

Long-term stability of an aqueous solution containing lidocaine hydrochloride, dexamethasone sodium phosphate and adrenaline hydrochloride for electromotive administration

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ABSTRACT

Study objectives: In the Urology Department of the State Hospital of Baden, females with non-infectious chronic cystitis are treated with electromotive drug administration of lidocaine hydrochloride (20 mg/mL), dexamethasone sodium phosphate (0.2 mg/mL) and adrenaline hydrochloride (0.01 mg/mL). The aim of this study was to investigate the long-term stability of the solution administered.

Methods: The solution investigated was stored at three different temperatures (-20°C, 4°C and 20°C). Concentrations were measured by high-performance liquid chromatography (HPLC) on day 0 (baseline), 7, 14, 21, 28 and after two, three and six months. Lidocaine was analysed according to the chromatographic system described in the *United States Pharmacopeia (USP)* [1]. The analysis of dexamethasone was performed by the same chromatographic system as for lidocaine. Adrenaline was analysed separately, also according to the *USP*, but with a modified mobile phase. Validation of the methods was performed regarding the reproducibility, the linearity and the selectivity.

Results: Lidocaine was stable during the study period of six months at all three temperature conditions (98%-99%). The degradation of dexamethasone did not exceed 5%; the content after six months was 98% at both -20°C and 4°C, and 95% at 20°C. The concentration of adrenaline was constant at -20°C; at 4°C it was stable for three months (100%, expressed as a percentage of the initial dose) and declined to 94% after six months.

Conclusion: The aqueous solution of lidocaine, dexamethasone and adrenaline is stable for six months at -20°C and for three months at 4°C.

KEYWORDS

Adrenaline, dexamethasone, electromotive administration, HPLC, lidocaine, long-term stability

INTRODUCTION

Electromotive drug administration (EMDA), which is also known as iontophoresis, involves the active transport of ionised drugs into the deeper bladder layers by the application of an electric current.

The treatment of female patients suffering from non-infectious chronic cystitis (NICC) with EMDA of lidocaine and dexamethasone, followed by hydrodistension of the bladder is reported to be convenient and well tolerated [2-4]. Other studies have shown the effectiveness of lidocaine with adrenaline [5], and of either lidocaine [6] or dexamethasone [7] as the sole active agent. Intravesical EMDA in NICC patients is effective and safe. The therapeutic concept combines the advantages of increased drug administration without systemic side effects [2-7].

In the Urology Department of the State Hospital of Baden, females with NICC are treated with EMDA of lidocaine, dexamethasone and adrenaline. Limited information is available about the long-term stability and compatibility of these three compounds. Therefore, the solution needs to be mixed just before administration and under aseptic conditions by the pharmacy staff. Large scale preparation helps to optimise deployment of personnel and minimise time spent on vial production;

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the stability of the solution allows enhancement of the supply inventory.

The aim of this study was to investigate the long-term stability of lidocaine hydrochloride (20 mg/mL), dexamethasone sodium phosphate (0.2 mg/mL) and adrenaline hydrochloride (0.01 mg/mL), in aqueous solution at three different temperatures.

MATERIALS AND METHODS

Solution preparation and storage

The solution to be investigated was prepared with lidocaine hydrochloride (PhEur, Hänseler AG, Herisau, Switzerland, batch number: 2004.06.0792, expiry date: 08/2008), dexamethasone sodium phosphate (Mephameson injection solution 50 mg/3 mL, Mepha Pharma AG, Aesch, Switzerland, batch number: 0370006, expiry date: 02/2006) and adrenaline hydrochloride (Adrenalin Sintetica injection solution 1 mg/mL, Sintetica SA, Mendrisio, Switzerland, batch number: 04070, expiry date: 04/2006). The solution was divided between 32 brown glass 20 mL vials and eight white glass 20 mL vials; all the vials were of type II glass quality. Eight brown glass vials were stored at three different temperatures (-20°C, 4°C and 20°C) each. In addition, the solution was exposed to stress conditions (eight brown glass vials at 40°C and eight white glass vials at daylight and 20°C).

