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The Physical Compatibility of Clinically Used Concentrations of Diltiazem Hydrochloride With Heparin Sodium

Sydney R. Dobson, BS[1], Vincent F. Mauro, PharmD[1], Sai H. S. Boddu, PhD[2], and Mariann D. Churchwell, PharmD[1]

Abstract

Background: Acute treatment of atrial fibrillation often requires concomitant intravenous (IV) continuous infusions of unfractionated heparin and diltiazem. Concomitantly infusing these medications through the same IV line minimizes multiple IV sites. Diltiazem and heparin visual compatibility have been previously investigated but with limited drug dwell times and differing drug concentrations leading to inconsistent published results. **Objective:** To investigate the physical compatibility of diltiazem hydrochloride at concentrations of 5 and 1 mg/mL combined with an equal volume of heparin sodium 100 units/mL. **Methods:** Using a 0.22-µm filter, 15 mL of heparin sodium were placed into a polyvinyl chloride infusion bag followed by 15 mL of either diltiazem hydrochloride 5 or 1 mg/mL. Admixtures were prepared in triplicate. Each admixture was investigated for visual precipitation, spectrophotometric absorbance, and pH change at baseline and 1, 5, 8, and 24 hours after mixing. Physical incompatibility was determined by visual observation, increased spectrophotometric absorbance, and demonstrative pH changes. **Results:** Each diltiazem 5 mg/mL admixture exhibited a slight haze and enhanced absorbance readings indicating turbidity while none revealed a demonstrative pH change. None of the diltiazem 1 mg/mL assessments revealed visual precipitation or suggested turbidity. Only one pH reading at 5 hours revealed a demonstrative change from baseline. **Conclusions:** Our findings indicate that infusing diltiazem hydrochloride 5 mg/mL with heparin sodium 100 units/mL in the same IV line cannot be advocated. In contrast, our findings suggest that heparin sodium 100 units/mL infused with diltiazem hydrochloride 1 mg/mL is physically compatible but chemical stability was not assessed.

Keywords

diltiazem, calcium-channel blockers, heparin, admixtures, pharmaceutics, clinical pharmacy, clinical practice, drug administration, compatibility

Background

Intravenous (IV) diltiazem hydrochloride is used for the acute treatment of atrial fibrillation.[1] Diltiazem is frequently given as an IV bolus dose at a concentration of 5 mg/mL followed by an IV continuous infusion at a concentration of 1 mg/mL. Thromboembolism is a complication of atrial fibrillation, which often leads to the concomitant continuous IV infusion of heparin sodium with diltiazem.[1] The simultaneous administration of medications through the same IV line minimizes the number of IV access sites in a patient; therefore, it is of interest to know if diltiazem and heparin are intravenously compatible.

The compatibility of diltiazem and heparin has been previously investigated; however, these trials only utilized visual observation, and their methodology utilized limited admixture dwell time or the use of heparin concentrations uncommonly used in clinical settings.[2,3] Chiu and Schwartz studied diltiazem (1 mg/mL) and heparin (100 units/mL) and observed compatibility, but their investigation was limited to 4 hours.[2] Gayed et al examined diltiazem (5 and 1 mg/mL) with heparin (80, 5000, 10 000, and 20 000 units/mL) immediately after mixing the solutions. Incompatibility was only seen when heparin 20 000 units/mL was mixed with diltiazem 5 mg/mL.[3] This investigation evaluated clinically relevant concentrations of diltiazem hydrochloride and heparin sodium over 24 hours using spectrophotometric and pH analysis in addition to visual observation.

[1]University of Toledo, Toledo, OH, USA
[2]Ajman University, Ajman, United Arab Emirates

Corresponding Author:
Vincent F. Mauro, University of Toledo, 3000 Arlington Avenue, Toledo, OH 43614-2598, USA.
Email: vmauro@utoledo.edu

Table 1. Specifics of Admixture Medications Used in This Investigation.

Medication	Dose/solution	Manufacturer	Lot number
Heparin sodium[a]	25 000 units in 5% dextrose injection 250 mL, premixed	Hospira, Lake Forest, IL	79-804-KL
Diltiazem HCl[b]	125 mg/25 mL	Akorn, Lake Forest, IL	121506A
5% Dextrose injection, USP		Baxter, Deerfield, IL	P372524

[a]Heparin sodium excipients: dextrose monohydrate, anhydrous citric acid, trisodium citrate dihydrate, and sodium metabisulfite.
[b]Diltiazem hydrochloride excipients: citric acid monohydrate, sodium citrate, sorbitol, sodium hydroxide, and hydrochloric acid.

Objective

To investigate the physical IV compatibility of diltiazem hydrochloride at concentrations of 5 mg/mL and 1 mg/mL, when infused with heparin sodium at a concentration of 100 units/mL over 24 hours utilizing visual, spectrophotometric, and pH analysis.

