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

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.

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.22,24 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.\textsuperscript{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.\textsuperscript{23-28}

After centrifugation, the samples were visually inspected again in normal fluorescent light while awaiting evaluation. The sample test tubes were visually inspected in normal laboratory fluorescent light and sized by accelerated degradation.\textsuperscript{23,24}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Time (Hours)} & \textbf{Palonosetron Hydrochloride} & \textbf{Propofol} \\
\hline
1 & 99.03 ± 0.42 & 100.17 ± 0.71 \\
4 & 100.24 ± 1.59 & 98.80 ± 0.77 \\
\hline
\end{tabular}
\caption{Stability of Palonosetron Hydrochloride and Propofol During Simulated Y-site Administration.}
\end{table}

\textbf{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.\textsuperscript{24} The analytical method for propofol was adapted from the method of Bhatt-Mehta et al.\textsuperscript{26} The analytical methods were validated in our laboratory to verify their suitability for this testing. Two high-performance liquid chromatographs, 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 multiwell 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). Triplet 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.

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\hline
\end{tabular}
\caption{High-Performance Liquid Chromatographic Analytical Methods Used for Palonosetron Hydrochloride and Propofol.}
\end{table}

\textbf{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 tests3-21 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,22 most likely due to the acidic pH (pH 4.5 to 5.5) 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.

REFERENCES

25. Palonosetron HCl IV Injection 0.05 mg/mL and 0.15 mg/mL end product test procedure. Minneapolis, MN: MGI PHARMA, Inc.; [Undated].

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