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Stability of piritramide in patient-controlled analgesia (PCA) solutions

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For patient controlled analgesia, syringes with solutions of 1.5 mg/ml piritramide in 0.9% aqueous sodium chloride are used. The physical and chemical stability for dilutions of the commercially available preparation of piritramide is limited up to 72 hours by the manufacturer. Since application duration for patient-controlled analgesia can exceed that limited time, stability was investigated by HPLC. Our results show that these solutions are chemically stable over a time period of 60 days.

1. Introduction

In addition to the normal intravenous application of opioids, patient-controlled analgesia (PCA) is part of the clinical management of postoperative pain. Due to good clinical experience, especially the lower risk of adverse effects and the high potency, morphine and piritramide are commonly used for PCA (Freye 2001). The standard intravenous dose of piritramide is 0.1 mg/kg body weight (Fachinformation 2000). In PCA solutions of 1.5 mg/ml piritramide in 0.9% aqueous sodium chloride are used at the hospital of the University of Jena. As primary packaging material Perfusor®-Syringes, B. Braun Melsungen AG are used routinely. To obtain the commonly used concentration the commercially available preparation need to be diluted. The physical and chemical stability for dilutions of piritramide in 0.9% aqueous sodium chloride is limited up to 72 h by the producer (Fachinformation 2000). Since storage and application duration can exceed the limited time interval this point needs to be addressed. Therefore, this study evaluated the stability of piritramide infusion in syringes.

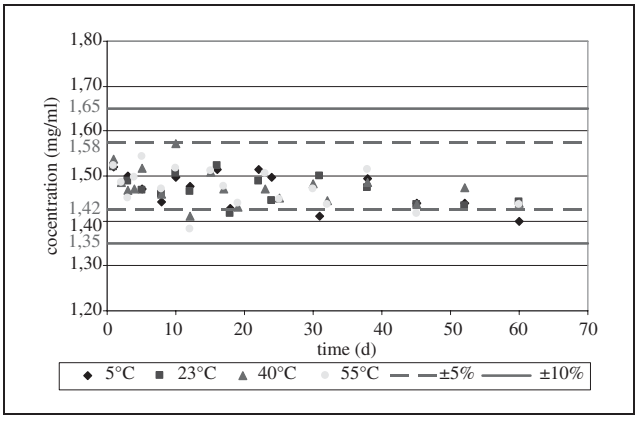

Fig.: Concentrations of a solution of 1.5 mg/ml piritramide in aqueous sodium chloride solution over a time period of 60 days; primary packaging material syringe

2. Investigations and results

The containers were incubated at 5 °C, room temperature, 40 °C and 55 °C over a time period of 60 days. Samples were withdrawn at selected intervals and stored at −20 °C until analyzed by HPLC. The concentration measured on day one was 1.51 mg/ml and the pH was 3.94.
The concentration of samples stored in syringe slightly decreased during the maintained period (Fig.) independent of the storage conditions. However the concentration of piritramide remained over the 90 percent level, demanded by the APV guidelines (APV 1985). It was therefore concluded that the preparations are chemically stable for at least 60 days.

3. Experimental

The test solution was prepared using the commercially available preparation, Dipidolor® ampoule, Janssen-Cilag GmbH, piritramide 15 mg/2 ml. For packaging, a Perfusor®-Syringe, B. Braun Melsungen AG were used. To achieve equal concentrations in each syringe the test solution was prepared by adding 560 ml drug solution and 2240 ml 0.9% aqueous sodium chloride, Fresenius Kabi GmbH, to an empty 3 l infusion bag and mixed thoroughly. Each syringe was filled with 25 ml test solution. The concentration in each syringe was 1.5 mg/ml. After preparation, samples of contents of all syringes were withdrawn and analyzed. The mean represents the concentration of the preparation day, shown as day one.
The syringes were incubated at 5 °C, room temperature, 40 °C and 55 °C over a time period of 60 days. Samples were withdrawn at selected intervals and stored at −20 °C until analyzed. Before analyzing the samples were thawed and vortexed. Pipamperon solution 250 µl was added as internal standard to 500 µl aliquot and mixed thoroughly. The final concentration of pipamperone was 0.1 mg/ml. The concentration of the samples was obtained by HPLC.
HPLC was performed on a Dionex instrument equipped an ASI-100 auto sampler and a 170S UV-VIS detector set

Table: Intra-day precision and inter-day precision of piritramide vs. the internal standard pipamperone of the LC assay

	c (mg/ml)	s (mg/ml)	RSD (%)
intra-day precision	1.015	0.0035	0.35
inter-day precision	1.042	0.0017	0.17

at 258 nm. For data acquisition Chromeleon™, version 6.20 (Dionex) was used. Analytes were separated on a C-18 reverse phase column Acclaim™, 250 × 4.6 mm; 5 μm (Dionex, Idstein, Germany). The mobile phase was a mixture of 50% acetonitrile/50% phosphate buffer (0.05 M; pH 4.5). The flow rate was set at 0.8 ml/min. UV detection was performed at 258 nm. Quantitation of the analytes was based on the peak area ratio method. All analyses were performed at room temperature.

The method was validated with respect to linearity, range, limit of quantitation (LOQ) and limit of detection (LOD) as well as precision. The terms are used according to the definition of the ICH guideline Q2B (Guidance for Industry 2006). Piritramide was calibrated in the concentration range 0.1–1.2 mg/ml. Calibration curve was constructed from seven different concentrations. Each concentration was prepared in triplicate. Linear relationship with a regression coefficient of 0.9948 was obtained. The lowest concentration with a signal/noise ratio of 1 : 10 was assayed at 37.5 μg/ml. This is shown as the LOD for this assay. The LOQ defined as a signal/noise ratio of 1 : 3 was 125 μg/ml. By analyzing a solution of approximately 1 mg/ml on seven independent series on the same day and on seven consecutive days obtained the repeatability and intermediate precision of this method. The obtained data is listed in the Table.

The data shows that this method is selective and sensitive and therefore suitable for analyzing piritramide in aqueous solution.

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