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Short Communication

ADRENALINE AMPOULES QUALITY ASSESSMENT–THE ISRAELI EXPERIENCE

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ABSTRACT

Objective: To characterize the differences in stability of L-adrenaline in adrenaline ampoules from different manufacturers that are used by the Israel Defense Forces (IDF).

Methods: Adrenaline ampoules from three different vendors (Products A, B and C; 52, 13, and 19 batches, respectively) were purchased by the IDF and were stored under the recommended storage conditions (room temperature) for different time periods. The content of L-adrenaline in these samples was determined using a chiral high-performance liquid chromatography (HPLC) assay with UV detection.

Results: The three analyzed drug products showed very dissimilar patterns of L-adrenaline degradation. The content of L-adrenaline in Product C was variable and declined below the 85% threshold much earlier than at the end of the 24-months storage period. Products A and B had less variable content of L-adrenaline and were more stable.

Conclusion: L-adrenaline is prone to degradation in solution. Its content in adrenaline ampoules from certain vendors can decline rapidly, below the stipulated threshold, and compromise their clinical effectiveness (e. g., during resuscitation). Stability of adrenaline ampoules from individual vendors should be analyzed at different storage conditions, using a chiral HPLC-based assay, to define the shelf-life period that can differ substantially between the vendors.

Keywords: Adrenaline ampoules, Stability, Shelf-life, Chiral HPLC-based assay

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Adrenaline (Epinephrine) is used to treat a number of conditions including anaphylaxis, cardiac arrest, and superficial bleeding. Adrenaline is a chiral compound, and only the L-isomer has significant pharmacological activity and is incorporated as an active component into adrenaline formulations [1, 2]. L-adrenaline is available in a form of aqueous solution filled into ampoules (used mainly by the health care professionals) or auto injectors (for self-injection by the patients).

L-adrenaline is relatively unstable in aqueous solutions and degrades via a number of pathways, including oxidation, racemization (to D-adrenaline) and reaction with the inactive formulation ingredients (e. g., bisulfite) [3-7]. These chemical reactions and pathways have been investigated thoroughly over the past decades. Different methods have been suggested to improve the drug's chemical stability, such as maintaining acidic pH, storage at low temperature, protection from light and use of antioxidants other than bisulfite [5, 8-11].

During the process of registration of a new drug product, the pharmaceutical company is required to investigate and report its chemical stability to the national regulator. The active compound in these stability studies can be quantified using the manufacturer's in-house analytical method, or a method adopted from the relevant Pharmacopoeia: the United States, British or European Pharmacopoeia (USP/BP/EP), depending on the geographic region of marketing. Prior to 2018, all these Pharmacopeias did not require separate quantification of adrenaline enantiomers in the drug products, despite the availability of several stereo-selective analytical methods [2, 4, 12-14]. Since 2018, the BP requires a separate quantification of L-adrenaline (that should be>85% of the labeled amount in the injectable adrenaline drug products) [15], using a chiral High Performance Liquid Chromatography (HPLC) method that is similar to the method used in our laboratory for more than 20 y [14], in addition to the old non-chiral HPLC assay [15]. USP has not yet updated the monograph of adrenaline/epinephrine [16] to allow quantification of the individual enantiomers.

Based on the above-mentioned Pharmacopoeial requirements, adrenaline injections from majority of manufacturers were approved based on the total content of adrenaline enantiomers, without quantification of L-adrenaline initial content and its change during the storage period. Therefore, the quality and efficacy of adrenaline injections from different vendors can be compromised, especially towards the end of their shelf-life, if a substantial amount of L-adrenaline undergoes racemization to the D-enantiomer.

