Stability of Pantoprazole in Parenteral Nutrition Units

E. Valverde Molina, V. González Muñiz, J. Gómez-Maldonado, and I. Muñoz Castillo

Servicio de Farmacia, Hospital Carlos Haya, Málaga, Spain

Abstract

Introduction: Pantoprazole is a weak base (pka ~ 4) with its stability in aqueous solution dependent on pH. Keeping in mind that the pH of the parenteral nutrition units (PNU) can range between 6.0 and 6.5 and since pantoprazole seems to be the most stable proton pump inhibitor (PPI) for pH acid, we want to assess the possibility of adding it to PNU with the aim of simplifying its administration to patients.
Methods: Using high performance liquid chromatography (HPLC) to measure pantoprazole content in PNU at different time intervals.
Results: The chromatographic determination of pantoprazole concentration reflected a rapid and progressive aging of the sample. After 24 h the quantity of drug detected in the PNU was below 50% of the total added.
Conclusions: In view of these results, we therefore do not suggest this as a suitable vehicle for pantoprazole administration as it could put patients at risk of being under-dosed and therefore exposing them to potential unknown side effects of the different drug degradation products.

Key words: Drug stability. HPLC. Pantoprazole. Parenteral nutrition.

Estabilidad de pantoprazol en unidades para nutrición parenteral.

Introducción: El pantoprazol es una base débil (pka ~ 4) y su estabilidad en solución acuosa es dependiente del pH. Teniendo en cuenta que el pH de las unidades de nutrición parenteral (UNP) puede oscilar entre 6,0 y 6,5, y puesto que pantoprazol parece ser el inhibidor de la bomba de protones más estable a pH ácido, se evaluó la posibilidad de adicionarlo a las UNP con objeto de facilitar su administración a los pacientes.
Métodos: Se determinó por cromatografía líquida de alta resolución (HPLC, del inglés high performance liquid chromatography) la riqueza de pantoprazol en una UNP a diferentes intervalos de tiempo.
Resultados: La determinación cromatográfica de las concentraciones de pantoprazol reflejó un rápido y progresivo envejecimiento de la muestra. Pasadas 24 h la cantidad de fármaco detectado en la UNP es inferior al 50% del total adicionado.
Conclusiones: A la vista de estos resultados se desaconseja este vehículo para la administración de pantoprazol, ya que puede poner en riesgo la seguridad de los pacientes al infradosificar la medicación que requieren y exponerlos a los posibles efectos desconocidos de los diferentes productos de degradación del fármaco.

Palabras clave: Estabilidad fisicoquímica. HPLC. Pantoprazol. Nutrición parenteral.

INTRODUCTION

Pantoprazole, one of the most used proton pump inhibitors, is a weak base (pka ~ 4) with its stability in aqueous solution dependent on pH. Its hydrolysis increases as pH decreases. At room temperature, its degradation half-life varies to a few minutes at pH 1.0-2.0[1] and 220 h to pH 7.8,[2] with optimal stability at pH 9.

All benzimidazoles used as PPI are unstable in acid environments, but previous studies have shown significant differences in the degradation time of different molecules based on the pH levels in which they are found. Pantoprazole is the PPI least sensitive to acid pH.[3] Keeping in mind that the pH of parenteral nutrition units (PNU) can range between 6.0 and 6.5, the possibility of adding pH to the units was evaluated.

Correspondence: E. Valverde Molina.
Servicio de Farmacia. Hospital Carlos Haya.
Camino de Antequera, s/n. 29011 Málaga. España.
E-mail: esteban.valverde.sspa@juntadeandalucia.es

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Pantoprazole is widely used in hospitals. In hospitals, patients with a significant amount of fluid therapy due to the high quantity of intravenous medication they need is frequently seen. The reduction of perfusion volumes for patients who require restricted fluid therapy is very helpful for clinics. A regular way of decreasing fluid volume is by adding drugs to the PNU, and this also decreases injection points.

After reviewing bibliographic information, studies on PPI stability in various solutions were found,[4-6] but no study made reference to PPI stability in PNU.

METHODS

Preparation of the Parenteral Nutrition Unit

Standard type PNU was used (Table 1) and prepared according to registered procedure.

Preparation of the Sample

To prepare the sample, 40 mg vials of sodium pantoprazole in freeze-dried powder for injectable solutions were used (Anagastra®, Altana Pharma AG). Ten mL of the PNU solution was put into each vial and shaken in a vortex; later, 3 L of PNU were added to the bottle by syringe, and a final concentration of 13.3 µg/mL was drawn. The sample time interval was set at 3, 6, 9, 12, 24, and 48 h. PNU were kept at room temperature and protected from the light. The PNU pH was determined before the addition of pantoprazole and at 0, 24, and 48 h after its addition. Samples were prepared aseptically, but their sterility was not evaluated.

Preparation of the Calibration Curve and Internal Standard

An internal standard solution was prepared (IS), with propylparaben (Farmaquímica Sur SL), at a final concentration of 0.2 mg/mL HPLC water (Merck S.A.), and its stability was determined for at least 1 week at room temperature (variation coefficient of 3.47%). An aliquot of IS (20 µg/mL) was injected at each time interval with no changes in the appearance of the peak and no strange peaks.

