

Compatibility and stability of propafenone hydrochloride with five critical-care medications

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ABSTRACT

The chemical compatibility of propafenone hydrochloride 1 mg/mL in dextrose 5% in water (D5W) was studied with the following critical-care medications: amiodarone 3 mg/mL in D5W, amrinone 2 mg/mL in sodium chloride 0.9% (NS), amrinone 5 mg/mL (undiluted), dopamine 2 mg/mL in D5W, dopamine 5 mg/mL in D5W, lidocaine 10 mg/mL in D5W, potassium chloride 0.5 mmol/mL in D5W and potassium chloride 40 mmol/L in D5W. Three test solutions of each combination were prepared and stored in polyvinyl chloride (PVC) IV bags at $21.5 \pm 1.0^\circ\text{C}$ under fluorescent light. Samples were drawn from each of the test solutions at 0, 1, 4, 8, and 24 hours. Test solutions were visually inspected for precipitation or colour change each time a sample was obtained. All samples were frozen at -20°C until assayed. Propafenone content was determined using a stability-indicating high performance liquid chromatographic assay.

Potassium chloride-propafenone hydrochloride solutions precipitated on freezing and were not analyzed. Mean propafenone concentrations of the remaining test solutions were greater than 90% of the initial concentration throughout the study period. None of the solutions exhibited signs of a colour change or precipitation at any time during the study period.

Propafenone hydrochloride solutions in D5W were compatible with the additives listed above other than potassium chloride for 24 hours when stored in PVC bags at $21.5 \pm 1.0^\circ\text{C}$ under fluorescent light. The chemical stability of the additives in the presence of propafenone was not determined but must be considered when assigning expiry dates to these solutions and evaluating clinical response.

Key words: amiodarone, amrinone, compatibility, dopamine, lidocaine, propafenone.

RÉSUMÉ

La compatibilité chimique de l'hydrochlorure de propafénone dans des solutions de 1 mg par mL de dextrose à 5 % dans l'eau (D5W), a été analysée avec les médicaments suivants administrés en soins critiques : amiodarone/D5W (3 mg/mL), amrinone/chlorure de sodium à 9 % (NS) (2 mg/mL), amrinone (non diluée) (5 mg/mL), dopamine/D5W (2 mg/mL), dopamine/D5W (5 mg/mL), lidocaïne/D5W (10 mg/mL), chlorure de potassium/D5W (0,5 mmol/mL) et chlorure de potassium/D5W (40 mmol/mL). Trois solutions d'essai de chacun des mélanges ont été préparées et stockées dans des sacs de polychlorure de vinyle (PVC) pour administration

I.V. à $21,5 \pm 1,0^\circ\text{C}$ sous tube fluorescent. Des échantillons ont été prélevés de chacune des solutions d'essai à 0, 1, 4, 8 et 24 heures. Les solutions d'essai pour chacun des échantillons ont été inspectées visuellement pour détecter toute précipitation ou changement de couleur. Tous les échantillons ont été congelés à -20°C jusqu'à ce qu'ils soient analysés. La concentration en propafénone a été déterminée par épreuve de stabilité par chromatographie liquide à haute pression.

Les solutions de chlorure de potassium/hydrochlorure de propafénone ont formé un précipité lors de leur congélation et n'ont pas été analysées. Les concentrations moyennes de propafénone des autres solutions d'essai étaient supérieures à 90 % des concentrations initiales durant toute la période de l'étude. Aucune des solutions n'a montré de signes de changement de couleur ni de formation de précipité, en aucun temps au cours de la période d'étude.

Les solutions d'hydrochlorure de propafénone dans du D5W étaient compatibles avec les additifs énumérés plus haut, autre que le chlorure de potassium, durant une période de 24 heures lorsqu'elles étaient entreposées dans des sacs en PVC à $21,5 \pm 1,0^\circ\text{C}$ sous éclairage fluorescent. La stabilité chimique des additifs en présence du propafénone n'a pas été déterminée, mais on doit en tenir compte lorsqu'on fixe les dates de péremption de ces solutions et qu'on évalue la réponse clinique.

Mots clés : amiodarone, amrinone, compatibilité, dopamine, lidocaïne, propafénone.