The Israel Defense Forces (IDF) use adrenaline ampules for administration by the Advance Life Support (ALS) providers, in the clinics and in pre-hospital field conditions. Adrenaline ampoules, and additional drug products that are stored and used at the uncontrolled field conditions, are subjected to a dedicated stability surveillance program. Until 2016, the IDF have purchased adrenaline ampoules from a single local manufacturer (A). These ampoules were made of amber glass, filled under inert gas, and contained 1 mg/ml L-adrenaline in aqueous solution with acidic pH and sodium metabisulfite, that served as an antioxidant preservative. This Product's shelf-life period has been altered several times over the years, reflecting the comprehension of L-adrenaline degradation kinetics and the assays that were used for its assessment. After cessation of manufacture of Product A, adrenaline ampoules were purchased from 2 different European manufacturers (B and C). This report describes significant differences in the stability of L-adrenaline in these three Products. It focuses on the content of L-adrenaline only, which is a single indicator of the clinical effectiveness of the studied samples.

The following materials were used: L-adrenaline bitartrate and potassium chloride were from Sigma (St. Louis, MO). Glacial acetic acid and HPLC-grade acetonitrile were from J. T. Baker (Deventer, Holland). Water was purified with a tandem RiOs (reverse osmosis)/Milli-Q Gradient A-10 system (Millipore, Molsheim, France). All other chemicals used in this study were of analytical or HPLC grade.

The HPLC method was based on a chiral Shodex ODS 5 mm column, 150x4.6 mm (Showa Denko K. K., Tokyo, Japan) and HP1100

chromatographic system (Hewlett Packard, Palo Alto, CA) interfaced to an HP Chem Station [14]. The mobile phase was 0.2 M potassium chloride in water: 0.2 M potassium chloride and 0.4% (v/v) acetic acid in water: acetonitrile (96:1:3, v/v). The samples were diluted 1:20 in the mobile phase, and 50 µL of these diluted samples were injected. The column temperature was 10 °C, the flow rate was 0.7 ml/min, the run time was 20 min, and the detection wavelength was 280 nm. This method undergo a thorough validation in our laboratory [14], and the limit of detection and limit of quantitation values for L-adrenaline were 0.11 µg/ml and 0.36 µg/ml, respectively.

In this study, we analyzed 52, 13, and 19 individual batches of Products A, B and C. These batches were purchased by the IDF, and stored under the recommended storage conditions (room temperature). Majority of these batches were stored beyond their shelf-life and were analyzed more than once during their storage period, as required by the IDF drugs' stability surveillance program. Data from the most recent set of assays are shown in fig. 1.

The shelf-life of Products B and C is 24 mo, as defined by the manufacturer. The shelf-life of Product A has been changed several times, from 2 y (before 2006) to 6 mo (from 2006, for several years), and to 18 mo (during the last years of its production, until end of manufacture in 2016). In the years 1997-2016, the Product A was produced for the IDF with enhanced content of the active compound (103-115% of the stipulated content of L-adrenaline). This manufacturing change prolonged the period of L-adrenaline content above 85% of the stipulated strength (i.e., 0.85 mg/ml), which was set as a threshold for a shelf-life of this drug product in the IDF.

Product A maintained stability for 24 mo, but not longer, and was characterized by apparently small inter-batch variability of L-adrenaline content, during the drug product shelf-life and beyond it.

Product B showed a remarkably stable content of L-adrenaline, which remained well above 85% of the stipulated content even after 24 mo of storage, as well as small inter-batch variability of L-adrenaline content, similar to that of Product A. A relatively small number of batches of this drug product were evaluated in our laboratory, and data from additional batches are needed to verify this trend.

L-adrenaline in Product C apparently undergo rapid degradation during storage. The L-adrenaline content in Product C declined below 90% and below 85% (which were set as the shelf-life thresholds for this drug product by the manufacturer and the IDF, respectively) much earlier than at the end of the 24-months storage period. We found large variability in the drug content between the individual batches of Product C, with 45% and 98% out-of-trend results after 8.5 and 50 mo, of storage, respectively. This finding indicates a lack of reproducibility in the manufacturing process of this drug product or/and non-uniform drug degradation rate in the individual batches.

