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Palonosetron Hydrochloride Compatibility and Stability with Three β-Lactam Antibiotics During Simulated Y-Site Administration

Michel Ben, MS
Analytical Research Laboratories
Oklahoma City, Oklahoma

Craig Trusley, PharmD, MS
Ernest Mario School of Pharmacy
Rutgers, The State University of New Jersey
Piscataway, New Jersey

Thomas C. Kupiec, PhD
Analytical Research Laboratories
Oklahoma City, Oklahoma

Lawrence A. Trissel, BS, RPh, FASHP
TriPharma Research
Cashiers, North Carolina

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Abstract

Palonosetron hydrochloride is a relatively long-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 with the β-lactam antibiotics cefazolin sodium 20 mg/mL, cefotetan disodium 20 mg/mL, and the combination ampicillin sodium–sulbactam sodium 20 mg/mL and 10 mg/mL, respectively, during simulated Y-site administration. The effects of each of the antibiotics on palonosetron hydrochloride in these admixtures were tested in triplicate. 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 in admixtures with cefazolin sodium, cefotetan disodium, and the combination ampicillin sodium–sulbactam sodium 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 relatively long-acting selective 5-HT3 receptor antagonist that has been approved for the prevention of chemotherapy-induced nausea and vomiting[1-4] and has recently completed phase III trials for the prevention of postoperative nausea and vomiting. Palonosetron HCl injection has been evaluated for compatibility with a number of chemotherapy and supportive care drugs, and it may be administered with many other drugs by simultaneous or sequential Y-site administration, including β-lactam antibiotics.[5-19]

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 the combination ampicillin sodium–sulbactam sodium 20 mg/mL and 10 mg/mL, respectively; with cefotetan disodium 20 mg/mL diluted in 0.9% sodium chloride; or with cefazolin sodium 20 mg/mL diluted in 5% dextrose.

Methods

Materials

Palonosetron HCl injection (Lot HPA 109; MGI PHARMA, Inc., Bloomington, Minnesota) was supplied by the manufacturer. Ampicillin sodium–sulbactam sodium (Lot R494A; Roerig, a division of Pfizer Laboratories, New York, New York), cefazolin sodium (Lot 900116; Watson Pharmaceuticals, Morristown, New Jersey), and cefotetan disodium (Lot 013C04; AstraZeneca, Wilmington, Delaware) injections were obtained commercially. The infusion solutions, 0.9% Sodium Chloride Injection, USP (Lot P170449; Baxter Healthcare, Deerfield, Illinois), and 5% Dextrose Injection, USP (Lot C647339; Baxter Healthcare), in polyvinylchloride bags, also 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 ampicillin (Lot 056K0603; Sigma-Aldrich, St. Louis, Missouri), sulbactam (Lot HOC396; United States Pharmacopeia, Inc., Rockville, Maryland), cefazolin sodium (Lot VA1007; Spectrum Chemical, Gardena, California), and cefotetan disodium (Lot IDE277; United States Pharmacopeia, Inc.,) also 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.[20] 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 ampicillin sodium–sulbactam sodium 20 mg/mL and 10 mg/mL, respectively, in 0.9% sodium chloride; cefotetan disodium 20 mg/mL in 0.9% sodium chloride; or cefazolin sodium 20 mg/mL in 5% dextrose; this mixing was done in colorless 15-mL borosilicate glass screw-cap culture tubes (Kimble, Division of Owens-Illinois, Toledo, Ohio) with polypropylene caps (Kimble) as described elsewhere.[21] The individual drug admixtures were filtered through appropriate 0.22-mcm filters (Millex-GS, Millipore Corporation, Bedford, Massachusetts) into the culture tubes. All manipulations were carried out in a Class 100 biological safety cabinet. The samples were kept under ambient laboratory conditions, including normal laboratory fluorescent light, throughout the test period.

Physical Stability

The physical stability of the admixtures was assessed by visual examination and by measuring turbidity and particle size and content.[21-23] 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 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. 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 by stability-indicating HPLC assay methods. The details of the analytical methods used in this study

Table 1. High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron Hydrochloride and Ampicillin–Sulbactam.

	Palonosetron[a]	*Ampicillin*[b]*–Sulbactam*[c]
Mobile phase	720 mL water 280 mL acetonitrile 0.67 mL trifluoroacetic acid	3 g sodium phosphate monobasic 400 mL water 85 mL methanol 25 mL acetonitrile
Diluent	Mobile phase	0.138 g sodium phosphate monobasic 0.2 mL glacial acetic acid 1000 mL water
Column	Zorbax SB-C8[d] (250 × 4.6 mm, 5 mcm)	Phenomenex Gemini-C18[e] (150 × 4.6 mm, 5 mcm)
Flow rate	1.0 mL/min	1.0 mL/min
Detection	254 nm	225 nm
Sample injection volume	50 mcL	10 mcL
Retention times		
Palonosetron Hydrochloride	9.3 min	2.6 min
Ampicillin	3.9 min	5.3 min
Sulbactam	4.9 min	3.1 min
Decomposition products	Multiple 2.3 to 2.5, 3.1, and 3.3 min	2.1, 2.5, 3.9, and 17.4 min

[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]Ampicillin precision: Mean ± SD (n = 9) diluted to a nominal concentration of 500 mcg/mL; percent RSD was 0.22%. Standard curve range was 125 to 625 mcg/mL. The correlation coefficient was >0.9999.
[c]Sulbactam precision: Mean ± SD (n = 9) diluted to a nominal concentration of 250 mcg/mL; percent RSD was 0.19%. Standard curve range was 62.5 to 312.5 mcg/mL. The correlation coefficient was >0.9997.
[d]Supplied by Agilent (Palo Alto, California).
[e]Supplied by Phenomenex (Torrance, California).

