International Journal of Pharmaceutics, 31 (1986) 65–68
Elsevier

IJP 01027

Photodegradation of frusemide during storage in burette administration sets

A.M. Yahya, J.C. McElnay and P.F. D'Arcy

Department of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, Lisburn Road, Belfast BT9 7BL, Northern Ireland (U.K.)

(Received November 1st, 1985)
(Modified version received January 13th, 1986)
(Accepted January 21st, 1986)

Key words: frusemide – photodegradation – burette administration sets – Amberset burettes

Summary

The stability of frusemide (1 mg/ml) in 0.9% w/v sodium chloride infusion has been examined under different lighting conditions, when stored in burette administration sets. Frusemide was found to be stable when exposed to diffuse daylight/fluorescent strip room lighting but decomposed quickly when exposed to sunlight. Prevention of this photodegradation was achieved by covering the burette sets with aluminium foil; however, being opaque, this would make monitoring of infusion rates very difficult in the clinical setting. A more convenient method of preventing photodegradation was the use of Amberset burettes. These are coated with a transparent yellow plastic material which inhibits penetration of light in the wavelength range 220–470 nm. Since frusemide was stable in these latter sets when exposed to sunlight, it is recommended that they are used for frusemide infusions in hospital units in which direct exposure of the drug to sunlight or other ultraviolet light sources is possible.

Introduction

Several workers have studied the photodegradation of frusemide. Rowbotham et al. (1976), for example, reported that ultraviolet irradiation of frusemide for 48 h in alkaline solution produced 4-chloro-5-sulphoanthranilic acid while Moore and Tamat (1980) reported complete dechlorination after ultraviolet irradiation in deoxygenated neutral aqueous solutions. Further work by Moore and Sithipitakas (1983) showed that ultraviolet irradiation (365 nm) of frusemide in methanol resulted in photoreduction to N-furfuryl-5-sulphamoyl-anthranilic acid and photohydrolysis to saluamine. The most recent data, produced by Neil et al. (1984), indicated that when frusemide injection was kept in polypropylene syringes at room temperature for 24 h without protection from light, the content of saluamine remained at 0.2% w/v (within the compendial limit of 1% w/v; B.P. 1980 Vol. 2). When added to Compound Sodium Lactate Intravenous Infusion or Sodium Chloride Intravenous Infusion, frusemide was also found to be stable for 24 h without protection from light.

Although low dose frusemide (20–50 mg) can be given intramuscularly or intravenously, if larger doses are required they should be given by slow infusion and titrated according to response. The recommended diluents are Sodium Chloride Injec-

Correspondence: J.C. McElnay, Department of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, Lisburn Road, Belfast BT9 7BL, Northern Ireland, U.K.

tion B.P. or Compound Sodium Lactate Injection with the drug diluted to a concentration of 1 mg/ml.

The aim of the present investigation was to quantify frusemide and its principal hydrolytic product saluamine in saline solutions stored under different lighting conditions in Avon Medicals A200 or A2000 (Amberset) burettes. The latter set, which has only recently become available, is covered with a yellow PVC sleeve which inhibits penetration of light in the wavelength range 220–470 nm.

Materials and Methods

The frusemide solution used in the present stability study was prepared by mixing frusemide injection (Lasix 250 mg/25 ml; Hoechst U.K.) with sodium chloride (0.9% w/v) to give a final frusemide concentration of 1 mg/ml. Aliquots (100 ml) of this solution were stored in either A200 or A2000 burettes.

Exposure to sunlight

Five burette sets of each type were exposed to sunlight (beside laboratory window) at room temperature (25°C) on two successive days (a total of 19 h). The light flux was not measured; however, information from the local meteorological centre indicated that the total radiation recorded during the experimental days had a mean of 700 $mW \cdot h \cdot cm^{-2}$. The burettes were stored overnight at 2°C in the dark between the two exposure periods. Frusemide solutions were also stored in two burettes of each type under exactly the same experimental conditions but protected from light throughout using an aluminium foil wrapping. Although infusion times are unlikely to exceed 6 h in the clinical situation, in order to gain maximal information from the study the stability was monitored over the complete 19 h period with samples (5 ml) being taken from each burette at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 10.0, 13.0, 16.0 and 19.0 h. The samples were assayed for the content of frusemide and photodegradation products using HPLC.

Exposure to fluorescent light

A similar protocol to that of the sunlight study was used in this part of the investigation; however, exposure to the fluorescent light was continuous and extended over 48 h. The exposure was carried out in a laboratory lit by overhead fluorescent strip lighting (Thorn fluorescent White 85 Lamp covered with a diffuser made from polystyrene; distance from light to burette was 1.2 m). The fluorescent light intensity was measured using a Lightmaster Photometer (Evans Electroselenium, Essex, U.K.) and was 822 lux. During daylight hours diffuse daylight also entered the room from a window. The weather was cloudy throughout with a mean total radiation of 395 $mW \cdot h \cdot cm^{-2}$. Room temperature was somewhat lower in this case (due to the lack of heating effect of the sun) and remained at 18°C. Samples were collected from control and test burettes after the following periods: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 12.0, 24.0, 36.0 and 48.0 h. As before all samples were assayed using HPLC.

