Ready-to-use parenteral amiodarone: a feasibility study towards a long-term stable product formulation

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ABSTRACT

Objectives To determine the feasibility of preparing a long-term stable ready-to-use parenteral amiodarone formulation using cyclodextrins as dissolution enhancer.

Methods A preformulation study was performed with different molar ratios of hydroxypropyl-beta-cyclodextrin (HP-BCD) or sulfobutylether-beta-cyclodextrin (SBE-BCD) to amiodarone in order to investigate enhancement of amiodarone's water solubility. Further, effects of pH and temperature on the dissolution rate during production were investigated. Shelf-life was determined for a ready-to-use iso-osmotic preparation of 1.8 mg/mL amiodarone with SBE-BCD in a molar ratio of 1:3. Amiodarone content was assessed using a validated high-pressure liquid chromatography ultraviolet method.

Results Amiodarone–SBE-BCD in a molar ratio of 1:3 at pH 4.0–5.0 yielded the best results in terms of increased solubility and dissolution time (90 min). With SBE-BCD, a smaller molar ratio to amiodarone was needed than with HP-BCD. The amiodarone content of the final formulation stored 12 months at 21°C in daylight remained unchanged.

Conclusions A ready-to-use or ready-to-administer amiodarone product, prepared in a hospital pharmacy, for intravenous application in an acute clinical setting is a feasible option from a chemical, physical and microbiological point of view. The availability of such a product will have a significant impact on medication safety, and production should therefore be considered.

INTRODUCTION

Amiodarone (as hydrochloride) is administered intravenously in the acute hospital setting to treat severe arrhythmias or arrhythmias with moderate structural disease in cases where other interventions are unsuccessful or contraindicated. In our public hospital (Martini Ziekenhuis, Groningen, the Netherlands), parenteral amiodarone was administered to 131 patients in 2014. The standard therapy consists of a single loading dose of 300 mg (or 5 mg/kg) to control the sinus rhythm, followed by a maintenance dose of 10–20 mg/kg/24 h during the first few days.

Amiodarone is administered to the patient using a syringe pump filled with an appropriate dilution of commercially available amiodarone ampoules. These ampoules, obtained from different manufacturers, contain 3 mL = 150 mg (50 mg/mL) amiodarone. However, the preparation of the maintenance dose of 10–20 mg/kg/24 h from these ampoules is complex. To obtain a syringe with 1200 mg = 50 mL amiodarone, the content of eight

ampoules (24 mL) is added to 26 mL of glucose 5%. The complex nature of the preparation hampers the risk of calculation mistakes and microbial contamination during preparation. This can be a serious obstacle, especially in acute situations where rapid handling is required. Furthermore, hypotension may occur in up to 26% of patients as reported in various clinical studies with intravenous amiodarone.^{1–4} The cause of this serious side effect probably lies in the presence of the excipients polysorbate 80 and benzylalcohol used in the formulation of the ampoules to enhance the solubility of amiodarone.^{5,6} Finally, once the dilution is prepared at the ward, both the chemical and microbiological stability of the product is limited to a maximum of only 24 h.

In 2010, a new amiodarone product, Nexterone, was launched by Baxter for the US market. Nexterone is a ready-to-use, sterile, non-pyrogenic, iso-osmotic solution of 1.5 mg/mL amiodarone in 100 mL and 1.8 mg/mL in 200 mL single-dose containers for intravenous use. In this preparation, the amiodarone is dissolved in a glucose solution using 15 or 18 mg/mL sulfobutylether-beta-cyclodextrin (SBE-BCD) respectively instead of polysorbate 80 and benzylalcohol. Unfortunately, Nexterone is not available for the European market and, to our knowledge, registration in Europe is not planned.

To overcome the serious drawbacks associated with the dilution of polysorbate and benzylalcohol containing amiodarone formulations, we explored the feasibility of manufacturing a long-term stable (preferably at least six months) amiodarone ready-to-use product using cyclodextrins as solubility enhancer, to be used in our hospital in acute care setting.

MATERIALS

Amiodarone HCl (molecular weight (MW) 682 g/mol; in this article, further designated as amiodarone) and SBE-BCD (MW 2163 g/mol; substitution grade 6.7) were obtained from GIHI Chemicals (Zhejiang, China). Hydroxypropyl-beta-cyclodextrin (HP-BCD; MW 1400 g/mol; substitution grade 0.8) was obtained from Aldrich Chemistry (Steinheim, Germany). The identity and purity were controlled by the laboratory of our hospital. Citric acid monohydrate, glucose monohydrate, sodium citrate dihydrate and sodium hydroxide, all European Pharmacopoeia quality, were obtained from Spruyt-Hillen, IJsselstein, the Netherlands. Water for injection was used throughout the study.

