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Research Article

A Potential Cost Savings Strategy for Isoproterenol Hydrochloride Using Novel Stability Data

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Abstract

Background

A dramatic increase in the price of isoproterenol hydrochloride has elicited a substantial financial burden to health systems. Published strategies to reduce the use of isoproterenol hydrochloride in electrophysiology (EP) testing are lacking, and preparation of multiple doses from a single ampule has not been previously described.

Objective

The objective of this study was to investigate the stability of isoproterenol hydrochloride 0.2 mg/mL in sterile glass vials and polypropylene syringes at 5°C for 9 days, thereby determining an extended beyond-use date for partial volumes stored in these closures after removal from the manufacturer ampule.

Methods

Isoproterenol hydrochloride was transferred to syringes and vials and then analyzed by a validated high-performance liquid chromatography analytical method at days 8 and 9. The isoproterenol hydrochloride solutions were considered stable if they had absence of particles, color variation, or changes in pH and a remaining drug concentration > 90%.

Results

The remaining isoproterenol hydrochloride concentrations at day 8 in the syringe and vial were 98.1% and 98.9%, respectively. Remaining concentrations at day 9 were 93.1% and 93.9%, respectively. All solutions remained clear and colorless throughout the study. All samples had a pH of 3.8.

Conclusion

We concluded isoproterenol hydrochloride prepared in sterile glass vials and polypropylene syringes was stable at 5°C for 9 days. These findings allow for a potential cost savings strategy, supporting the preparation of multiple doses from a single ampule to facilitate multiple EP studies.

Keywords: Cardiac electrophysiology; Chromatography, high performance liquid; Drug stability; Isoproterenol; Tilt-table test

Introduction

Over the last 4 decades, electrophysiology (EP) studies have become a standard diagnostic approach for the characterization of cardiac arrhythmias [1,2]. Early advancements in EP testing began with the first intracardiac catheter recordings from the bundle of His in 1969 and the emergence of programmed stimulation techniques in the late 1960s and 1970s [1]. Isoproterenol hydrochloride, a non-subtype selective β-adrenergic receptor agonist, has been utilized to facilitate EP studies by altering autonomic tone, thereby promoting the induction of certain cardiac arrhythmias and assisting the diagnostic process [3,4]. Isoproterenol hydrochloride is also classified as a sympathomimetic amine used in the treatment of refractory torsade de pointes; Brugada syndrome with electrical storm; and bradycardia following cardiac transplant [2,5]. Given its utility for the diagnosis and treatment of cardiovascular diseases, isoproterenol is widely used in both hospital and clinic settings.

Sudden price increases on older drugs with sole ownership are eliciting substantial financial burden to health systems. In February 2015, Valeant Pharmaceuticals acquired isoproterenol hydrochloride from Marathon Pharmaceuticals and increased the price per ampule (1mg/5mL) from $218.30 USD to $1200 USD-an almost 2600% price increase since 2013 when the same unit was sold for $44.50 USD [6]. This cost strain has been experienced by institutions performing EP studies where isoproterenol hydrochloride is commonly utilized. The most recent iteration of the American College of Cardiology, American Heart Association, and European Society of Cardiology Practice Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death suggest no alternative pharmacologic agent for this purpose [2].

The isoproterenol hydrochloride dose required to facilitate an EP study is of great interest as it is typically less than the contents of a 1mg/5mL ampule [4,7]. Valeant Pharmaceuticals offers a smaller ampule containing one-fifth of the dose (0.2mg/1mL), but the cost is a mere 17-20% less than the 1mg/5mL presentation. Thus, the ability to prepare multiple doses from a single 1mg/5mL ampule within a sterile intravenous medication preparation area has the potential to introduce substantial cost savings by utilizing one 1mg/5mL ampule of isoproterenol hydrochloride for multiple EP studies.

The primary determinant of catecholamine stability in intravenous admixture is the pH of the solution [8]. The pharmacologic efficacy of catecholamines is dependent on the stability of their phenolic hydroxyl (Ar-OH) groups, and autoxidation of these groups is a common reason for drug instability [8,9]. Catecholamine degradation (autoxidation of the Ar-OH groups) increases sharply above a pH of 6 [8]. In a previously described stability analysis, isoproterenol hydrochloride was stable for greater than 24 hours at a pH of 3.7 to 5.7 but exhibited significant decomposition at a pH greater than 6 [10,11].