Assay of frusemide

An HPLC assay was developed based on that of Moore and Sithipitakas (1983). The system utilized a 5 μm Hypersil reversed-phase column (15 cm × 4.6 mm internal diameter) linked to a UV detector operated at 254 nm (Perkin Elmer LC75). The mobile phase consisted of 0.5% v/v acetic acid in a methanol–water (35 : 65) mixture; the flow rate was 1.5 ml/min (Gilson 302 HPLC pump). The measurement of peak areas (Hewlett Packard 3390A Integrator) was used to quantify unknown concentrations of frusemide and saluamine after injection of 20 μl samples (Rheodyne 7125 injector valve) on to the column. All samples were injected in saline. Pure samples of frusemide and saluamine were obtained from the Sigma Chemical Co. and Hoechst U.K., respectively.

Results and Discussion

The assay methods for frusemide and saluamine (see chromatogram; Fig. 1) were reproducible and both gave a correlation coefficient of 0.996 over the concentration ranges of 0.2–1.6 and

0.01–0.4 mg/ml, respectively. The coefficient of variation (n = 10) for frusemide was 1×10^{-5}% and for saluamine was 8.5×10^{-5}%. Typical variation in the five replicate data values, i.e. from the 5 administration sets in each group, were so small that the standard deviation bars fell within the graphed symbols (Figs. 2 and 3) and are therefore not included in the figures.

The concentration versus time profiles of frusemide and its breakdown products when stored in the normal type of burette set (A200) and exposed to sunlight are shown in Fig. 2. It is clear that the concentration of frusemide decreased markedly while that of saluamine increased throughout the exposure period. The saluamine content increased well above the compendial limit of 1% after exposure for only half-an-hour. The concentration of an unknown photodegradation product increased to reach a maximum at 10 h and then declined, probably due to further breakdown. Since the identity of this latter compound is unknown it was quantified as saluamine equivalents (assuming the same peak area for the same weight/ml of product).

Data obtained for sunlight exposure of frusemide in the Ambersets are shown in Fig. 3. Although there was a slight fluctuation in the measured frusemide concentrations, no new peaks appeared on the chromatogram for frusemide breakdown products and hence the minor fluctuations were more likely due to slight variation in assay sensitivity due to room temperature changes. Superimposable data were obtained in the control A200 sets which were completely protected from light using aluminium foil (data not shown).

The results of the study on the exposure of frusemide to diffuse daylight/fluorescent strip light gave quite different results from those obtained during sunlight exposure. No frusemide degradation products were detected even after 48 h exposure in both the normal and Amberset burette sets, indicating that photodegradation had not taken place. A small peak at 6 min which was present in all samples (including control) increased slightly visually over control values but still remained below the level of assay sensitivity.

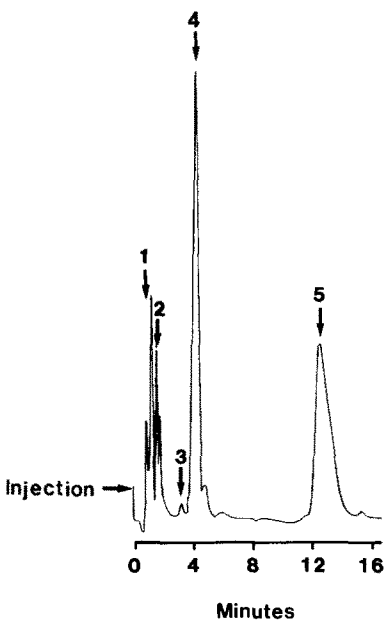

Fig. 1. Chromatogram of frusemide in 0.9% w/v sodium chloride after exposure to sunlight. Key: 1, twin peaks for saline; 2, twin peaks for saluamine; 3, third peak attributed to saluamine; 4, unknown photodegradation product; 5, frusemide. N.B. Saluamine obtained from Hoechst U.K. Ltd. gave rise to the peak pattern shown above. The combined peak areas of the three peaks were used when calculating saluamine concentration.

