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CLINICAL INVESTIGATION

Stability of dilute indomethacin sodium trihydrate

Eric B. Hoie, PharmD, Jennifer L. DiGiacinto, PharmD, and Warren A. Narducci, PharmD

From the Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska

Objective The purpose of this study was to determine the stability of reconstituted indomethacin sodium trihydrate at concentrations of 200, 100, and 50 μg/mL stored at room temperature in polypropylene syringes.

Background Indomethacin, 0.5 mg/mL, has been shown to be stable for at least 14 days at room temperature when stored in polypropylene syringes. Dilute concentrations of indomethacin would be more suitable for continuous infusions of indomethacin for the treatment of patent ductus arteriosus.

Methods The stability of reconstituted indomethacin sodium trihydrate was determined over 48 hours. Immediately following reconstitution, the pH of the indomethacin solutions were measured and concentrations determined by high performance liquid chromatography (HPLC). Twenty-four and 48 hours following reconstitution, pH and indomethacin concentration were measured again.

Results Indomethacin remained stable over the 48-hour period. There was minimal change in the pH and concentrations.

Conclusions Indomethacin sodium trihydrate at concentrations of 200, 100, and 50 μg/mL is stable at room temperature for at least 48 hours when stored in polypropylene syringes.

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INTRODUCTION

Indomethacin is used to close a patent ductus arteriosus (PDA) in newborn infants. Dosage recommendations range from 0.1 to 0.25 mg/kg as an intravenous bolus or infused intravenously over 1 to 2 hours. Many of the adverse effects associated with indomethacin in premature infants are likely due to vasoconstriction following rapid intravenous administration.[1-4] Rapid administration of indomethacin is known to cause vasoconstriction leading to decreased blood flow to the brain, kidneys, and intestine. It has been demonstrated that continuous infusion of indomethacin over 36 hours did not decrease cerebral blood flow and was equally efficacious to bolus administration for closure of a PDA.[4]

Reconstitution directions in the package insert recommend that indomethacin sodium trihydrate (IST) be reconstituted with preservative-free normal saline or sterile water to a final concentration of 0.5 or 1 mg/mL, and that unused drug be discarded.[5] It has been shown that indomethacin sodium trihydrate at a concentration of 0.5 mg/mL is stable for 12 days at room temperature when stored in glass vials, and over 14 days when stored in syringes at both room temperature and 2-6°C.[6] Concentrations of indomethacin less than 0.5 mg/mL would be more suitable for continuous infusion. There is no stability data available for concentrations of indomethacin less than 0.5 mg/mL. This study determined the stability of indomethacin over 48 hours at concentrations suitable for continuous infusion.

Address correspondence and reprint request to Eric B. Hoie, PharmD, 986045 Nebraska Medical Center, Omaha, Nebraska 68198-6045
e-mail address: ehoie@unmc.edu

METHODS

The high performance liquid chromatography (HPLC) system consisted of a Spectra Physics isocratic pump, ultraviolet (UV) absorbance detector, and system integrator. Assay conditions were similar to those previously used.[7] The mobile phase consisted of acetonitrile and 6 mM phosphoric acid (50:50, v/v) flowing through a Phenomenex Bondoclone 10 C18 column (150 x 3.9 mm) at 2 mL/min. The UV detector was set at 205 nm. IST (Indocin, Merck & Co., West Point, PA, Lot # 1499J, expiration date, May, 2001) was used for both the standard curve and the study concentrations. All other reagents were obtained from Sigma Co. (St. Louis, MO.).

Validation of the HPLC system was determined by testing accuracy, reproducibility, and the ability of the assay to be stability indicating. A standard curve was constructed by diluting freshly reconstituted IST with normal saline to concentrations of 25, 50, 100, 125, 200, and 250 μg/mL. Each concentration was analyzed five times by injecting 50 μL onto the column. The next 2 days, 5 samples from the 200 μg/mL standard were assayed. The 200 μg/mL standard was stored at 20°C over the 48-hour period. Stability-indicating studies were conducted by diluting IST to a concentration of 100 μg/mL in normal saline and adjusting the pH of the solution to 11 with 1N sodium hydroxide. The solution was boiled for 20 minutes, allowed to cool, and the pH was adjusted to 7 with 1N hydrochloric acid. The treated solution was then assayed for indomethacin.

IST stability was determined at concentrations of 50, 100, and 200 μg/mL. IST was reconstituted in preservative-free normal saline to a concentration of 1 mg/mL and further diluted to the study concentrations with preservative-free normal saline. Following dilution, the pH of IST was measured and duplicate aliquots of the samples were placed in 10 mL polypropylene syringes. Triplicate samples from each syringe were assayed immediately (time 0). Twenty-four and 48 hours after the IST was reconstituted, the pH of each concentration was measured and triplicate samples from each syringe were assayed for indomethacin concentration. IST was stored at ambient room temperature and ambient light for the duration of the study.

Table 1. pH of indomethacin sodium trihydrate over 48 hours

	0 Hours	24 Hours	48 Hours
50 μg/mL	6.71	6.64	6.45
100 μg/mL	6.69	6.51	6.30
200 μg/mL	6.60	6.51	6.57

RESULTS

Validation of the assay

Degradation of IST was nearly complete with base and heat treatment (Figure 1). Indomethacin concentrations were negligible with at least 3 degradation products detected. Intra-day variability averaged 1.7% and inter-day variability was 2.5%. The standard curve was linear over the concentrations tested ($r^2 = 0.999$)

Indomethacin stability

Indomethacin remained stable at room temperature for 48 hours maintaining stable pH (Table 1) and retaining at least 95% of initial concentrations (Table 2). There was no evidence of degradation products in any of the chromatograms (Figure 2).