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INTRODUCTION

Propafenone is a class IC antiarrhythmic agent which is currently available in Canada on an emergency release basis for intravenous administration in the critical-care setting to control ventricular or supraventricular dysrhythmias.¹ Fluid volumes and vascular access are frequently restricted in patients, most especially children, requiring propafenone injection. However, data regarding the compatibility of propafenone with other medications are limited. Information provided by Knoll Pharma Inc. indicates that propafenone hydrochloride 3.5 mg/mL solutions are compatible with lidocaine 10 mg/mL and 20 mg/mL in an unspecified diluent (personal communication, Valerie South, Clinical Research Associate, Knoll Pharma Inc., November 8, 1990). No other information regarding the compatibility of propafenone hydrochloride injection with other medication is available in the English literature.

The purpose of this study was to determine the chemical compatibility of propafenone hydrochloride 1 mg/mL in D5W with several commonly used critical-care medications (Table 1).

METHODS

Propafenone Assay

Solutions were assayed for propafenone content by means of a previously published, stability-indicating high-performance liquid chromatographic assay for propafenone in serum² which was adapted in order to accommodate the differences in matrix and concentration.³

Briefly, propafenone was quantified using a reverse phase liquid chromatographic system with UV detection at 214 nm. The mobile phase was prepared by mixing 33 parts of acetonitrile and 67 parts of 10 mM phosphate buffer at a pH of 2.5. This mobile phase was pumped (Model 6000A; Waters Scientific, Mississauga, ON) at 3.0 mL/min through a 10 cm x 9.4 mm, 5mm column (Whatman Partisil 5 ODS RaC, Mandel Scientific, Guelph ON). A guard column was not used. Injections were made with an automated injector (WISP 710, Waters Scientific, Mississauga, ON). Propafenone was detected at 214 nm using a variable wavelength detector (Lambda-Max, Model 481 spectrophotometer, Waters Scientific, Mississauga ON).

The suitability of this method for use as a stability-indicating assay was tested by accelerating the degradation of propafenone. Equal volumes of a 1 mg/mL solution of propafenone hydrochloride in D5W was mixed with 6 N hydrochloric acid or 10 N potassium hydroxide. These solutions were incubated in a water bath for 24 hours at 95°C. Control solutions were stored at 4°C.

Chromatograms were inspected for the appearance of additional peaks and the propafenone peak was compared between samples for changes in concentration, retention time and peak shape. Interference with propafenone peak quantification was also evaluated for each one of the additives.

Standard curves were constructed using a propafenone hydrochloride reference standard (provided by Knoll Pharma, Markham, ON). Six standards, ranging in concentration from 0.5 to 20 mg/mL were prepared in distilled water. All samples were assayed in duplicate. Samples were diluted 1:200 with distilled water to achieve a concentration within the standard curve range. The limit of assay sensitivity for propafenone was 30ng/mL.

Solution preparation

Propafenone hydrochloride 70 mg/20mL for injection (Knoll Pharma Inc., lot #16928) was used to prepare the study solutions. This product also contains glucose monohydrate 53.8 mg/mL in water for injection and has a pH of 4.7 to 6.0 (personal communication, Hitesh Tailor, Medical Information, Knoll Pharma Inc., August 12, 1996).

Propafenone hydrochloride 1 mg/mL solutions were prepared in D5W (Baxter Health Care Corp, Mississauga, ON. Lot ZP055830). Solutions of the additives (Tables I and II) were prepared and added to the propafenone solution in an empty 150 mL polyvinyl chloride (PVC) bag (Baxter Healthcare Corp., Deerfield, Illinois) in a

Table I. Solutions assessed for compatibility with propafenone hydrochloride 1 mg/mL in D5W

Additive	Propafenone: Additive volume ratio
Amiodarone 3 mg/mL in D5W	1.4:1
Amrinone 2 mg/mL in NS	1.0:1
Amrinone 5 mg/mL (undiluted)	1.0:1
Dopamine 2 mg/mL in D5W	1.2:1
Lidocaine 10 mg/mL in D5W	1.2:1
Potassium chloride 0.5 mmol/mL in D5W	1.2:1
Potassium chloride 40 mmol/L in D5W	1.2:1

D5W = dextrose 5% in water for injection
NS = sodium chloride 0.9% for injection

Table II. Source of additives

Additive	Concentration	Manufacturer	Lot#
Amiodarone hydrochloride	50mg/mL	Labaz	81444800
Amrinone lactate	5mg/mL	Sanofi Winthrop	B550KJA
Dopamine hydrochloride	40mg/mL	Dupont Pharma	3AAZ07
Lidocaine hydrochloride	200mg/mL	Astra	209013
Potassium chloride	2mmol/mL	Astra	352
Sodium chloride	0.9%	Baxter	AP4Z1P2
Dextrose	5%	Baxter	ZP055830

volume ratio ranging from 1:1 to 1.4:1 (Table I). The solutions were mixed well and then stored at $21.5 \pm 1^\circ\text{C}$ for 24 hours under continuous exposure to fluorescent light. Three solutions of each combination were prepared. Two 0.5 mL samples were drawn from each of the three solutions at 0, 1, 2, 4, 8, and 24 hours and frozen in polystyrene tubes (Becton Dickinson and Co., Franklin Lakes, New Jersey) at -20°C until assayed. Solutions were visually examined for colour change or precipitation each time a sample was obtained.

