Evaluation of the Physicochemical Stability of Amiodarone Hydrochloride in Syringes for the Intensive Care Unit

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Abstract

In some emergency clinical situations, the injection of a more concentrated drug solution in the intensive care units is common. The purpose of this study was to evaluate the physicochemical stability of concentrated solutions of amiodarone hydrochloride in polypropylene syringes during 28 days of storage at 5°C ± 3°C, with protection from light. Five syringes of 50 mL, containing 25 mg/mL of amiodarone in dextrose 5%, were prepared and stored at 5°C ± 3°C with protection from light during 28 days. Immediately after preparation and periodically during the storage, amiodarone hydrochloride concentrations were measured by ultra-performance liquid chromatography. Spectrophotometric absorbance at different wavelengths, pH measurement, and microscopic observations were also performed. All solutions were physicochemically stable during the study period when stored at 5°C ± 3°C. No color change, turbidity, precipitation, opacity, significant pH variations, or optic densities were observed in the solutions. No crystals were seen by microscopic analysis. The concentration of amiodarone did not decrease during the 28 days of storage. Solutions of amiodarone 25 mg/mL in syringes of dextrose 5% are physically and chemically stable for at least 28 days when stored in syringes at 5°C ± 3°C with protection from light and may be prepared in advanced by a centralized intravenous additive service.

Introduction

Amiodarone hydrochloride (HCl) is generally considered a class III antiarrhythmic drug indicated for the acute treatment of life-threatening rhythm disorders such as[1-5]:

- Atrial arrhythmias
- Atrioventricular (AV) nodal arrhythmias
- AV reentrant tachycardia
- Recurrent ventricular fibrillation
- Recurrent, hemodynamically unstable ventricular tachycardia in patients refractory to other therapies or in cases where other treatments cannot be used
- For patients who are unable to take oral medication

In extreme clinical emergency situations where a rapid response is required, the intensivist may sometimes prefer to administer a direct intravenous (IV) injection of a higher concentration of amiodarone using an injection syringe.[1] This situation requires close monitoring including, appropriate ambulatory electrocardiogram (EKG) monitoring (e.g., Holter monitoring) and/or programmed electrical stimulation (PES).[2,4] The total volume of infusion administered to patients admitted into intensive care units (ICUs) is important. Fluid overload is commonly implicated in fluid resuscitation and is associated with increased hospital costs, morbidity, and mortality. Sometimes fluid overload can also induce other side effects such as hypernatremia. There is a huge interest to build strategies that reduce excessive fluid infusions.

In order to reduce the perfusion volume and prevent fluid overload, the intensivists and the obstetricians may prefer to administer a higher salbutamol IV concentration using an injection syringe.[6-8]

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Most of the published stability studies about amiodarone HCl focused on the compatibility with other injectable drugs or solutions such as adsorption to polyvinyl chloride (PVC) tubing and leaching out of plasticizers (e.g., DEHP [di-(2-ethylhexyl)phthalate]) from IV tubing.[4] The chemical stability of amiodarone HCl in IV fluids has been investigated for concentrations from 0.6 mg/mL to 12.5 mg/mL, at 5°C ± 3°C or ambient temperature, and for different periods (24 hours to 180 days).[9-13]

The purpose of this study is to evaluate the physical and chemical long-term stability of a higher concentration of amiodarone HCl (25 mg/mL) diluted in glucose 5% in polypropylene syringes.

Materials and Methods

SOLUTION PREPARATION

Five 50-mL polypropylene syringes (Lot 1701210P, Per: 12/2021; BD, Erenbodegem, Belgium), containing 25 mg/mL of amiodarone HCl (Lot CY023, Per: 09/2018; SANOFI, Diegem, Belgium) in glucose 5% (Lot 17c06GC1, Per: 02/2019; Baxter, Lessines, Belgium) were prepared under laminar airflow and stored at 5°C ± 3°C during 28 days with protection from light.