Table 1. Quantitative Composition of Parenteral Nutrition

Amino acids	84 g
Nitrogen	13.5 g
Glucose	250 g
Sodium	85 mEq
Potassium	60 mEq
Chloride	90 mEq
Acetates	165 mEq
Phosphates	13 mMol
Calcium	15 mEq
Magnesium	15 mEq
Final volume	2355 mL

The standard solution prepared was with a pantoprazole concentration of 160 µg/mL, and the preparation of sodium pantoprazole in commercial freeze-dried powder was dissolved into an injectable solution of 250 mL of PNU. As has occurred with other authors,[5] pure pantoprazole could not be obtained by the manufacturer for use as a reference standard. Therefore, "Anagastra®" the commercial product for injections, was used to prepare the standards. Five calibrators were prepared by diluting the standard solution of pantoprazole with the PNU solution at concentrations of 2, 5, 10, 15, and 30 µg/mL. Both the propylparaben and pantoprazole standard solutions were evaluated daily at the sampling intervals.

Analysis of Samples by Using High Performance Liquid Chromatography

The original method by Dentinger et al[5] was used for pantoprazole determinations by HPLC, with small modifications made by Johnson.[4] Equipment from HPLC Waters Corporation 1525, a binary pump and a VIS-UV W 2487 detector was used. For data acquisition and processing, Breeze (Waters Corporation) software was used. Chromatographic conditions used included the reversed phase Symmetry 300™ C_{18} column 3.3 µm 4.6×150 mm used at room temperature and with a wavelength of 280 nm. The mobile phase consisted of a 40% (v/v) proportion of HPLC grade acetonitrile (Merck SA) in a 50 mM (pH 7) phosphate buffer (Merck S.A. Lot 4871). The phosphate buffer was prepared with HPLC grade water and was filtered by 0.2 µm filter membranes (Millex® GS. Millipore). The mobile phase was degassed using helium, and the flow rate was set at 1 mL/min. The final injection volume was 30 µL, and determinations were carried out in duplicate. For integrating the chromatograms, the retention times for pantoprazole and the IS were set after reevaluating the method at 3.5 and 5.7 min, respectively.

Analysis of Samples

For each analysis, 500 µL of PNU with added pantoprazole were drawn together, and this was placed in a centrifuge tube. Subsequently, 100 µL of IS solution (0.2 mg/mL) and 400 µL of acetonitrile were added. This was shaken for 20 s in a vortex and centrifuged for 10 min at 10 000 rpm and at room temperature. The supernatant was collected in a centrifuge tube, and 100 µL were placed in microvials for later analysis by HPLC.

Data Analysis

Pantoprazole stability was determined through evaluation of the concentration at each time interval.

Table 2. Pantoprazole Concentration Data in the Parenteral Nutrition Unit at Time Intervals of the Trial

Time, h	Pantoprazole Concentration (SD), µg/mL
Theoretical value	13.30
0	12.80 (0.15)
3	11.60 (0.45)
6	10.59 (0.67)
9	9.93 (0.33)
12	9.77 (0.06)
24	5.68 (0.27)
48	2.70 (0.05)

SD indicates standard deviation.

RESULTS

Chromatographic determination of pantoprazole concentrations at different sampling times (Table 2) shows the sample's aging (the decrease of pantoprazole over time). This activity loss is related to the decrease of pantoprazole content. Less than 80% of added pantoprazole could be detected in the PNU after 6 h, and its concentration was reduced to less than 50% at 24 h.

With the aim of seeing if the added drug could destabilize the mixture, pH measurements of PNU were carried out simultaneously with the chromatographic determination of pantoprazole. No significant modifications were detected in the pH evolution of PNU throughout the study, and an average pH of 6.11 (6.16-6.06) was established. However, PNU color changes were observed, with a yellowish color at 12 h which had intensified after 24 h.

DISCUSSION

This study was designed to determine stability, and therefore suitability of pantoprazole inclusion in parenteral nutrition mixtures prepared daily in hospitals. Showing pantoprazole stability in parenteral nutrition mixtures provides medical departments with a new system for administering medication, and therefore, increases available treatment alternatives. This new administration method could provide significant advantages both clinically and for the patients' safety.

In developing the study, a standard PNU without lipids was selected to simplify analysis. Although a limitation can be considered, pantoprazole stability depends on the pH of the mixture. The inclusion of the lipid mixture does not affect, a priori, the pH of the mixture. Consequently, it can be assumed that pantoprazole stability in PNU is similar with and without lipids.

For finding pantoprazole determinations, the HPLC method was selected because of its efficacy, sensitivity, and repeatability. The selection of a sampling schedule for taking measurements was done keeping in mind that approximately 6 h pass for parenteral nutrition preparation to be completed and administered to the patient. Also, considering that parenteral nutrition mixtures perfuse in less than 48 h and usually no more than 24 h, 48 h was established as the upper time limit and 24 h as the critical time for stability.

A yellow coloration was observed in the PNU tested, which in view of data obtained, seems to be related to the appearance of degradation products from pantoprazole. Nevertheless, the Johnson[4] study concludes that the appearance of a yellow tonality in pantoprazole solutions is not related to an unacceptable decrease in the concentration of the molecule. In consideration of these apparently contradictory results, it would be necessary to design new studies which correlate the variation of pantoprazole solution tonality with its percentage of degradation.

Pantoprazole is one of the most stable PPI in terms of pH change. However, it has a very fast activity loss in PNU; its concentration falls below the tolerable lower limits within a few hours after its addition; and its concentrations reduce to less than 50% at 24 h. Based on these results, this vehicle for pantoprazole administration is not recommended, as it does not provide any benefit for patients, but could put them at risk of underdosing their needed medication, and could expose them to possible unknown effects from the drug's various degradation products.

The results obtained in this study encourage pharmacy departments to communicate the risk of adding unstudied drugs to parenteral solutions and also promote research on the stability of other compounds with the end of ensuring correct dosage and minimizing possible dangers of inappropriate drug use.

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