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Chemical stability and adsorption of atracurium besylate injections in disposable plastic syringes

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SUMMARY

Atracurium besylate (AB) is supplied as a sterile, non-pyrogenic aqueous solution for intravenous use. Hospitals pre-fill disposable plastic syringes with these solutions so that they are ready for immediate use when required. Drug loss due to potential adsorption on to the plastic material of the syringes has not been studied. Atracurium is also administered by intravenous infusion using a diluted solution in either 5% dextrose injection (USP) or 0·9% sodium chloride injection USP. Drug solutions not used within 24 h are usually discarded, resulting in tremendous waste. The purpose of these investigations was to determine the adsorption behaviour of atracurium when stored in plastic syringes, and to study the degradation of atracurium in i.v. fluids. For the adsorption study, 10 mg/ml solutions were used, whereas the diluted infusion solutions were prepared to contain 0·5 mg/ml of atracurium. Drug degradation was monitored using a stability-indicating high-performance liquid chromatography method. Degradation studies were conducted at 5°C, 25°C and 40°C. Refrigeration was observed to improve drug stability. The manufacturer's recommended expiry period was too conservative. Storage at room temperature for up to 6 weeks can be safely recommended, without significant loss of chemical stability.

INTRODUCTION

Atracurium besylate (AB) is a non-depolarizing neuromuscular blocking agent with an intermediate duration of action. The drug is available commercially as a sterile, non-pyrogenic aqueous solution (10 mg/ml) in single use and multiple-dose vials for intravenous administration. The pH is adjusted to 3·25–3·65 with benzenesulfonic acid. The multiple-dose vials contain 0·9% benzyl alcohol added as a preservative. The package insert for Tracrium® (Burroughs Wellcome Co.) specifies that the injection should be refrigerated to preserve potency (1). If removed from refrigeration to room temperature, it should be used within 14 days even if re-refrigerated. This results in tremendous wastage in the hospital setting, where disposable plastic syringes are frequently pre-filled with the drug solutions so that they are ready for immediate use in certain clinical settings. In actual clinical practice, it is also not usually convenient to have all the AB stored in the refrigerator. One study conducted to determine the room temperature stability of AB indicates that the drug is stable for 14 days at 15–30°C (2).

AB can also be administered by continuous infusion by admixing the injection with an appropriate diluent, such as 5% dextose injection USP or 0·9% sodium chloride injection USP. No reports were found in the scientific literature on the stability of extemporaneous AB solutions diluted with i.v. fluids or by itself when stored in plastic syringes. Furthermore, the possible adsorption of AB onto the plastic material of the syringes needs to be evaluated. The aim of this study was to determine the stability and adsorption of AB by itself and in i.v. fluids when stored in disposable plastic syringes. The study was conducted at three temperatures (5°C, 25°C and 40°C), selected to represent conditions that the drug solutions may encounter during shipping, handling and storage.

MATERIALS AND METHODS

Chemicals and reagents

All the chemicals and reagents were United States Pharmacopeia-National Formulary (USP-NF) or

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American Chemical Society (ACS) quality and were used without further purification. The AB was of a commercial lot (Burroughs Wellcome Co., Research Triangle Park, NC 27709, lot no. 3Y2017).

Equipment

A high-pressure liquid chromatograph (Model 590, Waters Associates, Milford, MA) equipped with an autoinjector (WISP Model 710, Waters Associates), a multiple wavelength detector (Hitachi-Model 100-40 spectrophotometer, Tokyo, Japan) and a recorder (Model BD41, Kipp & Zonen, Holland) were used. A Partisil 5 column (Microporasil (3·9 × 300 mm), Waters Associates) was used as the stationary phase.

Chromatographic conditions

The AB solutions were analysed by a stability-indicating method reported in the literature (3). The mobile phase consisted of a mixture of acetonitrile : water : phosphoric acid (specific gravity (SG) 1·75) in the proportion 900 : 90 : 10. The flow rate was 0·6 ml/min, the sensitivity was 0·05 AUFS at 280 nm, the chart speed was 2 mm/min and the temperature was ambient.

Preparation of atracurium besylate solutions for stability studies

A commercial batch of AB injections was used to prepare the study solutions of the drug. One set of solutions was prepared by filling the injection (10 mg/ml) into disposable plastic syringes. A second set was prepared by diluting the injection 20 times using either 5% dextrose injection USP or 0·9% sodium chloride injection USP (Baxter Healthcare Corporation, Deerfield, IL). The final drug concentration in this set was 0·5 mg/ml. After the initial data (physical appearance and assay) were recorded, the first set of injections were filled into 12 ml plastic monoject syringes (fill volume 10 ml). The diluted i.v. solutions of the drug were also assayed and distributed in amber coloured glass bottles. All solutions were stored at 5°C, 25°C and 40°C (± 1°C). The data were recorded again at appropriate time intervals. All experiments were preformed in triplicate.