Standard solutions

The standard solutions were prepared with working standards: lidocaine hydrochloride (PhEur, Hänseler AG, Herisau, Switzerland), dexamethasone sodium phosphate (Ciba Vision Ltd, Hettlingen, Switzerland, batch number: 0846299, expiry date: no expiry data available) and both the laevo- and dextro-enantiomers of adrenaline hydrochloride (Sigma-Aldrich Chemie GmbH, Buchs, Switzerland, batch number: 123K1187, expiry date: 04/2006). The concentrations of these working standards were specified by the corresponding reference substances (Chemical Reference Standard, European Directorate for the Quality of Medicines & HealthCare, Strasbourg, France; lidocaine hydrochloride: batch number 1; dexamethasone sodium phosphate: batch number: 3; adrenaline: batch number: 1; no expiry dates available). In the following text, the three drugs under investigation will be referred to as lidocaine, dexamethasone and adrenaline.

Analytical methods and chromatographic conditions

The lidocaine content was determined according to the chromatographic system described in the *USP* [1]. The analysis of dexamethasone was performed with the same chromatographic system as for lidocaine, in the same chromatogram. Although this is not the *USP* method

for the determination of dexamethasone, the validation showed that the same system could be used for both drugs.

The eluent used in the analysis of lidocaine and dexamethasone was prepared with four volumes of methanol to six volumes of an aqueous solution—the sodium salt of 1-octane sulphonic acid at ten times the usual concentration, the disodium salt of ethylenediamine-tetraacetic acid dehydrate, sodium dihydrogen phosphate, ortho-phosphoric acid, 85% and freshly demineralised water.

Adrenaline was analysed separately, according to the chromatographic system described in the *USP* [1], but with a modified eluent that was prepared with one volume acetonitrile to four volumes of an aqueous solution (glacial acetic acid, sodium hydroxide 1 mol/L and demineralised water) with a pH of 3.4.

The chromatographic apparatus and the conditions of the HPLC methods were as follows: the HPLC system (Metrohm 2250, Metrohm AG, Herisau, Switzerland) was used with a pump (model Z 1010, Bischoff GmbH) and an ultra violet/visible (UV-VIS) detector (Lambda 1010, Bischoff GmbH) and a data acquisition and processing module (Metrohm IC Net, version 2.3, Metrohm AG). Symmetry columns were C8 (adrenaline) and C18 (lidocaine hydrochloride and dexamethasone sodium phosphate), both, size 4.6 × 250 mm and particle size 5.0 µm (Waters Associates, Baden-Dättwil, Switzerland).

For lidocaine and dexamethasone, the flow rate was 1.5 mL per minute, with a column temperature of 25°C ± 1.0°C and ultraviolet detection at 254 nm. For adrenaline, the flow rate was 1.0 mL per minute, with a column at room temperature and ultraviolet detection at 280 nm. The calculation of the area under the curve was carried out automatically by intrapolation (Metrohm IC Net, version 2.3, Metrohm AG).

Validation of the analytical methods

Validation of the methods was performed regarding reproducibility, linearity and selectivity. Furthermore, the stability-indicating ability of the test was examined.

Reproducibility

The within-day relative standard deviation was determined by measuring each drug eight times at the concentrations investigated. Each measurement was performed in the presence of all three compounds.

Linearity

Linearity was evaluated by serial dilutions with demineralised water to 50%, 80%, 100%, 120% and 150% relative to the concentrations investigated. Each measurement was performed in the presence of all three compounds. The correlation coefficients were calculated by linear regression analysis of the peak area.

Selectivity

The selectivity of each compound was tested in the presence of the other agents including the adjuvant substances in Mephameson injection solution (sodium chloride, propylene glycol and ethylenediamine-tetraacetic acid disodium salt dehydrate). The adjuvant substances were added to the standard solutions resulting in the following concentrations: 0.01 mg/mL sodium chloride, 1.2 µl/mL propylene glycol and 0.01 mg/mL ethylenediamine-tetraacetic acid disodium salt dihydrate. In order to test the assay as a concomitant indicator of the stability of the drugs, they were stressed at 40°C for six months.

Stability study

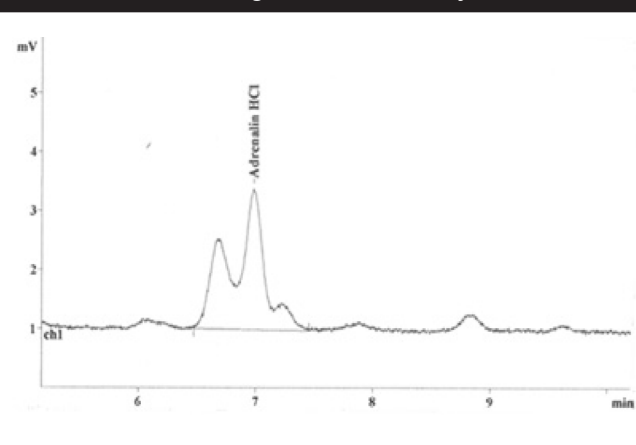
Concentrations were measured by HPLC on day 0 (baseline), 7, 14, 21, 28 and after two, three and six months. Solutions were measured under stress conditions only during the first month. Each solution was prepared and measured twice. Data were expressed as mean values of the percentage of the initial dose.