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METHODS

Solubility enhancement and preformulation study

The optimal ratio of amiodarone with the two cyclodextrin derivatives, HP-BCD and SBE-BCD, in order to enhance the solubility of amiodarone in water was determined. To a suspension containing 1.8 mg/mL amiodarone, cyclodextrin was added in the following molar ratios of amiodarone to cyclodextrin: 1:0; 1:0.25; 1:0.50; 1:2; 1:2.50; 1:3; 1:3.50; and 1:4. The tests were carried out in closed test tubes in a volume of 10 mL. After thorough mixing, the test tubes were continuously gently shaken at room temperature and observed for 7 days. The time needed for the formation of a clear solution was recorded and samples taken at day 7 were analysed for their amiodarone content.

The combination amiodarone:SBE-BCD in a 1:3 molar ratio was used for further studies including stability testing. First, the effect of pH (4.0, 4.5 and 5.0) on the dissolution rate was studied. Then the dissolution rate was measured at different temperatures: 20°C, 40°C, 60°C, 80°C and 100°C. The mixtures in the test tubes were visually inspected at fixed time intervals and the time required to obtain a clear solution was recorded ($t=0-30$ continuously, $t=60-180$ every 30 min). Subsequently, the effect of steam sterilisation at 121°C for 15 min and of heat treatment at 100°C for 30 min (using a Sanamij/Belimed autoclave) on the stability of the final formulation was investigated. Therefore, the amiodarone content and the occurrence of decomposition products in the final formulation (see table 1) were determined using high-pressure liquid chromatography ultraviolet (HPLC/UV) (see 'Analytical procedure'). The pH was adjusted to 4.0–5.0 and measured before and after sterilisation and heat treatment.

Shelf-life

Stability experiments were performed with the final amiodarone formulation (table 1) upon storage at 21°C and at 4°C in continuous daylight and protected from light in type 1 glass bottles. A small batch of 3000 ml ($n=60$ flasks) was prepared. The amiodarone content, purity and other related substances (including decomposition products) were determined at 0, 1, 3 and 6 months using HPLC/UV. Shelf-life measurements at 12, 18 and 24 months are ongoing.

Analytical procedure

The amiodarone amount in the final product was determined by a validated HPLC-UV method (Waters 600S, Waters 616 Pump). Chromatographic separation was performed on a C18 column (LiChroart 250–4), length 150 mm with isocratic elution (99.5% methanol; 0.3% diethylamine; 0.2% water). The flow was set at 1 mL/min, injection volume was 50 μ L and UV detection of amiodarone at 240 nm by diode array detection (Waters 996 Photodiode Array). Promazine (dissolved in

methanol) was used as an internal standard. Total run time per injection was 10 min. HP-BCD and SBE-BCD did not interfere with the amiodarone absorbance at 240 nm. The amiodarone content in the samples was calculated by using a calibration curve ($R^2=0.999$) obtained with pure amiodarone dissolved in methanol. Samples were reprocessed by diluting 100 μ L of the sample with 100 μ L methanol and 500 μ L of the internal standard (0.5 mg/mL). The sample was centrifuged at 10 800 rpm, and the clear solution was transferred to an HPLC sample vial. Samples were analysed immediately after reprocessing.

Osmolarity was determined at the Clinical Chemistry lab of the Martini Hospital by freezing point depression using an OsmoMat 3000 (Gonotec).

RESULTS

Solubility enhancement and preformulation study

The solubility of amiodarone alone in water was measured to be 0.24 mg/mL (C_0). The water solubility of amiodarone was enhanced by both types of cyclodextrine used (figure 1). With HP-BCD, the required solubility of 1.8 mg/mL amiodarone was reached at an amiodarone to cyclodextrin molar ratio of 1:3 after 3 days. With SBE-BCD, the required solubility was reached after 3 days at a molar ratio of 1:1.5, but with a molar ratio of 1:3 (amiodarone:SBE-BCD), complete dissolution was already achieved after 90 min. The dissolution rate was slightly slower at pH 4.0 compared with pH 4.5 or 5.0. Complete dissolution was reached within approximately 2 h at pH 4.0 compared with 1.5 h at pH 4.5–5.0. Based on these results and on physical-chemical data on amiodarone, the optimal pH range was set at 4.0–5.0 for the solution before heat treatment.

The final formulation consisted of 1.8 mg/mL amiodarone with SBE-BCD in a molar ratio of 1:3 (amiodarone:SBE-BCD) and excipients mentioned under 'Materials'. The complete formulation is given in table 1. The pH was 4.0–5.0, and the solution was iso-osmotic (280–320 mOsmol/kg).

The dissolution rate of amiodarone in the presence of SBE-BCD (molar ratio 1:3) was temperature dependent. The highest dissolution rate occurred at a temperature of 55–60°C, complete dissolution was within 1 h. Higher temperatures did not further increase the dissolution rate, whereas lower temperatures yielded a slower dissolution taking >3 h.