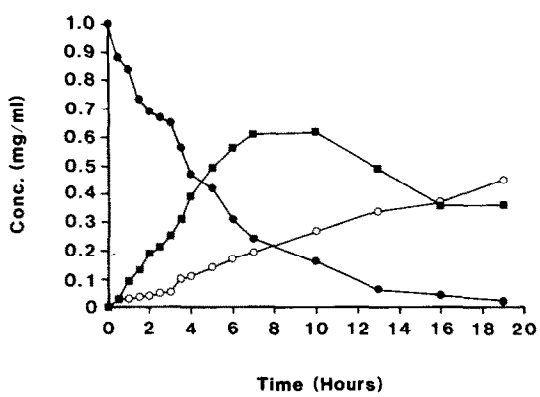

Fig. 2. Concentration versus time profile of frusemide (●———●) and breakdown products (saluamine O———O; unknown photodegradation product ■———■) when frusemide was stored in normal saline in A200 burettes exposed to sunlight. Each point is the mean for five burettes analyzed in duplicate; S.D. bars are not shown since they fall within the graphed symbols. N.B. Concentration of unknown photodegradation product given as saluamine equivalents assuming the same peak area for the same weight/ml of product.

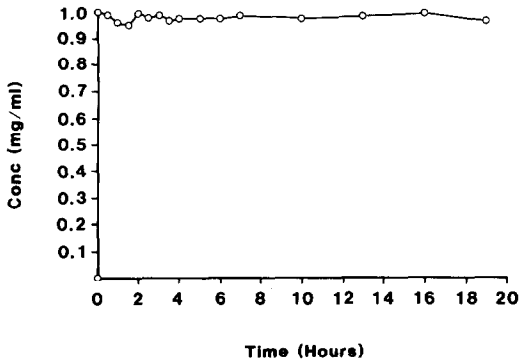

Fig. 3. Concentration versus time profile of frusemide when stored in A2000 burettes exposed to sunlight. Each point is the mean for five burettes analysed in duplicate; S.D. bars are not shown since they fall within the graphed symbols.

The results clearly indicate that frusemide is stable in 0.9% w/v sodium chloride during exposure to diffuse daylight/fluorescent strip room lighting over a 48-h period. This period would exceed normal periods of infusion in the clinical setting. In the work of Neil et al. (1984) frusemide was also found to be stable when stored unprotected from light at room temperature under 'normal conditions of artificial light, near a window to simulate ward conditions'. The authors, however, did not mention the weather conditions outside, i.e. whether it was cloudy or whether the sun was shining. The present work clearly shows that although stable in normal daylight, frusemide is labile when exposed to sunlight, with detectable breakdown occurring after only 30 min exposure (Fig. 2). It was also clear that it was the exposure to sunlight, and not the increased room temperature caused by the sunshine, that was responsible for the frusemide breakdown since there was no breakdown in the control burettes which were stored under the same temperature conditions but were covered with aluminium foil.

In the clinical use of frusemide infusions it appears paramount that the drug should be protected from direct sunlight. Photodegradation would be most problematic in countries where sunshine is frequent and intense. Protection will not be required in those wards or units which have no windows facing the outside of the building since the drug is stable in artificial light unless an ultraviolet source is present, e.g. high UV output lamps used in Intensive Care Units to reduce infection risks.

Protection from sunlight in other wards could be carried out simply by placing aluminium foil over the complete administration apparatus, including the infusion bag. This would, however, be rather awkward in the ward situation since visual examination of any part of the administration apparatus would be impossible and it would therefore not be possible for nursing staff to monitor the drug administration rate. According to the manufacturer's recommendations the rate of infusion of frusemide should not exceed 4 mg/min.

A much more convenient way of achieving the same goal would be to use the Amberset range of products which includes transparent yellow PVC sleeves to cover the fluid bag together with a range of simple administration sets and burette sets. Using these products the frusemide will be protected from radiation in the 220–470 nm range and will therefore be stable.

Acknowledgements

The authors wish to thank Avon Medicals, Redditch, Worcestershire, U.K. for their support for the study, Hoechst U.K. Ltd. for the gift of saluamine and Mr. A. Campbell, Meteorological Station, Belfast International Airport for his kind assistance in providing sunlight data.

References

British Pharmacopoeia, Vol. 2, Her Majesty's Stationery Office, London, 1980, pp. 609–610.

Moore, D.E. and Sithipitakas, V., Photolytic degradation of furosemide. J. Pharm. Pharmacol., 35 (1983) 489–493.

Moore, D.E. and Tamat, S.R., Photosensitisation by drugs: photolysis of some chlorine containing drugs. J. Pharm. Pharmacol., 32 (1980) 172–177.

Neil, J.M., Fell, A.F. and Smith, G., Evaluation of the stability of furosemide in intravenous infusions by reversed-phase high performance liquid chromatography. Int. J. Pharm., 22 (1984) 105–126.

Rowbotham, P.C., Stanford, J.B. and Sugden, J.K., Some aspects of photochemical degradation of frusemide. Pharm. Acta. Helv., 51 (1976) 304–307.