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Rapid Communication

The stability of erythromycin injection in small-volume infusions

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Summary

The stability of erythromycin injection after reconstitution and storage in small volume infusions was investigated to ascertain the rate of degradation of the drug over extended periods. Analysis was by a stability-indicating HPLC method. Injections were prepared according to manufacturer's instructions and stored at 5 °C. The $t/95\%$ was found to be 73.5 days. It is concluded that erythromycin injections prepared under aseptic conditions as part of a central IV additive service can be assigned a shelf-life of 2 months.

Erythromycin must be administered slowly by intravenous injection after dilution in 0.9% sodium chloride injection (normal saline). The manufacturer of Erythromycin IV Lactobionate (Abbott Laboratories Ltd) recommends that the drug is reconstituted by dissolving the vial contents in 20 ml Water for Injections and adding this solution to not less than 100 ml normal saline. The manufacturer indicates that this infusion retains potency for not more than 8 h (Anon, 1990). The antibiotic has been shown to be stable for 24 h at room temperature in normal saline (Bergstrom and Fites, 1975; Tung et al., 1980). Stability over longer periods was not studied. Information reported by Trissell (1988) suggests that reconstituted solution for injection may be stable for 14 days when stored under refrigeration conditions, or 24 h when kept at ambient temperature. This information is not substantiated by studies reported in the literature but derives from guidance issued by the American manufacturers. It is known that stability of erythromycin is pH-dependent. The antibiotic is most stable between pH 7 and 8.5 (Pluto and Morgan, 1986). The $t/90\%$ figures are quoted as between 4 and 7 days within this pH range. However, the storage temperature is not stated and therefore these data are of little practical value.

The preparation of antibiotic infusions on hospital wards is now considered to be undesirable, for a number of reasons, associated with patient safety, staff protection and economics. It is, therefore, preferable that these infusions are prepared in the hospital pharmacy, as a CIVA service activity. In order to include erythromycin infusion in such a service, the shelf-life of the reconstituted product should be extended if possible. The shelf-life is dependent upon the chemical stability of the drug. The stability of antibiotics has traditionally been determined by microbiological methods. In all the studies quoted, erythromycin concentrations have been determined by

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biological assay. Chromatographic methods are now available for erythromycin determination and, subject to appropriate validation against a microbiological assay, provide a more convenient and precise method of monitoring the degradation of antibiotics in CIVA products.

It was the purpose of this study to assess the stability of Erythrocin IV Lactobionate Injection in normal saline stored in small-volume infusion containers in the refrigerator, using a validated HPLC method of analysis to monitor degradation rates of the antibiotic.

Erythrocin IV Lactobionate was obtained from Abbott Laboratories Ltd, Queenborough, Kent. 0.9% Sodium Chloride Infusion, 100 ml Minibags, were obtained from Baxter HealthCare Ltd, Thetford, Norfolk. Solutions for testing were prepared according to the manufacturers recommendations. To each vial of Erythrocin, 20 ml Water for Injections was added and the vial shaken to dissolve the contents. The entire liquid contents were removed as efficiently as possible, transferred to a Minibag, using a 20 ml plastic syringe (Plastipak, Becton Dickinson Ltd) and 19 gauge needle. A 2 ml sample was removed for analysis, each bag overwrapped securely in a polythene over-cover, to prevent moisture loss, and stored in a refrigerator at 5 °C (±1 °C). For each experiment, 4 bags were prepared by this method. The study was conducted using three separate batches of Erythrocin IV Lactobionate Injection.

Analysis of Erythromycin was by a stability-indicating HPLC method, based on the method described by Tsuji and Goetz (1978). The column was Sphaerisorb Silica, 5 μm, 25 cm long, I.D. 0.4 cm. The solvent was acetonitrile : ammonium acetate 0.2 M : water (55 : 10 : 35), at a flow rate of 1.5 ml/min. Detection was at 285 nm. The injection volume was 20 μl, by fixed-volume loop (Rheodyne Model 7125 Injector). Quantitation was by electronic integration using PC Chrompac software (Phillips Scientific Ltd, Cambridge). Samples were injected without dilution.

In order to prepare standards, a vial from the same batch was dissolved in 20 ml Water for Injections and diluted to 100 ml in a volumetric flask. Aliquots were transferred to 10 ml vials and the vials sealed with a rubber crimp-on plug. These were stored at −20 °C. One vial was taken at each time interval and thawed to room temperature. This was used as the standard for the appropriate batch under test. Previous reports indicate that frozen solutions of erythromycin are stable (Trissell, 1988). The frozen standards were also checked against freshly prepared and frozen solutions of different ages to confirm the stability of the standards during the study.

The stability-indicating nature of the assay was confirmed by tests on aqueous solutions stored for 14 days at 32 °C. These solutions showed a peak reduction of approx. 35%, compared with a freshly prepared solution.

The HPLC method was also compared with the microbiological assay method described in the British Pharmacopeoia (1988), except that the organism used was Staphylococcus aureus NCTC strain 6571. Injections in normal saline stored for various intervals up to 5 months at 5 °C were compared. The concentration of erythromycin in each stored solution was assayed by both methods simultaneously. Six samples were tested and the results were not significantly different (Student's t-test, 1 tailed, 95% confidence limits). At each test point, solutions to be assayed were injected into the chromatogram three times, using the bracketing method, together with the appropriate standard. Results were calculated from the mean of the four bags. Coefficients of variation were less than 2% between bags. The analytical method was validated. Linear correlation of peak area with concentration (r) was 0.9997 and the coefficient of variation between injections was less than 1%.

pH was measured in undiluted solutions using a silver/silver chloride combined electrode.

The stability study on three different batches was conducted for periods up to 65 days. The data points include at least 3 results from each batch tested. Regression analysis was conducted on the pooled data. The degradation was approximately linear over this study period ($r = 0.8822$; slope = −0.068%). From this analysis, the t/95% was calculated to be 73.5 days.

The pH of freshly prepared solutions was approx. 6.9. The values for the three batches at the completion of the study (stored for different periods) were 6.69 (77 days), 6.75 (56 days) and 6.86

(28 days) respectively. There is, therefore, a slow fall in pH during storage. As Erythromycin lactobionate is most stable in the range pH 6–8 (Trissell, 1988), the pH values of the infusions studied are within the optimum range throughout the storage period.

It can be concluded that Erythrocin IV Lactobionate Injection, prepared according to the Data Sheet instructions, is relatively stable, as measured by HPLC, when stored at $5 \pm 1°C$. It can be assigned a shelf life of around 60 days, assuming that a maximum acceptable loss due to drug breakdown is restricted to 5%.

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