Methods

Preparation of Admixtures

A previously validated method was used to conduct this study.[4-6] Study drug details are listed in Table 1. The heparin sodium (25 000 units in 250 mL 5% dextrose injection, premixed; Hospira, Lake Forest, IL; Lot: 79-804-KL) and diltiazem hydrochloride 5 mg/mL (125 mg in 25 mL; Akorn, Lake Forest, IL; Lot: 121506A) preparations were available as manufacturer premixed solutions. Using aseptic technique, the diltiazem 1 mg/mL solution was prepared by diluting 25 mL of diltiazem hydrochloride 5 mg/mL with 100 mL of 5% dextrose (Baxter, Deerfield, IL; Lot: P372524). Using 0.22-μm filters with a 33-mm diameter (Fisher Scientific, Pittsburgh, PA), 15 mL of heparin solution were placed into a 150 mL polyvinyl chloride infusion bag (Baxter; Lot: DR18A04075) followed by 15 mL of diltiazem 5 mg/mL to result in a final volume of 30 mL within the polyvinyl chloride infusion bag. A total of 3 bags with heparin and diltiazem were prepared and labeled A, B, and C. This procedure was then repeated using the prepared diltiazem 1 mg/mL solution. The 6 admixtures were prepared, handled, and stored at room temperature ranging from 19 to 21 °C under ambient light with relative humidity ranging 38% to 44%. These conditions mimic typical preparation and administration under clinical conditions.

Evaluation of Admixtures

Admixture evaluations consisted of visual observation, spectrophotometric absorbance, and pH measurements at baseline and at 1, 5, 8, and 24 hours after mixing. Precipitation and absorbance of admixtures were assessed by placing 3.5 mL of each admixture into a 10-mm cuvette subsequently covered with polystyrene parafilm (Bemis, Neenah, WI). Visual assessments were performed by the same person and made by observing admixtures against a black-and-white background without magnification. Findings were categorized into 5 categories stating no evidence of precipitation, trace evidence of precipitation, slight haze, medium haze, and dense haze. For visual comparison, a positive control was prepared by mixing equal volumes of potassium phosphate 3 mM/mL with calcium gluconate 100 mg/mL. The negative control was prepared with only 5% dextrose. Any change in color was also assessed and recorded by the observer. Visual observations were further supported using spectrophotometry to measure absorbance. Absorbance was measured using a variable-wavelength spectrophotometer (Agilent 8453 ultraviolet-visible spectroscopy system, Waldbronn, Germany) at a wavelength of 547 nm, the wavelength at which the negative control had 100% transmittance of light. Samples whose absorbance value was >0.0100 units were identified as turbid. To determine the pH of each admixture, 5 mL of each admixture was placed into a polypropylene test tube (Becton Dickinson, Lincoln Park, NJ). A demonstrative change in pH was determined to be any change >0.100 from baseline. Measurement of pH was completed using a Seven Multi pH Meter with an Electrode LE409 probe (Mettler Toledo, Schwerzenbach, Switzerland). The pH meter was calibrated using standard buffer solutions of pH 4.00, 7.00, and 10.00 before every use. All measurements were carried out at room temperature. The arm of the pH meter was used to hold the probe steady to ensure the probe did not touch the sides of the test tube during measurement.

Results

The visual assessment of all diltiazem 5 mg/mL admixtures showed a slight haze at baseline and throughout the study. During the observation period, the haze did not increase in density for the diltiazem 5 mg/mL admixtures but did became more noticeable throughout the study. When samples were held against a black background, the hue appeared blue. In contrast, when the samples were held against a white background, the hue appeared yellow. No visual changes were observed in any of the diltiazem 1 mg/mL admixtures. Spectrophotometric and pH results are listed in Table 2. Spectrophotometric readings indicated turbidity in all diltiazem 5 mg/mL admixtures. None of the diltiazem 1 mg/mL admixtures exhibited turbidity. With regard to pH

Table 2. Spectrophotometric Absorbance and pH Measurements of Heparin Sodium (100 Units/mL) and Diltiazem Admixtures.

Admixture (diltiazem concentration), variable, sample	Study time (hours)				
	0	1	5	8	24
Heparin with diltiazem (5 mg/mL)					
pH					
A	5.194	5.183	5.208	5.105	5.202
B	5.144	5.116	5.202	5.097	5.166
C	5.201	5.121	5.285	5.116	5.155
Absorbance					
A	0.0290	0.0399	0.0506	0.0546	0.0701
B	0.0320	0.0416	0.0519	0.0595	0.0716
C	0.0318	0.0417	0.0518	0.0534	0.0685
Heparin with diltiazem (1 mg/mL)					
pH					
A	5.644	5.577	5.713	5.551	5.600
B	5.583	5.573	5.690	5.563	5.651
C	5.586	5.581	5.683	5.582	5.637
Absorbance					
A	0.0002	0.0006	0.0030	0.0016	0.0037
B	0.0011	0.0028	0.0028	0.0021	0.0035
C	0.0000	0.0000	0.0031	0.0034	0.0042

results, none of the diltiazem 5 mg/mL admixtures had a demonstrative change in pH. A single diltiazem 1 mg/mL sample (admixture B) did have a demonstrative change in pH of 0.107 from baseline at 5 hours after mixing. This sample's pH reading at 8 and 24 hours were within 0.1 of baseline reading. No other demonstrative changes in pH were noted in any of the other diltiazem 1 mg/mL admixtures. The reason for the isolated pH change in one sample at 5 hours is not entirely known, but consideration was given to technical error.