STANDARD AND QUALITY-CONTROL SOLUTIONS

A 50-mg/mL standard solution of amiodarone (Cordarone) IV (Lot CY023, Per: 09/2018; SANOFI) was diluted in purified water to obtain five standard solutions (50.0 mg/mL, 25.0 mg/mL, 12.5 mg/mL, 6.3 mg/mL, and 5.0 mg/mL) and two quality controls (25.0 mg/mL and 12.5 mg/mL).

CHROMATOGRAPHIC CONDITIONS

The chromatography was performed on a Waters Acquity ultra-performance liquid chromatography (UPLC) H-Class system (Waters Association, Milford, Massachusetts) with a photodiode array detector (PAD) (Waters Association) and a data acquisition and processing module (Empower 2 Software; Waters Association).

Separation was performed on a universal silica-based, reversed-phase column (Acquity UPLC HSS T3 1.8 µm, 100 × 2.1 mm; Waters Association).

Mobile phase A was constituted of 0.05 % formic acid (Grade UCL/MS; Biosolve BV, Valkenswaard, The Netherlands) and 99.95% purified water.

Mobile phase B was constituted of 99.95% acetonitrile (Lot 1025641, Per: 07/2019; Biosolve BV) and 0.05% formic acid. These UPLC-grade solvents were filtered through a 0.20-µm membrane filter (Lot R2BA85869; Durapore).

The step-gradient program is described in TABLE 1.

The flow rate was set at 0.4 mL/minute, the column temperature at 30°C, and the wavelength (PAD detector) fixed at 265 nm.

PHYSICAL COMPATIBILITY

Physical compatibility was defined as the absence of particulate formation, haze, precipitation, color change, and gas evolution.[14] At each time of the study, particle contamination was searched by visual and microscopical inspection, by optical density, and by pH measurements.

The samples were visually inspected with the unaided eye, in front of a black and white background, and the pellet obtained after centrifugation at 3000 rpm for 8 minutes was observed with a microscope 10 × (Carl Zeiss, Germany) for any observed crystals.

The optical densities were measured by a spectrophotometer (Genesys 10 UV; Spectronic Unican, New York, New York) at 350 nm, 410 nm, and 550 nm to detect subvisible particles.[15]

The pH of the solutions were measured with a pH-meter (Inolab WTW; Inolab, Weilhein, Germany) equipped with a glass electrode (Biotrode Hamilton Bonaduz, Switzerland) calibrated with two standard solutions at pH 4 and pH 7 (CertiPur; Merck, Darmstadt, Germany).

TABLE 1.

GRADIENT PROGRAM FOR ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD.

	TIME (MINUTE)	FLOW (ML/MINUTE)	MOBILE PHASE A (%)	MOBILE PHASE B (%)
1	Initial	0.4	95	5
2	5.00	0.4	30	70
3	7.00	0.4	0	100
4	8.00	0.4	0	100
5	13.00	0.4	95	5

Note: The percentages of mobile phase A and mobile phase B vary as a function of time.

ULTRA-PERFORMANCE LIQUID CHROMATOGRAPHIC ASSAY

The five standard solutions, both quality controls, and the samples were all diluted 1000-fold, and 5 µL of each were injected into the chromatograph.

Results were automatically calculated by interpolation of a four-level calibration curve (linear through zero), performed by the Empower 2 software using areas under amiodarone HCl peak versus standard concentrations.

VALIDATION OF THE METHOD

The within and between-day relative standard deviation (SD) values (n=10) were realized on two concentrations (25.0 mg/mL and 12.5 mg/mL).

The determination coefficient r^2 was determined by a linear-regression analysis of peak area.

Degraded samples of amiodarone HCl solutions were assayed to confirm separation of the parent drug from its degradation products. Amiodarone HCl solutions at natural, alkaline, and acidic pH were heated at 100°C during 15 minutes, 30 minutes, 45 minutes, and 60 minutes.