DISCUSSION

Many of the adverse effects associated with indomethacin are related to its ability to cause vasoconstriction. Cowan reported that indo-

Table 2. Indomethacin Sodium Trihydrate Concentrations

	0 Hours	24 Hours	48 Hours
50 μg/mL	50 ± 0.9 μg/mL	50 ± 2.1 μg/mL	49 ± 1.1 μg/mL
100 μg/mL	100 ± 2 μg/mL	95 ± 1.1 μg/mL	97 ± 1.3 μg/mL
200 μg/mL	200 ± 1.8 μg/mL	194 ± 3.2 μg/mL	194 ± 3.9 μg/mL

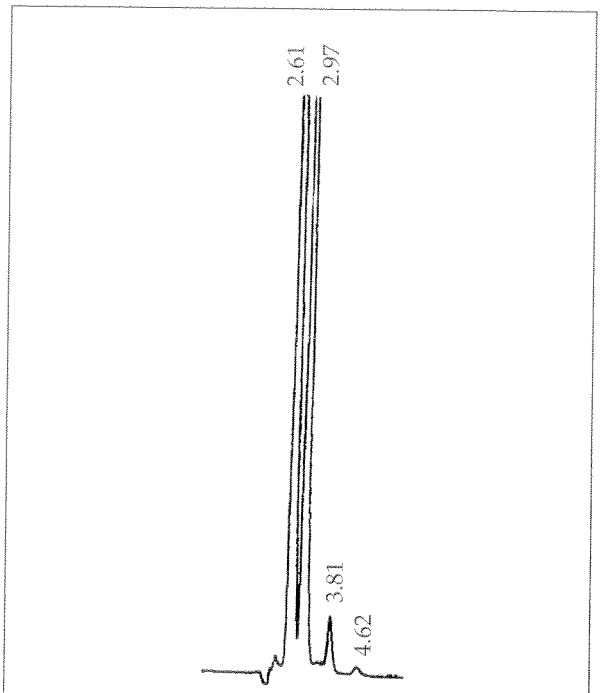

Figure 1. *Chromatogram of IST (100 μg/mL) following alkaline and heat degradation.*

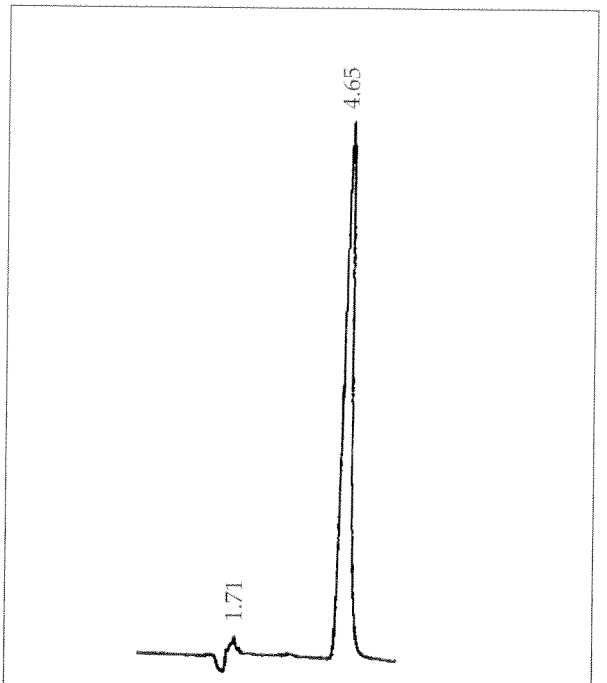

Figure 2. *Chromatogram of IST (50 μg/mL). Peak Indomethacin at 4.65 minutes.*

methacin given over 10 seconds to 4 minutes resulted in severe decreases in cerebral blood flow velocity with the largest effect seen in an infant that received indomethacin over 10 seconds.[1] Grosfeld reported an increased incidence of necrotizing enterocolitis (NEC) in infants with PDA treated with indomethacin compared to infants without PDA that did not receive indomethacin.[2] Van Bel reported that indomethacin administration resulted in a decrease in mesenteric artery blood flow velocity indicating a decrease in bowel perfusion suggesting that indomethacin-induced vasoconstriction increases the risk of NEC in newborn infants.[3] Hammerman found significant decreases in cerebral blood flow velocity in infants receiving indomethacin over 1 minute compared to infants receiving continuous infusions of indomethacin over 36 hours.[4] There was also a significant increase in serum creatinine in the rapid infusion group compared to the group that received continuous infusion. Both groups had similar rates of ductal closure. The concentration of indomethacin used in the study was not provided.

It should be noted that the manufacturer recommends reconstituting IST in preservative-free solutions. Because of the potential for microbiological contamination, we do not recommend long-term storage of reconstituted IST. Proper infection control policies should be adhered to when dealing with extemporaneously compounded preservative-free solutions.

We have demonstrated that indomethacin sodium trihydrate at concentrations of 50, 100, and 200 μg/mL is stable for at least 48 hours in syringes stored at room temperature. These concentrations would be more suitable for continuous infusions.

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