Discussion

In contrast to previously conducted trials, using concentrations reflective of those in current clinical practice, this investigation studied the IV compatibility of diltiazem hydrochloride and heparin sodium over 24 hours using visual, spectrophotometric, and pH analysis. The diltiazem 5 mg/mL concentration is administered to patients as a bolus dose and the diltiazem 1 mg/mL concentration is administered as a continuous IV infusions. Both diltiazem concentrations could be administered to a patient concomitantly receiving a continuous IV infusion of heparin. In this study, we selected a current clinically used heparin concentration of 100 units/mL for evaluation.

The results of this trial differed based on the diltiazem concentration. The diltiazem 5 mg/mL admixtures exhibited a visual haze at each time point throughout the trial. Although categorical, this was an important observation since visual changes are the first indication of incompatibility a health care professional would notice in clinical practice. In addition, admixtures' absorbance readings reported turbidity throughout the trial, and the degree of turbidity increased with time. In contrast, no changes in pH were >0.1 in any of the diltiazem 5 mg/mL admixtures. This could be attributed to the citrate buffer that is present in both the heparin sodium and diltiazem hydrochloride preparations.

With regard to the diltiazem 1 mg/mL admixtures, no suggestion of precipitation or turbidity was observed during the visual and spectrophotometric phases of the trial, respectively. On testing the pH of these admixtures, only one admixture reported a demonstrative pH reading of 0.107 on one occasion. This occurred at 5 hours after preparation of admixture B. This was an isolated reading as no future readings of any of the diltiazem 1 mg/mL admixtures revealed a demonstrative change in pH.

Gayed et al studied only visual observations, when brand name diltiazem (Cardizem) 1 mg/mL (diluted with 0.9% sodium chloride) and 5 mg/mL were mixed with heparin at a variety of concentrations ranging from 80 units/mL to 20 000 units/mL.[3] Our investigation found no evidence of physical incompatibility when diltiazem 1 mg/mL was mixed with heparin 100 units/mL. This finding is consistent with the results of Chiu and Schwartz[2] who studied these same concentrations; however, our study included a longer observation time with each admixture tested in triplicate at each time point. The only suggestion of incompatibility in their study occurred when diltiazem 5 mg/mL was mixed with heparin 20 000 units/mL. In our study, the mixing of diltiazem 5 mg/mL with heparin 100 units/mL revealed immediate and consistent evidence of incompatibility. Gayed et al did not study heparin at the same concentration used in our study but did examine concentrations of 80 units/mL and 5000 units/mL and did not find visual evidence of incompatibility.[3] The compatibility results of heparin 100 units/mL and diltiazem are of greater interest because this is the concentration frequently used in clinical practice. A reason for the difference in results between our study and Gayed et al[3] could be that their admixtures were examined immediately after mixing but not thereafter. Additionally, Gayed et al used brand name diltiazem (Cardizem) to conduct their study. This difference in brand versus generic could contribute to the difference in results.

The results of this trial suggest that the compatibility of diltiazem hydrochloride with heparin sodium is concentration dependent. Diltiazem hydrochloride at concentrations of 5 mg/mL is not physically compatible with heparin sodium 100 units/mL. In contrast, mixing diltiazem hydrochloride 1 mg/mL with heparin sodium 100 units/mL resulted in no visual or spectrophotometric evidence of incompatibility and there was essentially no evidence of a demonstrative pH change with the exception of a single,

thought to be spurious, pH reading in one admixture on one occasion. This suggests that these 2 medications at these concentrations are physically compatible.

Conclusion

The visual observation of a slight haze and turbid absorbance in all diltiazem 5 mg/mL admixtures indicate that concurrent infusion of heparin sodium 100 units/mL with diltiazem hydrochloride 5 mg/mL in the same IV line cannot be advocated. In contrast, incompatibility was essentially not observed when diltiazem 1 mg/mL was mixed with heparin 100 units/mL. This would suggest that diltiazem hydrochloride 1 mg/mL is physically compatible with heparin sodium 100 units/mL, but it should be noted that this study did not assess chemical stability. Therefore, extrapolation of these findings beyond physical compatibility is not recommended.

Declaration of Conflicting Interests

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ORCID iD

Vincent F. Mauro https://orcid.org/0000-0002-9306-9538

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