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Examination of sorption and photodegradation of amsacrine during storage in intravenous burette administration sets

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Summary

The sorption and photodegradation of amsacrine during storage in intravenous burette administration sets was examined. Amsacrine (150 μg/ml) was stable in 5% dextrose during exposure to diffuse daylight/fluorescent-tube room light and sunlight. No sorption was found to occur on storage with three types of Avon Medicals burette administration sets; Standard sets (A200), Suresets (A2001) and Ambersets (A2000).

Introduction

Disposable plastics products have been increasingly used in laboratory and clinical medicine in recent years. These include syringes, intravenous fluid bags and intravenous administration sets. In the past few years considerable interest has centred on the problem of interaction between drugs and these plastics materials. A significant loss of several drugs, e.g. nitroglycerine, diazepam and chlormethiazole due to binding to plastics administration sets has been reported (Yuen et al., 1979; Mackichan et al., 1979; Tsuei et al., 1980; Allwood, 1983; D'Arcy, 1983).

During parenteral drug therapy, for reasons of safety, efficacy and reliability of pharmacokinetic parameters, it is important that the full dose of a drug is delivered as prescribed without any loss of drug or the addition of extraneous materials. Also in certain circumstances drugs in infusion solutions require protection from light to avoid photodegradation e.g. frusemide (Yahya et al., 1986).

Amsacrine, 4′-(9-acridinylamino)methanesulphon-*m*-anisidide (AMSA; acridinyl anisidide) is a novel synthetic acridine derivative that has been used effectively in the treatment of acute leukaemias and lymphomas (Arlin et al., 1980; Tan et al., 1982). It is said by the manufacturer (Park-Davis Research Laboratories) to have limited stability, to be photodegradable and to interact with plastics materials (ABPI, 1986/1987).

Since plastics administration sets are used for intravenous AMSA therapy, the aim of this present study was to investigate the sorption of this drug together with its photodegradation when stored in a range of burette administration sets. Three types of burette sets manufactured by Avon Medicals, Redditch, U.K. were used: namely, A200 (Standard set) A2000 (Amberset) and A2001 (Sureset). The latter two set types have been specially developed by the manufacturers to help prevent photodegradation and drug sorption, respectively.

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Materials and Methods

HPLC analysis of amsacrine

All samples were assayed for AMSA content using high-pressure liquid chromatography (HPLC). The method used was based on that reported by Jurlina and Paxton (1983) with minor modifications. The HPLC apparatus used consisted of a Gilson Model 302 HPLC pump, Rheodyne Model 7125 injection valve (20 μl) and a Hypersil 5 ODS column (25 cm × 4.6 mm i.d.). The mobile phase was acetonitrile–water 50 : 50 plus triethylamine phosphate (0.01 mol/l, final pH 3.8) and a flow rate of 2 ml/min was used. The mobile phase was filtered through a 0.45 μm filter and thoroughly degassed using an ultrasonic bath before use. All aqueous solutions were prepared using reagent grade water (Millipore Milli-Q). Throughout all experiments, the mobile phase and column temperatures were maintained constant within a range of 19–21° C. Detection was achieved using a Perkin-Elmer Model LC-75 variable wavelength spectrophotometric detector operated at 270 nm. Peak areas were determined using a Hewlett-Packard Model 3390A integrator. All solutions were injected in duplicate.

A calibration curve of peak area versus concentration in the range of 60–180 μg/ml was prepared for AMSA and the concentration of AMSA in all samples were obtained using a regression analysis computer program (Calcurve).

To test the ability of the assay method to detect photodegradation, an attempt was made to promote photodegradation. AMSA (150 μg/ml) was therefore exposed to a variety of lighting conditions – exposure to UV light at the wavelength of 270 nm (λ_{max}) for a period of 5 h in a quartz cuvette (LKB, Ultraspec 4050, spectrophotometer), exposure to white tungsten light for 5 h and exposure to sunlight for 5 h.

To assist thermal degradation a stock solution was boiled for 10 min. Chromatograms of these solutions were examined for degradation peaks.