Data analysis

Significant drug loss was defined as a mean decrease of 10% or more from the initial concentration. The mean propafenone concentration \pm standard deviation was calculated based on the results of duplicate assays of the samples drawn from test solutions in triplicate. The mean was then expressed as the percent remaining of the initial observed concentration.

RESULTS

The retention time of propafenone was 6.4 minutes. None of the additives interfered with the propafenone peak on chromatography. These additives generally eluted with or very near the solvent front, or did not absorb ultraviolet light at 214 nm. During accelerated degradation, when propafenone was heated for 24 hours in a highly alkaline environment, the propafenone concentration was dramatically reduced but degradation products did not interfere with propafenone quantification. There was no detectable reduction in concentration when propafenone was incubated at 95°C with 6 N hydrochloric acid. Based on these results the assay was judged to be stability indicating.

The within-day coefficient of variation of the assay, based on five replicates for concentrations of 0.5 and 2 mg/mL, was less than 2% and the between-day coefficient of variation averaged less than 5%.

Table III. Mean % initial propafenone concentration remaining after admixture

Additive	Nominal initial propafenone concentration remaining* (mg/mL)	% of initial propafenone concentration remaining† at intervals				
		1 hr	2 hr	4 hr	8 hr	24 hr
Amiodarone 3 mg/mL in D5W	0.625	98.7 \pm 3.7	97.9 \pm 5.6	100.9 \pm 6.3	100.6 \pm 5.2	99.5 \pm 8.2
Amrinone 2 mg/mL in NS	0.500	104.6 \pm 1.8	102.6 \pm 3.5	100.8 \pm 3.5	101.8 \pm 3.0	100.8 \pm 3.0
Amrinone 5 mg/mL (undiluted)	0.500	102.2 \pm 5.0	102.3 \pm 5.3	103.4 \pm 5.2	101.0 \pm 4.3	98.1 \pm 2.8
Dopamine 2 mg/mL in D5W	0.540	102.0 \pm 4.2	102.4 \pm 3.8	97.8 \pm 8.2	103.4 \pm 4.0	98.7 \pm 4.9
Dopamine 5 mg/mL in D5W	0.540	100.0 \pm 1.7	105.9 \pm 2.3	99.5 \pm 5.9	99.8 \pm 2.7	98.8 \pm 4.3
Lidocaine 10 mg/mL in D5W	0.540	99.1 \pm 2.6	99.9 \pm 1.5	98.2 \pm 1.2	98.6 \pm 1.1	98.9 \pm 3.4

* Mean actual propafenone concentration was $104 \pm 4.6\%$ of the nominal propafenone concentration.

† Expressed as mean \pm standard deviation of duplicate assays of the samples from triplicate test solutions.

Study samples were frozen for up to three months prior to assay. Potassium chloride-propafenone hydrochloride solutions precipitated when frozen. The precipitate dissolved on warming to room temperature. However, these solutions were not analysed due to concerns regarding the reliability of the results.

Mean propafenone concentrations remained greater than 90% of the initial concentration when mixed with additives other than potassium chloride throughout the 24-hour study period (Table III). At no time during the study period did any of the solutions, including the potassium chloride-propafenone solutions, exhibit signs of a colour change or precipitation. Furthermore, significant peaks attributable to propafenone degradation products were not observed in any chromatogram of study samples.

DISCUSSION

At The Hospital for Sick Children, propafenone is most commonly administered as a continuous IV infusion to provide a dose of 4 to 7 $\mu\text{g}/\text{kg}/\text{minute}$. For study purposes, 1 mg/mL was chosen as a representative concentration.

Solutions of propafenone hydrochloride 1 mg/mL in D5W were chemically compatible with the additives listed in Table I other than potassium chloride when stored in PVC bags for 24 hours at $21.5 \pm 1^\circ\text{C}$ under fluorescent light. The chemical stability of each additive was not evaluated in the presence of propafenone but nevertheless must be taken into account when assigning expiry dates to these solutions and evaluating clinical response.

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