After sterilisation at 121°C during 15 min, 46.7% of the initial amount of amiodarone was decomposed. After heat

Figure 1 Effect of cyclodextrins on the solubility of amiodarone at a fixed concentration of 1.8 mg/mL. Molar ratio of amiodarone and cyclodextrins (water, pH 4.0–5.0) compared with the concentration of amiodarone measured by high pressure liquid chromatography ultraviolet (HPLC-UV). ●=sulfobutylether-beta-cyclodextrin. ▲=hydroxypropyl-beta-cyclodextrin. BCD, β -cyclodextrin.

Table 1 Final formulation of amiodarone aqueous solution stabilised by sulfobutylether-beta-cyclodextrin

Excipient	Amount (mg/mL)
Amiodarone HCl	1.80
Sulfobutylether-beta-cyclodextrin	18.0
Citric acid monohydrate	0.396
Glucose monohydrate	45.54
Sodium citrate dihydrate	0.183
Sodium hydroxide (to adjust pH to 4.0–5.0)	q.s.

q.s., quantum satis.

treatment at 100°C during 30 min, however, no decrease of the amiodarone content was seen. Further, no change in pH was observed due to the sterilisation and heat treatment.

Shelf-life

The amiodarone content of the final formulation remained unchanged during storage up to 6 months at 21°C: 97.6% at $t=0$ (coefficient of variation (CV) 1.20%, $N=2$) versus 101.4% in daylight (CV 0.60%, $N=3$) and 103.8% protected from light at $t=12$ months (CV 0.75%, $N=3$). Figure 2 shows a typical chromatogram of amiodarone standard (a) and amiodarone with its degradation products after forced degradation (b). Osmolarity was within the range of 280–320 mOsmol/kg and did not change during shelf-life. pH remained within the range of 4.0–5.0.

DISCUSSION

The aqueous solubility of amiodarone alone is low and hampers the production of a solution for intravenous use. Different approaches are followed to enhance the water solubility of amiodarone in order to produce an injectable solution of this drug compound. The use of co-solvents is one possibility, but these excipients may elicit adverse effects in patients and render an instable product when diluted to obtain a ready-to-use preparation. When applying the standard dosing regimen of commercially available intravenous amiodarone (10–20 mg/kg/24 h), the exposure to benzyl alcohol during the first 24 h exceeds the WHO maximum tolerated daily intake of 5 mg/kg.⁷ Current formulation-related problems like hypotension^{1–4} and the short

chemical stability of intravenous administration of amiodarone show the urge for a new formulation.

Over the past two decades, cyclodextrins have successfully been applied in various drug dosage forms, including parenterals, among others, to increase water solubility of poorly soluble drug compounds.⁸ Various types of cyclodextrin are used in pharmacy, but only two have been approved by the US Food and Drug Administration for parenteral administration: SBE-BCD and HP-BCD.⁹

The low aqueous solubility we found for amiodarone matches with characterisation of the European Pharmacopoeia as ‘lightly soluble in water’, meaning 0.1–1.0 mg/mL.¹⁰ In our study, SBE-BCD was superior to HP-BCD regarding the dissolution enhancement in terms of molar ratio of amiodarone to cyclodextrin and dissolution rate. Based on this, we selected SBE-BCD for further development. When applying the maximum standard dosing regimen of intravenous amiodarone HCl 20 mg/kg/24 h, the exposure to SBE-BCD is 200 mg/kg/24 h. This does not exceed the WHO maximum tolerated daily intake of 280 mg/kg/24 h.¹¹

With respect to the stability of amiodarone, slightly acidic solutions are preferred; a pH in the range of 4.0–5.0 is optimal. In addition, the aqueous solubility of amiodarone decreases at pH >5.¹² At the applied pH of 4.0–5.0, amiodarone with a pKa value around 6.6¹³ is largely charged (>99% protonated). Cationic drugs have been reported to positively affect the complexation with SBE-BCD by attraction.¹⁴ Dissolution tests showed best results at pH 4.5 and a less acidic solution is preferred in the context of tolerance of the infusion solution. The

Figure 2 (A) Typical chromatogram of amiodarone at a concentration of 1.8 mg/mL. Amiodarone retention time is around 6.3 min. (B) Typical chromatogram of amiodarone at a concentration of 1.8 mg/mL after forced degradation with H₂O₂ at pH 7.0. Degradation products are found around 1.8, 4.0 and 5.1 min. X-axis represents the retention time (minutes), and Y-axis represents the detection signal (aU).

pH of the preparation was therefore set at 4.5 (range 4.0–5.0). Nexterone has a pH of 3.6, which could lead to more irritation during infusion.