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Prescribing information from the current manufacturer of isoproterenol hydrochloride provides no stability information for the drug outside of the original ampule [12]. Isoproterenol hydrochloride has previously maintained biologic activity for 30 months when diluted in dextrose 5% and stored at room temperature [10]. A high-performance liquid chromatographic (HPLC) analysis by Newton and colleagues demonstrated a 10% drug loss after 250 hours when isoproterenol hydrochloride was diluted in dextrose 5% and protected from light [8]. When exposed to summer conditions in paramedic vehicles, a stability study of isoproterenol hydrochloride demonstrated 4% drug loss after 7 days and 11% drug loss after 4 weeks when analyzed by gas chromatography-mass spectrometry [13].

Outside of the data presented in our analysis, the authors are unaware of any stability information to date supporting the use of a single isoproterenol hydrochloride ampule for multiple EP studies. Our objective was to investigate the stability of isoproterenol hydrochloride 0.2mg/mL in sterile glass vials and polypropylene syringes at 5°C for 9 days, thereby determining an extended beyond-use date for partial volumes stored in these closures after removal from the manufacturer ampule.

Methods

Studies were conducted using commercially available 0.2mg/mL (1mg/5mL) ampules of isoproterenol hydrochloride solution for injection (Isuprel; Marathon Pharmaceuticals, LLC, Northbrook, IL); the same manufacturing lot was used for all stability studies. A United States Food and Drug Administration registered and International Organization for Standardization 17025 accredited analytical laboratory was consulted to advise and perform appropriate testing to determine stability (Avomeen Analytical Services; Ann Arbor, MI).

Preparation of isoproterenol hydrochloride syringes and glass vials

Isoproterenol hydrochloride solution supplied in manufacturer ampules was transferred into study containers. The investigators transferred 2.5mL isoproterenol hydrochloride into each of two sterile 10-mL glass vials (Model no. 18493; Health Care Logistics, Inc., Circleville, OH) and two sterile 6-mL polypropylene syringes (Kendall Monoject; Covidien, Mansfield, MA); syringes were capped and each container labeled. Preparation was performed under aseptic conditions in a laminar-airflow cabinet in accordance with the manufacturer's instructions. Upon transfer, isoproterenol hydrochloride solution was filtered through a 5-µm hypodermic filter needle (Monoject 305; Covidien, Mansfield, MA) when withdrawn from the manufacturer ampule. Study solutions were kept at room temperature and protected from light in their supplied carton until sample preparation, congruent with package insert recommendations.

Immediately following preparation, the syringes and glass vials were protected from light in opaque plastic bags, placed in containers with ice packs, and shipped overnight to the analytical laboratory for testing. Additionally, an unrefrigerated isoproterenol hydrochloride manufacturer ampule, protected from light in an opaque plastic bag, was simultaneously shipped to the analytical laboratory. All study solutions arrived at the analytical laboratory within 24 hours of sample packaging. The samples were received without compromise and appropriately stored upon arrival. The unopened, unrefrigerated isoproterenol hydrochloride ampule was stored at room temperature in an opaque plastic bag at the analytical laboratory. The two 10-mL glass vials and two 6-mL polypropylene syringes were stored at 5°C in opaque plastic bags.

Stability testing

Stability was defined as the absence of particles, color variation, or changes in pH and a drug concentration > 90% of the initial concentration. Contents of the manufacturer ampule were analyzed by HPLC to establish baseline control of stability. Contents of one 6-mL polypropylene syringe and one 10-mL glass vial were analyzed by the same HPLC method on day 8, and the other syringe and vial on day 9. Solutions were visually inspected at each time point to detect particulate matter and color change. Changes in pH were detected by means of a calibrated pH meter (ORION 3 Star; Thermo Fisher Scientific Inc., Beverly, MA).