STABILITY STUDY

After preparation, the syringes were stored for 28 days at 5°C ± 3°C. The concentrations of amiodarone HCl were determined in triplicate

daily for each of the syringes for the first 3 days, then the concentrations were determined every 3 to 4 working days until the 28th day.

STATISTICAL ANALYSIS

As recommended by the U.S. Food and Drug Administration, solutions were considered stable as long as the lower limit of the 95% one-sided confidence interval of the mean remained superior to 90% of the initial concentration[16] or 95% of the initial concentration when any signs of physical instability existed.[17] Currently, this definition of the chemical stability is questioned and some authors have recommended that a product should be considered stable as long as a suitably high quantile (e.g., 95%) of the batches remains superior to the acceptable limit.[18] The chemical stability of amiodarone HCl was thus confirmed with this alternative definition. The slope (in relative concentration) was computed for each batch, and the fifth percentile of the slopes (5PS) was obtained using the Student "*t*" distribution. The 5PS was then used to estimate the evolution of relative concentration in the fifth percentile of batches.

Results

VALIDATION OF THE METHOD

The within and between-day relative SD values are shown in TABLE 2 and could be considered as acceptable.

The linearity of the assay can be validated from 5.6 mg/mL to 50 mg/mL (determination coefficient r^2 >0.99).

No additional peak from decomposition products has been reported (FIGURE 1).

Two peaks with longer retention times than amiodarone are visible at alkaline and acidic pH without changing the concentration of amiodarone.

PHYSICAL STABILITY

Throughout the study, all solutions were physically stable during the 28-day storage period: no color change, turbidity, precipitation or opacity, significant variation in pH values in glucose 5% (mean ± SD: 3.9 ± 1.6; minimum: 3.7: maximum: 4.0), or optical densities were observed in the solutions. No crystals were seen by microscopical analysis.

TABLE 2.

INTRA- AND INTER-REPRODUCIBILITY OF THE ASSAY.

CONCENTRATIONS	WITHIN-DAY CV (%) ± Standard Deviation *n*=10	BETWEEN-DAY CV (%) ± Standard Deviation *n*=10
6.25 mg/mL	5.95 ± 0.19	Not Applicable
12.5 mg/mL	Not Applicable	12.3 ± 4.81
25.0 mg/mL	23.2 ± 0.6	24.0 ± 6.5

CV = coefficient of variation

CHEMICAL STABILITY

The amiodarone HCl content remained stable throughout the study (FIGURE 1 and TABLE 3). These data support a chemical stability of at least 28 days. Any additional chromatographic peak didn't appear over the study period.