Three drug products of adrenaline ampoules that were studied in our laboratory showed very dissimilar patterns of L-adrenaline degradation. The degradation kinetics of Product A matches the previously published data [14], and is coherent with the manufacturer's stability data upon which the 24 mo shelf-life at the room temperature has been set. Product B appears to be more stable, and has slower degradation kinetics, as compared to Product A, but has the same 24-months-long declared shelf-life.

The content of the pharmacologically-active L-adrenaline isomer in Product C declined rapidly during its storage at the recommended conditions, potentially leading to compromised efficacy and clinical effectiveness of this drug product, especially at the second half of its stipulated storage period. This problem is apparently aggravated in the pre-hospital ALS settings when the drug product can be exposed to the non-recommended storage conditions (e. g., extremes of temperature). Products A and B are more stable and thus preferable for ALS use in different settings.

The reason for the differences in the drug degradation kinetics between the studied products is not known. Apparently, it does not originate from the differences in the pH, exposure to light, or compromised sealing (all the studied drug products comprise amber glass ampules, filled with inert gas, and maintain steady pH during their storage; data not shown). It may be related to the inactive components of the studied formulations, or even trace concentrations of elements diffusing from glass containers and triggering the degradation of adrenaline [7, 17]. Further investigation is needed to reveal the factors that govern the degradation pathways of L-adrenaline in the studied drug products and to identify the most stable formulation of this drug. This investigation would benefit from adoption of uniform standards of L-adrenaline injections quality control, by all the Pharmacopeias and manufacturers, based on a chiral method for separate quantitation of the active L-adrenaline isomer, and of the D-adrenaline degradation product.

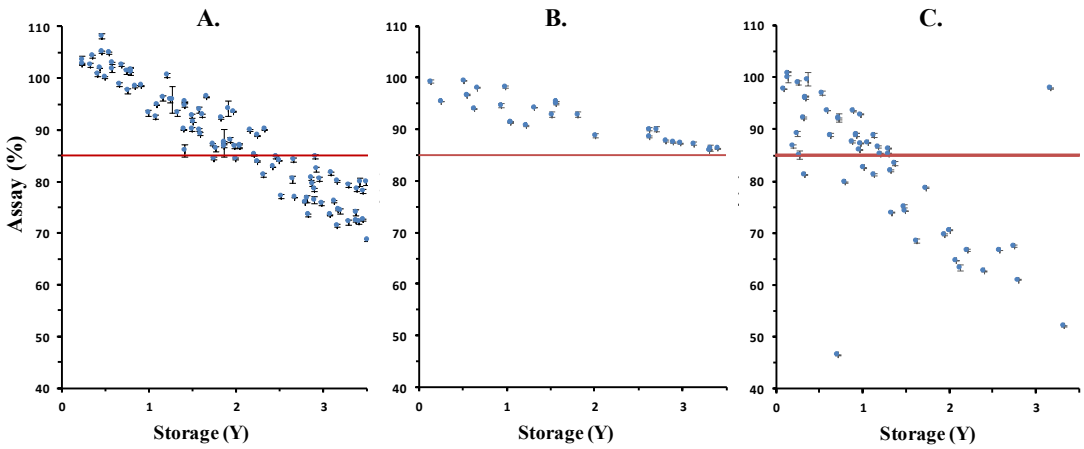

Fig. 1: The content of the L-adrenaline in the individual batches of products A, B and C. A. Product A (Israeli vendor, manufacture discontinued in 2016). B. Product B (European vendor, procurement started in 2017). C. Product C (European vendor, procurement started in 2017). The dots are the individual assayed batches. The red line represents the threshold for a shelf-life of this drug product in the IDF (L-adrenaline content above 85% of the stipulated amount). The same limit is set by the BP from 2018.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

All the authors of this manuscript declared no conflict of interest.

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