Table 2. High-Performance Liquid Chromatographic Analytical Methods Used for Cefazolin and Cefotetan.

	Cefazolin[a]	*Cefotetan*[b]
Mobile phase	0.77 g sodium phosphate dibasic 1.1 g citric acid 850 mL water 150 mL acetonitrile	90% 15 mM potassium phosphate monobasic 10% acetonitrile
Diluent	Purified water	5% acetonitrile 5% methanol 90% mobile phase
Column	Phenomenex Gemini-C18[c] (150 × 4.6 mm, 5 mcm)	Phenomenex Gemini-C18[c] (150 × 4.6 mm, 5 mcm)
Flow rate	2.0 mL/min	2.0 mL/min
Detection	254 nm	254 nm
Sample injection volume	10 mcL	20 mcL
Retention times		
Palonosetron Hydrochloride	16.9 min	Not detected
Ampicillin	Not detected	Not detected
Sulbactam	Not detected	Not detected
Cefazolin	3.1 min	Not detected
Cefotetan	Not detected	3.3 min
Decomposition products	Multiple 1.0 to 2.4, 4.5, 4.8 min	Multiple 0.9 to 2.1 min

[a]Precision: Mean ± standard deviation (SD) (n = 9) diluted to a nominal concentration of 400 mcg/mL; the percent relative standard deviation (RSD) was 0.09%. Standard curve range was 100 to 500 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; the percent RSD was 0.48%. Standard curve range was 25 to 125 mcg/mL. The correlation coefficient was >0.9997.
[c]Supplied by Phenomenex (Torrance, California).

are summarized in Tables 1 and 2. The palonosetron HCl analytical method was provided by the drug manufacturer.[24] The other analytical methods 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 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. The sample solutions were mixed with 1 N hydrochloric acid, 1 N sodium hydroxide, or 3% hydrogen peroxide and subjected to heating. Loss of 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 antibiotics were defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration. 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 with the antibiotics 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 0.14 NTU. Changes in turbidity for the samples were minor throughout the study, being less than 0.05 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 3 through 5. No loss of concentration of palonosetron HCl occurred in any of the drug admixtures over 4 hours. Similarly, no loss of the antibiotics occurred in 4 hours. Therefore, palonosetron HCl is compatible with and stable in the presence of the three antibiotics at the concentrations tested during simulta-

Table 3. Stability of Palonosetron Hydrochloride, Ampicillin Sodium, and Sulbactam Sodium in an Admixture During Simulated Y-site Administration.

	Percentage of Initial Concentration Remaining[a]					
Time (Hours)	*Palonosetron Hydrochloride*[b]		*Ampicillin Sodium*[c]		*Sulbactam Sodium*[d]	
	#1	*#2*	*#1*	*#2*	*#1*	*#2*
1	100.52 ± 0.10	100.63 ± 0.06	99.48 ± 0.00	99.99 ± 0.09	99.65 ± 0.06	100.07 ± 0.10
4	99.88 ± 0.02	99.55 ± 0.07	99.45 ± 0.03	99.96 ± 0.08	99.77 ± 0.10	100.17 ± 0.11

[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 20.00 and 19.88 mg/mL.
[d]Initial concentrations of the duplicate samples were 10.20 and 10.20 mg/mL.

Table 4. Stability of Palonosetron Hydrochloride and Cefazolin Sodium in an Admixture During Simulated Y-site Administration.

	Percentage of Initial Concentration Remaining[a]			
Time (Hours)	*Palonosetron Hydrochloride*[b]		*Cefazolin Sodium*[c]	
	#1	*#2*	*#1*	*#2*
1	100.52 ± 0.34	99.99 ± 0.15	100.27 ± 0.06	99.79 ± 0.06
4	100.42 ± 0.13	100.24 ± 0.15	99.90 ± 0.11	99.90 ± 0.11

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 26.40 and 27.47 mcg/mL.
[c]Initial concentrations of the duplicate samples were 10.06 and 9.60 mg/mL.

Table 5. Stability of Palonosetron Hydrochloride and Cefotetan Disodium in an Admixture During Simulated Y-site Administration.

	Percentage of Initial Concentration Remaining[a]			
Time (Hours)	*Palonosetron Hydrochloride*[b]		*Cefotetan Disodium*[c]	
	#1	*#2*	*#1*	*#2*
1	100.27 ± 0.00	100.31 ± 0.02	99.59 ± 0.10	99.58 ± 0.52
4	100.77 ± 0.08	100.24 ± 0.04	99.91 ± 0.05	99.76 ± 0.21

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 26.71 and 27.30 mcg/mL.
[c]Initial concentrations of the duplicate samples were 10.53 and 10.23 mg/mL.

neous 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.[5-19] None of the previous studies have found any loss of palonosetron HCl during the testing interval. In this series of tests of simulated Y-site administration with three antibiotics, palonosetron HCl once again demonstrated stability. Most of the drugs tested in the published studies were stable in the presence of and compatible with palonosetron HCl. When palonosetron was mixed with methylprednisolone sodium succinate, however, free methylprednisolone was precipitated,[12] most likely because of the acidic pH (4.5 to 5.5)[1] of the palonosetron HCl injection.While all of the β-lactam antibiotics in the present study were stable and compatible in admixtures with palonosetron HCl, it is useful to keep in mind that drugs that demonstrate such pH-dependent incompatibilities 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

ampicillin sodium – sulbactam sodium, cefazolin sodium, or cefotetan disodium during simulated Y-site administration.

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Address correspondence to Lawrence A. Trissel, BS, RPh, FASHP, TriPharma Research, P.O. Box 265, Cashiers, NC 28717-0265.