Sorption and photodegradation of amsacrine (AMSA)

AMSA solution (Amsidine, Park-Davis) was prepared, according to the manufacturer's instructions, by mixing 1.5 ml (50 mg/ml) of AMSA solution in anhydrous *N,N*-dimethylacetamide with 13.5 ml (35.3 mM) of L-lactic acid in a diluent vial. The mixture (15 ml) was diluted with 5% dextrose to 500 ml and was thoroughly shaken to ensure adequate mixing. The final AMSA concentration in dextrose (the stock solution) was 150 μg/ml. This solution was prepared in a borosilicate glass volumetric flask protected from light, using aluminium foil. In order to examine the sorption and photodegradation of AMSA when present in or in contact with the various individual plastics parts of the burette administration sets, the chambers and tubing were examined individually.

(a) Burette chambers. After mixing the stock solution a 5 ml sample was removed using a borosilicate glass pipette and transfered into a borosilicate glass tube protected from light and stored at −20° C for analysis of drug content (control, $t = 0$). The outlet needles of the administration sets were sealed to prevent drug solution leaving the chambers. The top of each burette was removed at the 75 ml mark; the valve together with the administration tubing were also removed. Further aliquots (40 ml) of the stock solution were then immediately poured into each of the 3 types of administration burettes and a stop-clock started. Duplicate burettes for Standard sets (A200), Suresets (A2001), Ambersets (A2000) and borosilicate glass flasks were used during each experimental run. One of each container type were protected from light using aluminium foil. The second of each type container was then exposed to diffuse daylight/fluorescent-tube room light (Thorn fluorescent White 85 Lamp covered with a polystyrene diffuser; distance from light to burette was 1.5 m). The total light intensity (822 lux) was measured using a Lightmaster Photometer (Evans Electroselenium). The storage temperature was between 19 and 21° C and did not vary with exposure to light. This arrangement allowed the assessment of sorption and photodegradation of AMSA separately. At times 2, 4, 8, 24 and 48 h thereafter, 2 ml samples were withdrawn from each burette. The samples were transferred into borosilicate glass tubes and stored with the $t = 0$ samples in the dark at −20° C prior to AMSA

analysis. AMSA was shown to be stable at this storage temperature. These experiments were repeated 3 times. Borosilicate glass tubes were chosen since they have been shown to be resistant to drug sorption (Yahya et al., 1985).

(b) Administration tubing. To study the sorption and photodegradation of AMSA when present in the administration tubing, duplicate lengths of tubing from each of the 3 types of sets (A200, A2000 and A2001) were filled by suction with the AMSA stock solution (150 μg/ml) and clamped to intravenous fluid stands. An administration tubing of each type was protected from light using aluminium foil. Samples (2 ml) were taken at time intervals of 0, 2, 4, 8, 24, and 48 h and stored in the dark at −20 °C prior to analysis. These experiments were also repeated 3 times. As in all experiments duplicate injections were made on to the HPLC system.

Results

HPLC analysis of amsacrine

The UV-visible spectrum of AMSA solution in mobile phase is shown on Fig. 1. In the UV region, the maximum absorption wavelength for AMSA was observed at 270 nm. This wavelength was therefore used in the HPLC assay. This differed from the analysis wavelength used by Jurlina and Paxton (1983) who used fixed wavelength UV detection at 254 nm. The use of this latter wave-

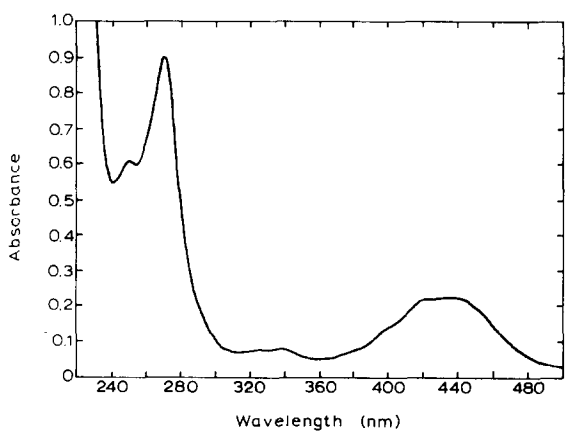

Fig. 1. UV-visible spectrum of AMSA in 5% dextrose. For absorbance measurements the original concentration of AMSA (150 μg/ml) was diluted 20-fold.

