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Original Contribution

Stability of suxamethonium in pharmaceutical solution for injection by validated stability-indicating chromatographic method☆

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Abstract

Study objective: To assess the stability of pharmaceutical suxamethonium (succinylcholine) solution for injection by validated stability-indicating chromatographic method in vials stored at room temperature.

Methods: The chromatographic assay was achieved by using a detector wavelength set at 218 nm, a C18 column, and an isocratic mobile phase (100% of water) at a flow rate of 0.6 mL/min for 5 minutes. The method was validated according to the International Conference on Harmonization guidelines with respect to the stability-indicating capacity of the method including linearity, limits of detection and quantitation, precision, accuracy, system suitability, robustness, and forced degradations.

Results: Linearity was achieved in the concentration range of 5 to 40 mg/mL with a correlation coefficient higher than 0.999. The limits of detection and quantification were 0.8 and 0.9 mg/mL, respectively. The percentage relative standard deviation for intraday (1.3-1.7) and interday (0.1-2.0) precision was found to be less than 2.1%. Accuracy was assessed by the recovery test of suxamethonium from solution for injection (99.5%-101.2%).

Conclusion: Storage of suxamethonium solution for injection vials at ambient temperature (22°C-26°C) for 17 days demonstrated that at least 95% of original suxamethonium concentration remained stable.

1. Introduction

Suxamethonium, also called *succinylcholine*, is a short-acting depolarizing skeletal muscle agent chemically designated as trimethyl-[2-[4-oxo-4-[2-(trimethylazaniumyl) ethoxy]butanoyl]oxyethyl]azanium. Suxamethonium is clinically used to facilitate endotracheal intubation and mechanical

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ventilation and in a wide range of other surgical, obstetric, and diagnostic procedures [1-6]. Its short duration of action is due to rapid hydrolysis by the endogenous plasma enzyme butyrylcholinesterase forming choline and succinic acid products. In a small subset of patients, genetic butyrylcholinesterase polymorphisms prolonged neuromuscular paralysis and risk of apnea, raising morbidity and mortality [7-11]. In an 8-year French survey of anaphylactic reactions during anesthesia, the greater risk was observed with neuromuscular blocking drugs (58%), and suxamethonium has been the most frequently incriminated (33.4%) [12]. Risk factors associated with allergic reactions to suxamethonium are however not clearly established. The French National Agency of Drug Safety and Health Products (ANSM) recommended in 2012 the use of suxamethonium solution that has only been stored between 2°C and 8°C, speculating a possible role of degradation products in the anaphylactic risk [13]. ANSM recommends to destroy any vial stored for 24 hours at ambient temperature. Some studies demonstrated the chemical stability of suxamethonium solutions (50 mg/mL) stored at room temperature for up to 7 days to several months without considerable loss of potency [14-16]. At 40°C, a study showed that suxamethonium concentrations fell below the acceptable limit of 90% within 63 days with the presence of a new peak, probably corresponding to the degradation product of hydrolysis, succinic acid [17]. Therefore, manufacturers gave 14 days of suxamethonium stability at room temperature [18,19]. Because of the significant discrepancies of these data, we revaluated suxamethonium solution stability and effects of storage with a new stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method. Indeed, literature survey shows that the reported HPLC suxamethonium assays are validated in biological tissues and fluids by methods using electrochemical, fluorescence, or mass spectrometry detection [20-23]. We developed the RP-HPLC according to the International Conference on Harmonization (ICH) for stability-indicating studies [24].

2. Material and methods

Suxamethonium chloride powder was supplied by Sigma-Aldrich (Lyon, France, lot 2585833). The pharmaceutical dosage form (suxamethonium chloride 50-mg/mL solution for injection vial) was purchased from Biocodex laboratory (Gentilly, France). Deionized water was purchased from Fresenius (Versylene; Sèvres, France).

2.1. HPLC instrumentation and conditions

The HPLC system, Dionex Ultimate 3000 (Thermo Scientific, USA), consisted of an integrated solvent and degasser (SRD-3200), an analytical pump (HPG-3200SD), a thermostated sampler (WPS-3000TSL), a thermostated column compartment (TCC-3000SD), and a multiple wavelength detector (MWD-3000). Data acquisition was carried out using Chromeleon software 6.80 SP2. The eluent was monitored at 218 nm. Chromatographic separation was achieved at room temperature using a reverse phase Nova-Pak C18 column (60 Å, 4 μm, 4.6 mm × 150 mm; Waters, Dublin, Ireland). The mobile phase consisted of sterile water for irrigation pumped at a flow rate of 0.6 mL/min. The injection volume was 25 μL.

2.2. Preparation of stock solution

Stock solution was prepared by accurately weighing 1000 mg of suxamethonium chloride and transferring to 10-mL

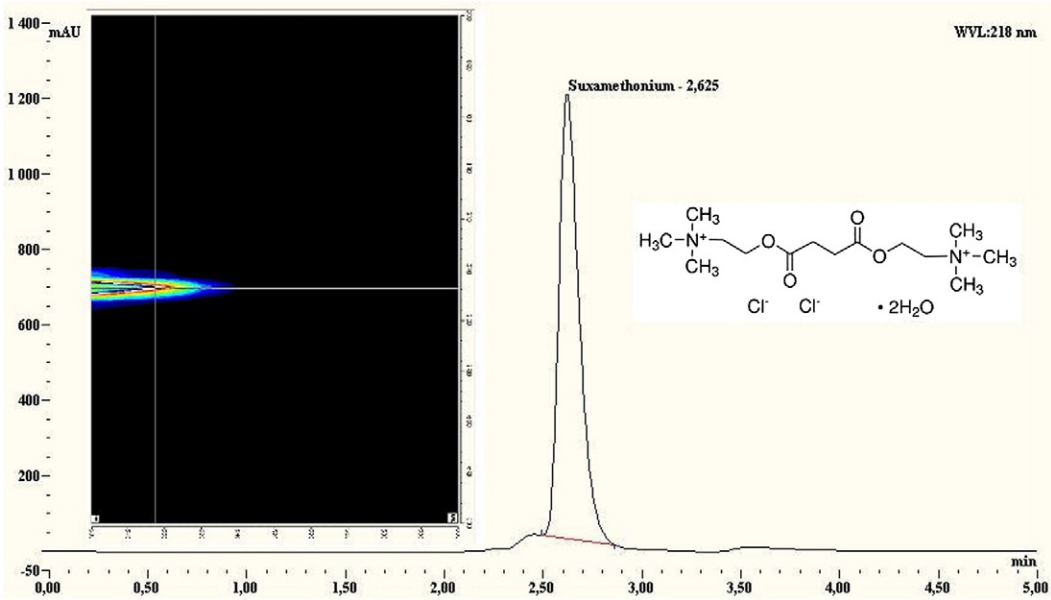

Fig. 1 Typical chromatogram and UV spectrum of suxamethonium (200-300 nm).