mobile phase to a nominal concentration of 25 mcg/mL; percent relative standard deviation was 0.08%. Standard curve range was 6.25 to 31.25 mcg/mL. The correlation coefficient was >0.9999.
[b]Precision: Mean ± standard deviation (n = 9) diluted in mobile phase to a nominal concentration of 250 mcg/mL; percent relative standard deviation was 0.17%. Standard curve range was 62.4 to 275.2 mcg/mL. The correlation coefficient was >0.9999.
[c]Precision: Mean ± standard deviation (n = 9) diluted in mobile phase to a nominal concentration of 500 mcg/mL; percent relative standard deviation was 0.10%. Standard curve range was 125 to 625 mcg/mL. The correlation coefficient was >0.9999.
[d]Supplied by Agilent (Palo Alto, California).
[e]Supplied by Phenomenex (Torrance, California).
[f]Peaks for cisatracurium and other components of the commercial formulation

TABLE 1 (CONTINUED). High-Performance Liquid Chromatographic Methods Used for Palonosetron and Neuromuscular Blockers.

	Succinylcholine[g]	Vecuronium[h]
	Mobile phase A 890 mL Water 9 mL 1 N Sulfuric acid 3.47 Pentanesulfonic acid sodium salt 2.61 g Sodium chloride 100 mL Methanol Mobile phase B 90% Methanol Time (minute) / % Mobile phase B 0 / 0 8.00 / 0 8.01 / 100 13.0 / 100 13.01 / 0	Mobile phase A 50 mM Monobasic sodium phosphate 0.1 g Heptanesulfonic acid sodium salt Phosphoric acid to pH 2.5 Mobile phase B 5% Mobile phase A 95% Methanol Time (minute) / % Mobile phase B 0 / 0 5.00 / 0 7.00 / 100 10.00 / 100 10.01 / 0
Column	Phenomenex Gemini-C18[e] (150 × 4.6 mm, 5 mcm)	Zorbax-C8[d] (250 × 4.6 mm, 5 mcm)
Flow rate	1.5 mL/minute	1.0 mL/minute
Detection	207 nm	210 nm
Sample Injection volume	75 mcL	50 mcL
Retention times		
Palonosetron	10.1 minutes	10.6 minutes
Cisatracurium	Not detected	Not detected
Rocuronium	Not detected	Not detected
Succinylcholine	4.0 minutes	Not detected
Vecuronium	Not detected	2.8 minutes
Decomposition products and other components	Multiple 1.3 to 1.9, 3.2, 6.5, multiple 10.3 to 11.6 minutes	6.9, multiple 9.5 to 9.9 minutes

[g]Precision: Mean ± standard deviation (n = 9) diluted in mobile phase to a nominal concentration of 1000 mcg/mL; percent relative standard deviation was 0.46%. Standard curve range was 200 to 1250 mcg/mL. The correlation coefficient was >0.9999.
[h]Precision: Mean ± standard deviation (n = 9) diluted in mobile phase to a nominal concentration of 500 mcg/mL; percent relative standard deviation was 0.05%. Standard curve range was 25 to 125 mcg/mL. The correlation coefficient was >0.9999.

Table 2. Stability of Palonosetron Hydrochloride with Various Drugs During Simulated Y-Site Administration.

	Percentage of Initial Concentration Remaining[a]			
Time (Hours)	*#1*	*#2*	*#1*	*#2*
	Palonosetron Hydrochloride[b]		*Cisatracurium Besylate*[c]	
1	99.25 ± 0.40	100.07 ± 0.00	99.62 ± 0.00	99.36 ± 0.22
4	99.16 ± 0.13	100.20 ± 0.15	99.12 ± 0.21	99.74 ± 0.22
	Palonosetron Hydrochloride[d]		*Rocuronium Bromide*[e]	
1	99.81 ± 0.19	100.01 ± 0.17	100.87 ± 0.20	99.73 ± 0.12
4	100.29 ± 0.08	100.00 ± 0.10	101.13 ± 0.31	99.46 ± 0.12
	Palonosetron Hydrochloride[f]		*Succinylcholine Chloride*[g]	
1	100.09 ± 0.08	100.01 ± 0.53	99.59 ± 0.33	100.07 ± 0.36
4	999.6 ± 0.09	99.69 ± 0.39	99.34 ± 0.63	100.11 ± 0.24
	Palonosetron Hydrochloride[h]		*Vecuronium Bromide*[i]	
1	99.47 ± 0.10	99.67 ± 0.06	100.33 ± 0.12	99.87 ± 0.23
4	99.73 ± 0.12	99.27 ± 0.20	101.14 ± 0.12	100.53 ± 0.00

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 25.49 and 25.41 mcg/mL.
[c]Initial concentrations of the duplicate samples were 0.264 and 0.261 mg/mL.
[d]Initial concentrations of the duplicate samples were 25.19 and 25.37 mcg/mL.
[e]Initial concentrations of the duplicate samples were 0.500 and 0.498 mg/mL.
[f]Initial concentrations of the duplicate samples were 26.53 and 25.78 mcg/mL.
[g]Initial concentrations of the duplicate samples were 1051.83 and 1036.77 mg/mL.
[h]Initial concentrations of the duplicate samples were 25.72 and 25.60 mcg/mL.
[i]Initial concentrations of the duplicate samples were 0.498 and 0.504 mg/mL.

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