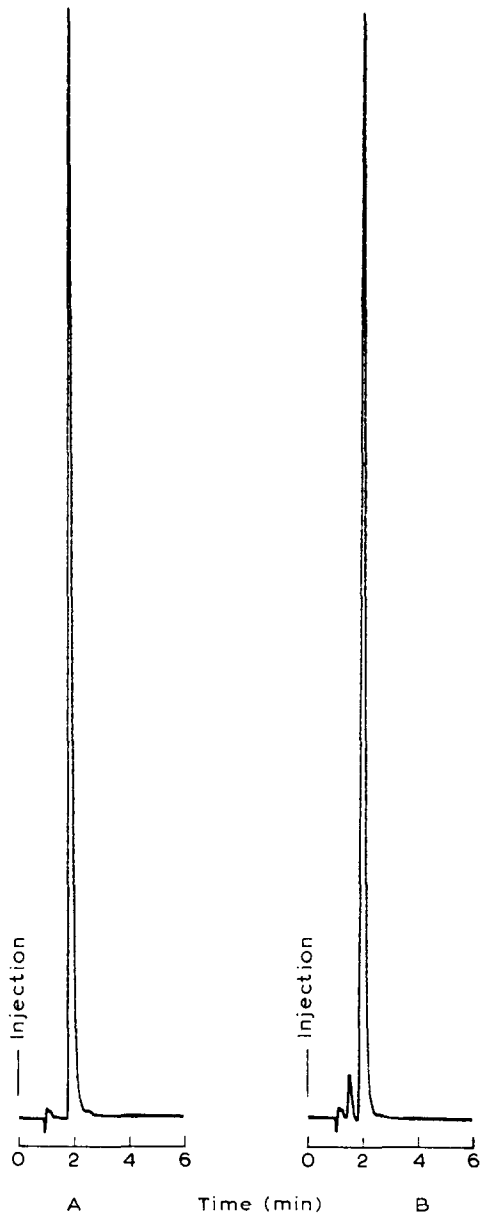

Fig. 2. Chromatograms of AMSA (150 μg/ml) in 5% dextrose. A: a typical chromatogram. B: AMSA subjected to thermal degradation (10 min boiling). Mobile phase: 50/50 acetonitrile/water containing 0.01 mol/l triethylamine phosphate (final pH 3.8) at a flow rate of 2 ml/min.

length results in a 20% loss of sensitivity. None of the components of AMSA solution i.e. *N,N*-dimethylacetamide, L-lactic acid or the diluent (5% dextrose) solution showed any spectral interference with the absorption maxima for AMSA. At the appropriate concentration all 3 components gave a steady baseline absorption (0–0.05 absorbance units), over the wavelength range examined (220–500 nm).

Using the chromatographic conditions described, the assay method for AMSA was highly reproducible with a coefficient of variation of 0.0177 ($n = 10$; 150 μg/ml). The calibration curve for AMSA over the range of 60–180 μg/ml was linear (correlation coefficient of 0.996). A typical chromatogram for AMSA is shown on Fig. 2A. None of the light exposures detailed in the Materials and Methods section resulted in any detectable AMSA photodegradation. When AMSA solution was boiled for 10 min, to assist thermal degradation, a small detectable peak attributable to degradation products was observed in the AMSA chromatogram (Fig. 2B). Although the assessment of the ability of the HPLC system to detect photodegradation was based at least partly on thermal degradation detection, efforts were made to exclude any co-elution of photodegradation products with the solvent peak or AMSA peak. This possibility was tested using different combinations of slow flow rates together with the lowering of the organic component of the mobile phase. This treatment resulted in an increase in the retention time associated with an increase in the capacity factor K' for the assay, i.e. an increase in the number of void volumes of the mobile phase required for elution of the drug (Giese, 1983). Although a decrease in the content of acetonitrile in the mobile phase from 50% to 30% resulted in an increase in the K' value (from approximately 1.2 to 3.5), no photodegradation product(s) were detected (Fig. 3).