Preparation of standard and assay solutions

The solutions for the standard curve were prepared by diluting the original injections with the eluent. The most commonly used standard solution contained 0·5 mg/ml of AB. The standard solution prepared in the i.v. fluids contained 0·05 mg/ml of AB. The study solutions were withdrawn from the respective syringe/bottle after allowing equilibration to room temperature. The assay solutions were prepared to contain the same theoretical amount of the drug as the standard solution.

Assay procedure

A 15·0 µl quantity of the assay solution was injected into the chromatograph using the conditions described above. For the purpose of comparison, an identical volume of the standard solution was injected after the assay sample eluted. The standard solution contained an identical concentration of AB.

Calculations

Preliminary investigations indicated that the peak height was directly related to the concentration of AB in the solution. The correlation coefficient for the standard curve was found to be 0·997. Therefore, the results were calculated using a simple equation:

$$(PH)_a/(PH)_s \times 100 = \text{percentage of the label claim found}$$

where $(PH)_a$ is the peak height of the assay sample, and $(PH)_s$ is the peak height of the standard solution.

RESULTS AND DISCUSSION

Stability of AB injections when stored in disposable plastic syringes

AB showed maximum stability at 5°C when stored in an undiluted form in disposable plastic syringes. Refrigeration provided essentially complete protection to the drug in solution. Even after storage for 42 days, there was no detectable decomposition of the drug (Table 1). There was no marked difference in the stability of the drug in 5% dextrose versus normal saline solutions. Because 100% drug recovery was obtained, based on the label claim, it can be assumed that there was no significant adsorption of the drug

Table 1. Stability of AB (mean ± SD) stored in disposable plastic syringes, and following dilution with either 5% dextrose injections or normal saline injections

	Percentage AB* remaining		
Days	5°C	25°C	40°C
In syringes			
7	—	—	100·32 ± 0·09
14	—	100·22 ± 0·31	—
21	—	—	84·78 ± 0·38
28	100·13 ± 0·99	97·72 ± 0·99	—
35	100·13 ± 0·46	97·30 ± 0·66	—
42	100·02 ± 0·14	96·73 ± 0·14	—
In 5% dextrose			
7	—	—	80·27 ± 0·54
14	53·20 ± 0·23	50·51 ± 0·22	—
In normal saline			
7	—	—	27·65 ± 0·28
14	45·32 ± 0·97	40·64 ± 0·97	—

*Based on 100% at day zero ($n=3$).

onto the plastic material of the syringes (Table 1). All the solutions were clear throughout the study period.

At room temperature (25°C), AB did show some degradation (less than 4%) in its undiluted form at the end of the 42-day study period (Table 1). According to the USP guidelines, drug solutions are considered potent as long as they maintain 90% of the intact drug (4). Using these guidelines in our study, AB was found to be chemically stable in its undiluted form when stored in disposable plastic syringes for the entire study period of 42 days. Therefore, storage at room temperature for periods up to 6 weeks does not result in significant chemical loss. This data suggests that syringes can be pre-filled with AB for use in the surgical setting. The 10 ml multiple-dose vial can be used to pre-fill syringes for single use and this would result in a reduction in costs.

Forty degrees Celsius was selected as being representative of the highest possible temperature that the drug solutions could be exposed to during transportation and storage. According to the FDA guidelines, if 90% of the drug stays intact for 3 months at 40°C, a tentative shelf life of 2 years may be assigned to the product at room temperature (5). Our results show that AB was chemically stable in its undiluted form for a period of 7 days (Table 1). Beyond this period, drug concentrations fell below the acceptable level of 90%. Thus, AB should be protected from extremes of temperature during handling.

When AB was diluted with either 5% dextrose injection USP or 0·9% sodium chloride injection USP, there was significant drug decomposition at all temperatures within 14 days (Table 1). It may be assumed that the pH change on dilution with i.v. fluids has a detrimental effect on the drug's stability, regardless of temperature. Therefore, solutions of AB diluted with i.v. fluids are not chemically stable for any appreciable length of time.

In conclusion, the recommendations from the manufacturer on the discarding of AB injections at room temperature after 14 days are too conservative. Our investigations show that solutions of AB in their undiluted form remain chemically stable for up to 6 weeks and show little adsorption onto the plastic material of the syringes. This study did not address the microbiological stability of the AB solutions. However, if the pre-filled syringes are prepared using proper aseptic techniques, the risk of contamination is reduced.

Our study indicates that AB is not chemically stable following dilution with either 5% dextrose injection USP or 0·9% sodium chloride injection USP. Caution must be exercised when handling solutions of AB diluted with i.v. fluids, and unused portions should be discarded immediately.

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