RESULTS AND DISCUSSION

Validation of the analytical methods

The results of the validation are shown in Table 1. Figure 1 shows the chromatogram of adrenaline hydrochloride and its decomposition products after 28 days at 40°C.

Figure 1: Chromatogram of adrenaline hydrochloride and decomposition products at 280 nm after stress testing at 40°C for 28 days



Adrenaline hydrochloride peak: retention time 6.99 minutes, area under the curve 47 mV × sec

Stability study

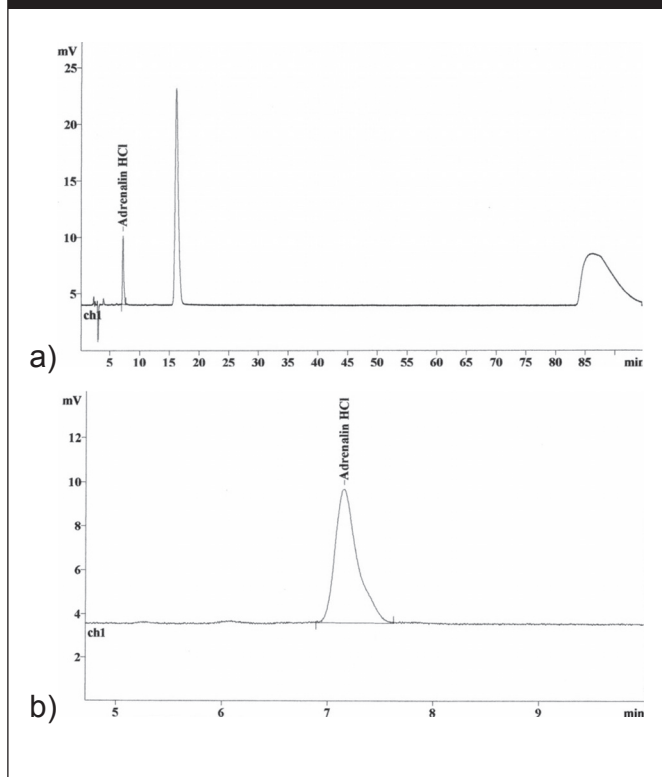
The retention time for lidocaine hydrochloride was four minutes and the area under the curve (AUC) ~2,200 mV × sec; dexamethasone showed a retention time of 22 minutes (AUC ~300 mV × sec). The retention time for adrenaline was approximately seven minutes, the AUC of the initial dose was represented by about 88 mV × sec (Figure 2).

Lidocaine was stable for the whole study period of six months under all three conditions (98-99%), even under stress conditions (97-98% after six months). Aqueous solutions of lidocaine are reported to be stable to heat, acids

Table 1: Results of the validation of the analytical methods: reproducibility (within-day, n = 8), linearity and selectivity

	Lidocaine hydrochloride	Dexamethasone sodium phosphate	Adrenaline hydrochloride
Reproducibility (area under the curve, standard deviation, relative standard deviation)	2,216.15 ± 7.02 (0.3%)	280.60 ± 6.50 (2.3%)	83.05 ± 0.62 (0.8%)
Linearity (correlation coefficient, r ²)	0.9988	0.9996	0.9996
Selectivity	The peak areas of the agents alone and together with the added substances, respectively, were identical for all three agents. No visible peaks at the corresponding retention times of the three drugs were detected on eluting the adjuvant substances alone.		
Stability-indicating test (at 40°C) (percentage of integer substance)	After six months: 97.6%; no visible decomposition products in the chromatogram at 254 nm	After six months: 58.0%; no visible decomposition products in the chromatogram at 254 nm	After 28 days: 28.7%; chromatogram showing decomposition products at 280 nm (Figure 1)

Figure 2: Chromatogram of a) adrenaline hydrochloride, lidocaine hydrochloride and dexamethasone sodium phosphate at 280 nm and b) adrenaline hydrochloride alone at 280 nm