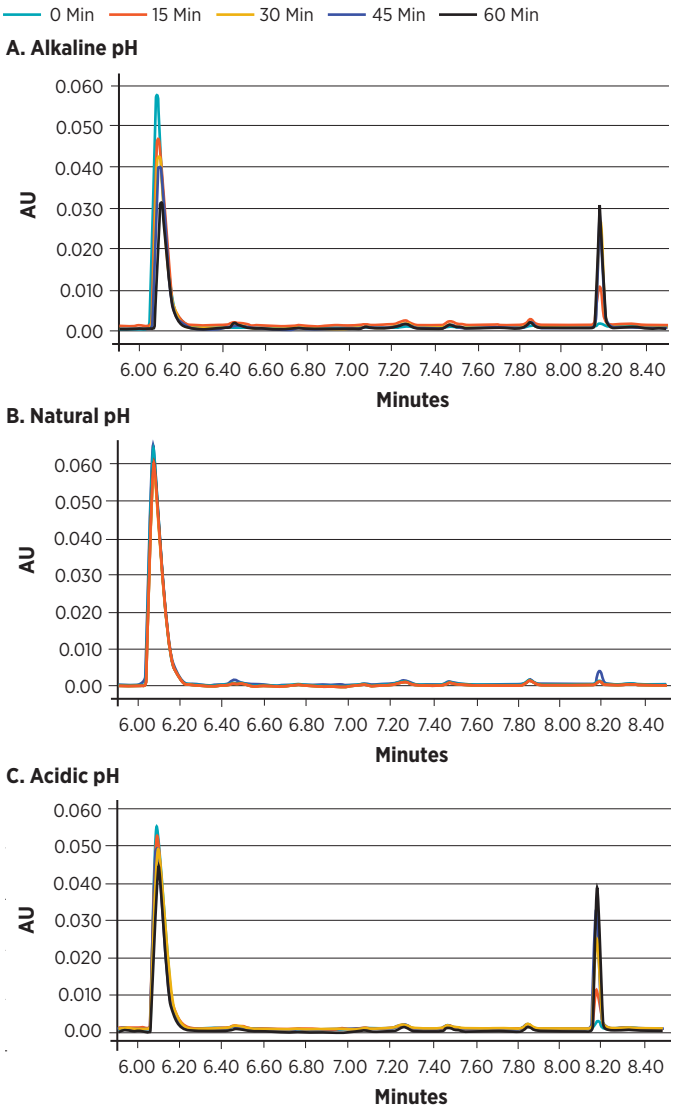
Discussion

As mentioned previously, most of the published stability studies about amiodarone HCl focused on drug compatibility or solution compatibility such as adsorption to polyvinyl chloride (PVC) tubing and leaching out of plasticizers (e.g., DEHP) from intravenous tubing.[4]

The manufacturer recommends to store the ampules at room temperature (15°C to 25°C) and to protect them from light,[1] although the

FIGURE 1.

DEGRADATION CHROMATOGRAMS.



manufacturer of the generic drug mentions that light protection is not necessary during administration.[4,14] No information is provided regarding the physicochemical stability of amiodarone HCl in infusion fluids in syringes.

Since the use of higher concentrations of amiodarone in acute clinical situations is necessary, it is important to note the risks associated with the infusion of a more concentrated solution.

This result of this study are in accordance with the previous physicochemical stability study published by Pramar,[10] and it allows us to add this solution to the list of our systematic studies of the chemical stability of ready-to-use and long-term IV-drug solutions.[19] Chemical stability was only evaluated and the microbiological aspects were not investigated. However, according to Chapter 797 of the *United States Pharmacopeia,* our preparation can be assimilated to low-risk compounding.[20] The advance preparation by a centralized intravenous additive service (CIVAS) may be considered.[21]

Conclusion

Solutions of amiodarone HCl 25 mg/mL in glucose 5% are physically and chemically stable for at least 28 days when stored in syringes at 5°C ± 3°C with protection from light and may be prepared in advanced by a CIVAS. This concentration may be used in ICUs to treat patients and prevent fluid overload.

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TABLE 3.

EVOLUTION OF THE RELATIVE CONCENTRATION OF AMIODARONE HYDROCHLORIDE FROM DAY 0 TO DAY 28.

DAY	OBSERVED VALUES		FITTED VALUES		
	MEAN	SD	MEAN	LL 95 CI	5PS
0	105.79	6.84	100.00	97.38	100.00
1	95.31	5.69	100.15	97.65	99.82
2	107.86	7.55	100.30	97.92	99.65
3	104.60	6.09	100.45	98.18	99.47
6	95.25	3.18	100.90	98.94	98.94
10	85.42	5.75	101.50	99.79	98.23
13	105.86	2.23	101.95	100.28	97.70
17	101.46	3.65	102.55	100.71	97.00
20	105.46	3.67	103.00	100.90	96.47
24	106.19	2.12	103.60	101.03	95.76
26	104.89	1.13	103.90	101.07	95.41
28	103.98	2.10	104.20	101.09	95.06

Initial concentration: 28.4 mg/mL ± 2.14 mg/mL. 5PS= fifth percentile of the slopes; LL 95 CI = lower limit of the 95% confidence interval on the mean; SD = standard deviation

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