The dissolution rate was temperature dependent. Increasing the temperature to 50°C–60°C considerably enhanced the dissolution rate but did not influence the stability of amiodarone. This temperature is favourable for a production process.

Based on the preformulation experiments, we came to the final amiodarone formulation (see table 1). The final formulation was subject to stability studies in order to determine the shelf-life of the product. No deviations from the product characteristics (amount, degradation products, pH, osmolality and appearance) were found during shelf-life at 21°C up to 6 months.

The new formulation offers significant advantages to producing a product in stock, taking into account that a reconstituted solution of the commercially available intravenous preparation has a shelf-life of only 24 h.

It is a disadvantage that amiodarone showed decomposition after sterilisation at 121°C during 15 min. From a microbiological point of view, sterilisation is preferred to heat treatment since it is more effective regarding reduction of microorganisms. However, by reducing the bioburden and applying a rigid microbiological control, heat treatment may substitute sterilisation if the stability of the drug compound requires so. The sterility of the final product was tested, which confirmed that the aseptic preparation method with subsequent heat treatment was sufficient to guarantee the microbiological quality. After 30 min exposure to 100°C, no decomposition of amiodarone occurred. Amiodarone as such in aqueous environment shows rapid hydrolysis: 5% after 1 h, 14% after 4 h and 69% after 3 days¹². The fact that an aqueous solution of amiodarone with SBE-BCD as a solubiliser remained stable to both elevated temperatures and longer-term storage can most probably be ascribed to protection of the amiodarone by complexation.

Based on microbiological and chemical data, the current shelf-life of our product is 6 months. We expect no limitations in microbiological quality during long-term storage. From a chemical point of view, the production of amiodarone with SBE-BCD is judged feasible. The feasibility of an amiodarone ready-to-use product also depends on the price and availability of the main excipients and physical–chemical aspects like long-term stability. We experienced that it was difficult to obtain amiodarone as well as SBE-BCD of European Pharmacopoeia quality. Moreover, the active ingredient and excipients were relatively expensive.

Several studies showed that medication errors in the preparation and/or administration occur frequently when preparing parenterals.^{15–18} Also, microbiological contamination is frequently observed when parenterals are prepared at the ward.¹⁹ It is plausible that a ready-to-use amiodarone product increases the quality of drug administration, reduces medication errors and thus improves the medication safety. This is an important step forward in pharmaceutical patient care. A ready-to-use amiodarone preparation would be more expensive than the commercially available amiodarone product. On the other hand, this product would be time saving since preparation operations at the ward are minimised.

The maximum concentration we prepared was nearly 1.8 mg/mL amiodarone when adding SBE-BCD in a 1:3 molar ratio. Ideally, the final concentration of a ready-to-use product would be 12 mg/mL in 100 mL or 4.8 mg/mL in 250 mL because the maximum intravenous maintenance dose of amiodarone is 1200 mg/24 h. A disadvantage of this is the necessity

to administer amiodarone through a central vein at concentrations >2 mg/mL because it may cause peripheral phlebitis.⁶ In further studies, we will explore the possibilities of a higher amiodarone concentration in the presence of the minimal possible amount of SBE-BCD and other co-solvents.

CONCLUSION AND PERSPECTIVE

A ready-to-use or ready-to-administer amiodarone product for intravenous administration in the acute clinical setting is a feasible option from a chemical, physical and microbiological point of view. The product, with an amiodarone concentration of 1.8 mg/mL, is based on the use of SBE-BCD to increase the water solubility of amiodarone. A higher concentration of amiodarone would render a further improvement. A concentration of 4.8–12 mg/mL is aimed at, depending on the final volume of the product. Based on the current feasibility study, research into that direction is in progress. It should be realised, however, that since the supply of amiodarone and SBE-BCD is not guaranteed within the EU, it is yet uncertain whether continuous supply to the hospital ward can be assured. As soon as these problems are solved, routine manufacturing of amiodarone in our hospital will be considered. A ready-to-administer amiodarone will have a great impact on medication safety, and production should therefore be considered.

Key messages

What is already known on this subject

- ▶ The dilution of polysorbate and benzylalcohol containing commercially available amiodarone formulations for use in a syringe pump is a complex preparation, and dilution is associated with a limited chemical stability.
- ▶ Hypotension may occur in up to 26% of patients as reported in various clinical studies with intravenous amiodarone, the side effect probably caused by the excipients polysorbate 80 and benzylalcohol.
- ▶ There is a need for a long-term stable, ready-to-use formulation of amiodarone available in Europe.

What this study adds

- ▶ Amiodarone can be prepared as a long-term stable (12 months), ready-to-use product using cyclodextrins as solubility enhancer.
- ▶ A ready-to-administer amiodarone will have a great impact on medication safety, and production should therefore be considered.

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