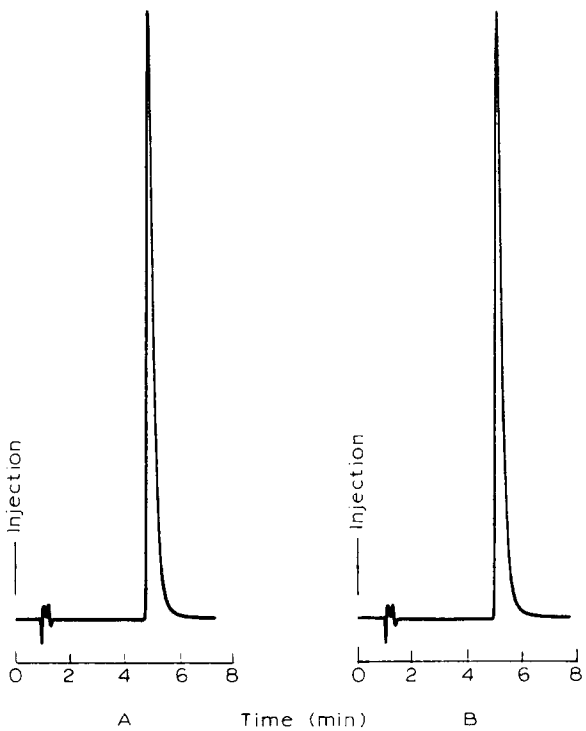

Fig. 3. Chromatogram of AMSA (150 μg/ml) in 5% dextrose. Mobile phase: 30/70 acetonitrile/water containing 0.01 mol/l triethylamine phosphate (final pH 3.8) at a flow rate of 2 ml/min. A: AMSA protected from light. B: AMSA exposed to UV-light at 270 nm for 5 h.

Sorption and photodegradation of amsacrine

The storage of AMSA in 5% dextrose in the 3 types of the administration sets resulted in no

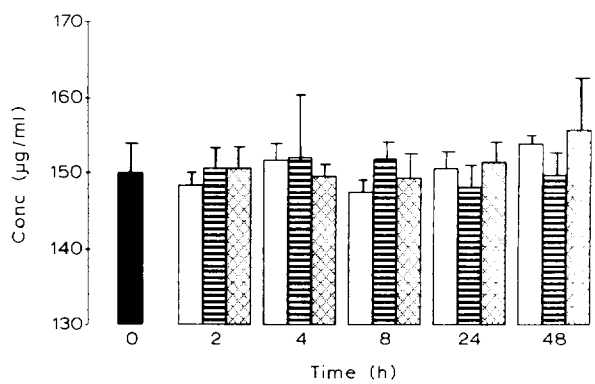

Fig. 4. Concentration versus time profile of AMSA (150 μg/ml) in 5% dextrose when stored in the Standard (A200) burettes □, Suresets (A2001) burettes ▤, and Ambersets (A2000) burettes ▨, all protected from light using aluminum foil. Each column represents the mean ± S.D. for 6 determinations except for control ■, $n = 11$, involving 3 independent experiments. (Volume of AMSA solution/plastic surface area = 0.08 ml/cm^2.)

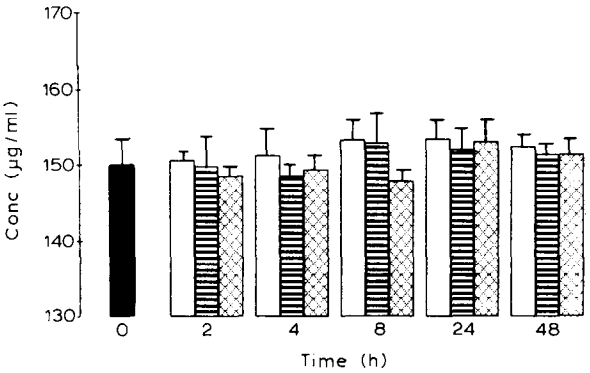

Fig. 5. Concentration versus time profile of AMSA (150 µg/ml) in 5% dextrose when stored in the Standard (A200) burettes □, Suresets (A2001) burettes ▤, and Ambersets (A2000) burettes ▨, all exposed to diffuse daylight/fluorescent-tube room light (822 lux). Each column represents the mean ± S.D. for 6 determinations except for control ■, $n = 11$, involving 3 independent experiments. (Volume of AMSA solution/plastic surface area = 0.08 ml/cm^2.)

significant difference ($P > 0.05$; two-factor analysis of variance with repeated measures of one factor) in the concentration of AMSA whether exposed to or protected from light (Figs. 4 and 5). Over the 48 h experimental period storage of AMSA in the administration tubings did not result in any statistically significant changes ($P >$