Isoproterenol hydrochloride solutions were analyzed using a previously described and validated HPLC analytical method [14]. The chromatograph was a HPLC value system (Agilent 1100; Agilent Technologies, Madrid, Spain) with quaternary pumps. The stationary phase included a 5µg, 250mm×4.6mm column (Kinetex; Phenomenex, Torrance, CA). The mobile phase consisted of 1.76 g of sodium 1-heptanesulfonate in 800mL of water, added to 200 mL of methanol (buffer and methanol 80:20) and adjusted with 1 M phosphoric acid to a pH of 3.0. The flow rate was 1.5ml/min. The injection volume was 100µL. Ultraviolet detection was performed at 280nm. A *United States Pharmacopeia* (USP) isoproterenol hydrochloride 20µg/mL solution was used as a reference standard to evaluate the isoproterenol sample solutions.

Results

An HPLC analysis of the isoproterenol hydrochloride samples demonstrated that all solutions remained > 90% of the initial concentration for 9 days (Table 1). All solutions remained clear and colorless throughout the study. All samples had a pH of 3.8.

Container	Vial		Syringe	
Time	Conc (mg/mL)	% Remaining	Conc (mg/mL)	% Remaining
Day 0 (ampule)	0.2248	100	0.2248	100
Day 8	0.2224	98.9	0.2206	98.1
Day 9	0.2110	93.9	0.2092	93.1

Table 1: HPLC Analysis Results.

Discussion

This study was designed to determine the stability of isoproterenol hydrochloride prepared in a manner that would reflect acceptable hospital pharmacy preparation. Doses were prepared aseptically, kept refrigerated, and tested at a 9-day endpoint due to the accepted beyond-use date recommendation for medium risk compounded products as defined by USP chapter 797 [15]. Our study evaluated solutions in sterile vials and polypropylene syringes to assess multiple storage possibilities. Isoproterenol hydrochloride from Marathon Pharmaceuticals was used for testing, not the currently available product from Valeant Pharmaceuticals. However, the formulation of isoproterenol hydrochloride did not change when acquired by Valeant Pharmaceuticals [12,16]. The results of this study, albeit small, support a 9-day beyond-use date for isoproterenol hydrochloride withdrawn from commercial ampules when stored under the conditions described. In lieu of recent price increases,

institutions performing EP studies are seeking an acceptable approach to steward isoproterenol hydrochloride. After evaluating the amount of drug typically used for these procedures in our facilities, we determined there was adequate drug in a 1mg/5mL ampule to facilitate 4 EP tests (250µg per test). The potential cost savings strategy proposed is to prepare one 250µg isoproterenol hydrochloride intravenous admixture from a 1 mg ampule in a hospital pharmacy at the time of an EP test, then transfer unused drug volume from the ampule into syringes each containing 250µg. These syringes could be stored for up to 9 days in the manner described and used to supply drug for subsequent EP tests. Facilitating 4 EP studies per 1mg/5mL ampule has the potential to provide a 66% reduction in drug cost compared to using commercially available 0.2mg/1mL ampules-approximately $600 USD in cost savings per EP test.

Limitations

This study has several limitations, including a small number of samples analyzed which did not allow for statistical analysis of the drug concentration results. Due to the cost of isoproterenol hydrochloride and limited funding, our capability to have additional samples tested was prohibitive.

Samples tested were shipped on ice (to simulate refrigerated conditions) for approximately 24 hours following preparation, and the temperature was not measured during that period. Additionally, the 3rd party laboratory experienced an unexpected delay in obtaining necessary testing supplies, and therefore the vial and syringe samples intended to be analyzed upon arrival (to determine day 1 concentration) had to be tested on day 8. Therefore, the drug concentration of a manufacturer ampule from the same lot was used to establish day 0 concentration. The solutions were visually examined for particulate matter and color change; no other colorimetric or turbidimetric evaluations were performed. No studies related to biological activity were conducted, and the authors cannot recommend the extrapolation of our findings to the biological activity of stored isoproterenol hydrochloride for 9 days. Despite these limitations, we consider our findings beneficial since the authors are not aware of information regarding isoproterenol hydrochloride stability in this context to date.

Conclusion

The findings of this study indicate that isoproterenol hydrochloride's stability was not significantly affected by refrigerated storage over 9 days, supporting an extended beyond-use dating strategy for drug withdrawn from a commercial ampule. Our study supports the stability of isoproterenol hydrochloride 0.2mg/mL aseptically prepared in sterile 10-mL glass vials and 6-mL polypropylene syringes stored at 5°C for 9 days. Our data provides a potential option to facilitate multiple EP studies from one isoproterenol hydrochloride ampule and may reduce drug waste.

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