Compatibility and Stability of Palonosetron Hydrochloride and Propofol During Simulated Y-Site Administration

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ACKNOWLEDGMENT

This study was supported by a grant from MGI PHARMA, Inc., Bloomington, Minnesota.

ABSTRACT

Palonosetron hydrochloride is a longer-acting, selective 5-HT3 receptor antagonist that has been approved for prevention of chemotherapy-induced nausea and vomiting and is being evaluated for 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 undiluted propofol 1% during simulated Y-site administration. Duplicate samples of this mixture were tested. Samples were stored and evaluated for up to 4 hours at room temperature. Physical stability was assessed by visual inspection. Chemical stability was assessed by high-performance liquid chromatographic analysis. All of the admixtures were opaque white when viewed in normal fluorescent room light and when viewed with a Tyndall beam. After centrifugation, no evidence of precipitation was found. The drug concentrations were essentially unchanged in all of the samples throughout the study. Palonosetron hydrochloride is physically and chemically stable when mixed with propofol as undiluted injections during simulated Y-site administration over 4 hours at ambient room temperature.

INTRODUCTION

Palonosetron hydrochloride (HCl) injection (Aloxi; MGI PHARMA, Inc., Bloomington, Minnesota) is a longer-acting, selective 5-HT3 receptor antagonist that has been approved for prevention of chemotherapy-induced nausea and vomiting;[1-4] phase 3 trials of the drug for 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.[5-21] However, palonosetron HCl may be administered with many additional drugs by simultaneous or sequential Y-site administration, including the lipid emulsion anesthetic propofol.

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 propofol 1%.

MATERIALS AND METHODS

Materials

Palonosetron HCl injection (Lot HPA109; MGI PHARMA, Inc.) was supplied by the manufacturer. Propofol 1% (10 mg/mL) injection (Lot 958412; Bedford Laboratories, Bedford, Ohio) 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. Because a reference standard for propofol was not available commercially, the commercial injection was used as a reference material. The acetonitrile, methanol, and other mobile phase components 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.[22] To simulate this in-line mixing, duplicate samples were prepared by mixing 5-mL samples of undiluted palonosetron HCl 50 mcg/mL with 5-mL samples of propofol 1% in colorless 15-mL polypropylene conical plastic centrifuge tubes (Becton Dickinson Labware, Franklin Lakes, New Jersey) with polypropylene caps as described elsewhere.[23,24] Palonosetron HCl was 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

Propofol 1% injection is an opaque white emulsion that requires an alternative to the approach typically used for the evaluation of solutions.[23,24] Duplicate test combinations

for propofol with palonosetron HCl were prepared for evaluation at each time point (immediately after mixing and after 1 and 4 hours) for a total of three pairs of test tubes, reversing the order of drug addition between the sample test tubes within pairs. The samples were held at room temperature and exposed to normal laboratory fluorescent light while awaiting evaluation.

The sample tubes were visually inspected at each time point. A pair of duplicate samples was then subjected to centrifugation at 12,000 RPM for 15 to 20 minutes, which has been demonstrated previously to result in maximum phase separation.[23,24] Centrifugation causes the fat component to separate and rise to the top. If the emulsion is intact, a white plug of fat will separate and rise to the top of the sample liquid. If the emulsion has broken, a layer of free oil will form on top of the sample. Centrifugation also will cause any precipitation or particulates that form to deposit on the bottom of the centrifuge tube.[23-24]

After centrifugation, the samples were visually inspected again in normal fluorescent room light with the unaided eye and by using a high-intensity monodirectional light (Tyndall beam) (Dolan-Jenner Industries, Woburn, Massachusetts) for particulates that may have formed. Because propofol is an opaque liquid and results in turbid samples, measuring the turbidity of the propofol samples, as would be done with solutions,[25-27] is not of value and was not performed. Similarly, particle counting and sizing is problematic with propofol due to its dense turbidity and was also not performed. This is consistent with previous evaluations of the compatibility of propofol or other lipid emulsion products.[23,24]

High-Performance Liquid Chromatographic Analysis

The drug concentrations in each admixture 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.[28] The analytical method for propofol was adapted from the method of Bhatt-Mehta et al.[29] The analytical 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 propofol. 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 there was no interference of the degradation product peaks or other drug peaks with the peak of the intact subject drug.

The initial concentrations of palonosetron HCl and the propofol 1% injection 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.

Table 1. High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron Hydrochloride and Propofol.

	Palonosetron Hydrochloride[a]	Propofol[b]
Mobile phase	720 mL Water 280 mL Acetonitrile 0.67 mL Trifluoroacetic acid	350 mL Water 550 mL Acetonitrile 100 mL Methanol
Diluent	Mobile phase	Mobile phase
Column	Zorbax SB-C8[c] (250 × 4.6 mm, 5 mcm)	Phenomenex Jupiter-C18[d] (250 × 4.6 mm, 5 mcm)
Flow rate	1.0 mL/min	2.0 mL/min
Detection	254 nm	272 nm
Sample injection volume	50 mcL	20 mcL
Retention times Palonosetron hydrochloride	9.3 min	Not detected
Propofol	6.9 min	4.5 min
Decomposition products	Multiple 2.3 to 2.5, 3.1, and 3.3 min	0.9, 1.8 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]Precision: Mean ± SD (n = 9) diluted in mobile phase to a nominal concentration of 100 mcg/mL; percent RSD was 0.75%. Standard curve range was 25 to 125 mcg/mL. The correlation coefficient was >0.9995.
[c]Supplied by Agilent Technologies, Palo Alto, California.
[d]Supplied by Phenomenex, Torrance, California.

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

	Percentage of Initial Concentration Remaining[a]			
Time	*Palonosetron Hydrochloride*[b]		*Propofol*[c]	
(Hours)	*#1*	*#2*	*#1*	*#2*
1	99.03 ± 0.42	100.24 ± 1.59	100.14 ± 0.21	100.10 ± 0.51
4	100.17 ± 0.71	98.80 ± 0.77	101.43 ± 0.05	100.43 ± 0.02

[a]Mean ± standard deviation for triplicate determinations of duplicate samples.
[b]Initial concentrations of the duplicate samples were 24.11 and 23.83 mcg/mL.
[c]Initial concentrations of the duplicate samples were 5.03 and 5.07 mg/mL.

RESULTS AND DISCUSSION

All of the admixtures of palonosetron HCl with the propofol 1% injection were

initially densely opaque white liquids in normal fluorescent room light. The visual appearance of the samples did not change within the 4-hour observation period. After centrifugation, a uniform white fat layer formed a plug on the surface of the sample, leaving a hazy liquid aqueous phase at the bottom, indicating that the propofol emulsion had remained intact. No evidence of particulate formation was observed in normal fluorescent room light or when using the Tyndall beam.

The results of the HPLC analysis are shown in Table 2. No loss of palonosetron HCl occurred with propofol over 4 hours. Similarly, little or no loss of propofol occurred in 4 hours. Therefore, undiluted palonosetron HCl is compatible and stable with propofol 1% injection during simultaneous or sequential Y-site administration.

Previous stability and compatibility tests[5-21] during simulated Y-site administration with a variety of parenteral medications have demonstrated that palonosetron HCl is a very stable drug. None of the previous studies have found any loss of palonosetron HCl during testing. Similarly, in this series of tests of simulated Y-site administration with propofol, palonosetron HCl once again demonstrated stability. The previous studies have shown 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)[1] of the palonosetron HCl injection. While propofol was stable and compatible in the present study, 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 propofol 1% injection during simulated Y-site administration.

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