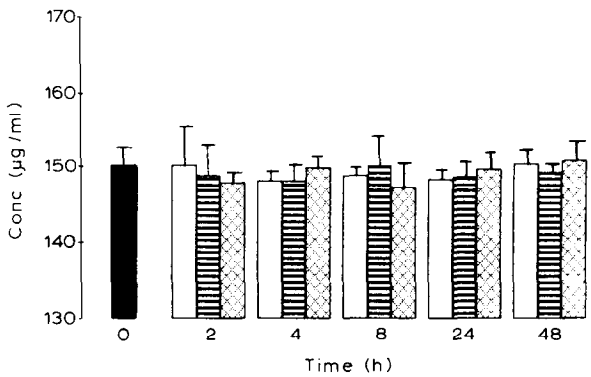

Fig. 6. Concentration versus time profile of AMSA (150 µg/ml) in 5% dextrose when stored in the administration tubings of the Standard (A200) burettes □, Suresets (A2001) burettes ▤, and Ambersets (A2000) burettes ▨, all protected from light using aluminum foil. Each column represents the mean ± S.D. for 6 determinations except for control ■, $n = 9$, involving 3 independent experiments. (Volume of AMSA solution/plastic surface area = 0.056 ml/cm^2.)

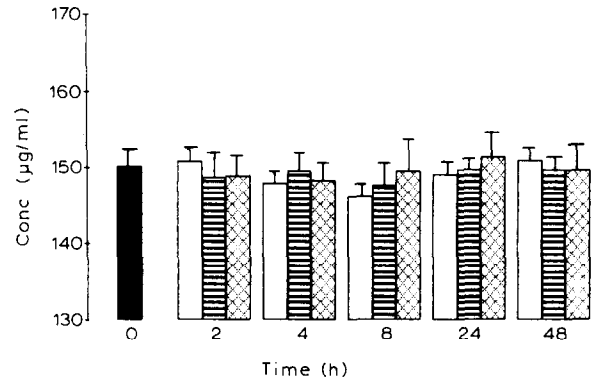

Fig. 7. Concentration versus time profile of AMSA (150 µg/ml) in 5% dextrose when stored in the administration tubings of the Standard (A200) burettes □, Suresets (A2001) burettes ▤, and Ambersets (A2000) burettes (▨), all exposed to diffuse daylight/fluorescent-tube room light (822 lux). Each column represents the mean ± S.D. for 6 determinations except for control ■, $n = 9$, involving 3 independent experiments. (Volume of AMSA solution/plastic surface area = 0.056 ml/cm^2.)

0.05; analysed as above) in AMSA concentrations (Figs. 6 and 7).

Discussion

The HPLC method used in this study was based on that reported by Jurlina and Paxton (1983). These workers were able to identify AMSA with a retention time corresponding to 3.4 min. In this study identification of AMSA was characterized with a sharp peak, minimum tailing and with a retention time of 2 min. Since exposure of AMSA to a variety of lighting conditions did not result in any detectable degradation, it would appear that AMSA is resistant to photodegradation under the conditions tested. This finding is in agreement with a recently discovered report by the U.S. Department of Health and Human Services (1981) in which AMSA was stated to be physically and chemically stable for at least 48 h when diluted in 5% dextrose solution under different storage conditions. Since photodegradation could not be observed following 5 h exposure at 270 nm or during 48 h exposure to diffuse daylight/fluorescent-tube room light in any of the administration sets, it appears that the protection of AMSA from light has no relevance to the normal clinical usage of the drug.

Results obtained also indicated that AMSA was not sorbed by the plastics used in the construction of the 3 types of administration sets namely, cellulose propionate (burette A200, A2000), polyvinylchloride (tubing A200, A2000), methacrylate butadiene styrene (burette A2001) and polybutadiene (tubing A2001).

Conclusions

AMSA (150 μg/ml) is stable in 5% dextrose during exposure to diffuse daylight/fluorescent-tube room light and sunlight. The drug requires no protection from light during normal clinical use or over a period of 48 h. No sorption was found to occur on storage with any of Avon Medicals burette administration sets.

Acknowledgements

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