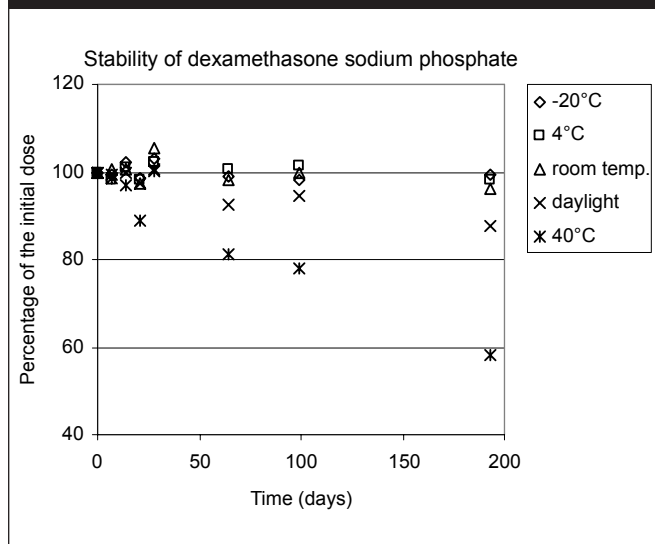
Adrenaline hydrochloride peak: retention time 7.12 minutes, area under the curve 88 mV × sec

and alkalis. Furthermore, the compatibility of lidocaine 2 mg/mL and dexamethasone 4 µg/mL was already proven. However, the time period of the stability analysis was not stated by Trissel [8].

The degradation of dexamethasone did not exceed more than 5%. The concentration after six months was 98%, both at -20°C and 4°C and 95% at 20°C (Figure 3). According to Trissel [8], the concentrated solutions (4 mg/mL and 24 mg/mL) should be protected from light and from freezing. Diluted solutions (0.2 mg/mL) were found to be stable at 4°C for 30 days followed by two days at 23°C [8].

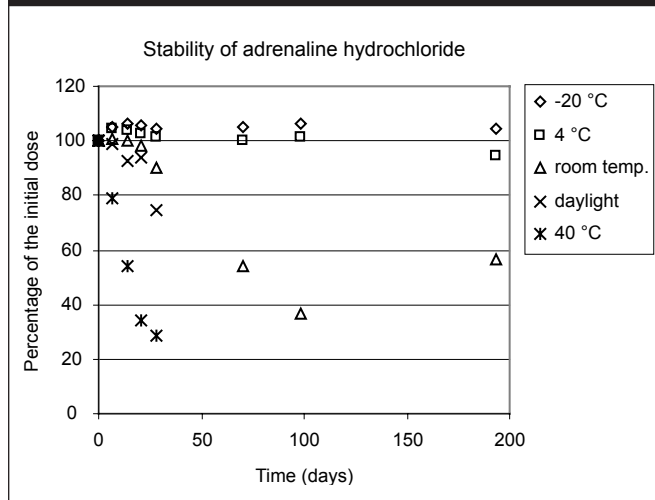
The concentration of adrenaline was constant at -20°C (Figure 4). At 4°C it was stable for three months (100%, expressed as a percentage of the initial content) and declined to 94% after six months. Faster degradation occurred at 20°C (98% after 21 days, 90% after 28 days

Figure 3: Stability of dexamethasone sodium phosphate at 0.2 mg/mL in aqueous solution with adrenaline hydrochloride (0.01 mg/mL) and lidocaine hydrochloride (20 mg/mL)



and 56% after six months) and under stress conditions (daylight or 40°C). It is possible that gassing of the vials with nitrogen would have resulted in a longer duration of stability, because adrenaline is sensitive to light and air [8]. The pH of the investigated solution was 5.7. Adjustment to the optimum pH for adrenaline (3-4) [8] could induce even longer stability.

Figure 4: Stability of adrenaline hydrochloride at 0.01 mg/mL in aqueous solution with lidocaine hydrochloride (20 mg/mL) and dexamethasone sodium phosphate (0.2 mg/mL)



Limitation

Because each solution was prepared and measured twice, we were able to calculate means, but without confidence intervals.

CONCLUSION

The aqueous solution of lidocaine hydrochloride (20 mg/mL), dexamethasone sodium phosphate (0.2 mg/mL) and adrenaline hydrochloride (0.01 mg/mL) is stable for six months at -20°C and for three months at 4°C.

This study shows that the solution does not have to be constituted just before administration, but can be made on a large scale according to the needs of the clinic, thus allowing for savings in time and economies in human resources.

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