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Rapid Communication

The influence of buffering on the stability of erythromycin injection in small-volume infusions

M.C. Allwood

Medicines Research Unit, Institute of Health and Community Studies, Derbyshire College of Higher Education, Mickleover, Derby (U.K.)

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Summary

The influence of pH on the stability of erythromycin in small volume infusions indicated that the optimum pH for stability was greater than pH 7.5. Infusions containing erythromycin lactobionate injection buffered to pH 7.5–8.0 using sodium bicarbonate 8.4% were stable for 60 days, while unbuffered infusions containing similar quantities of the drug were stable for up to 20 days, based on $t/95\%$ calculations.

In a previous study (Allwood, 1990), it was reported that Erythromycin IV Lactobionate Injection (Abbott Laboratories Ltd) in 0.9% sodium chloride infusions was relatively stable and could be assigned a shelf life of 60 days, at a concentration equivalent to 1 g added to 100 ml of 0.9% sodium chloride in Minibags. Although this is a higher concentration of drug than recommended by the manufacturer in the Data Sheet (Anon, 1991), it has been used without any adverse effects, provided the infusion rate is carefully controlled. Further studies in this laboratory to investigate the stability of more dilute solutions have shown that stability appears to be influenced by concentration. In addition, batch-to-batch variations in the diluent may also be influencing degradation rates of erythromycin. These studies therefore suggest that the results of the previous investigation cannot be relied upon for all situations. The effects of pH on the stability of erythromycin salts in aqueous solutions have been summarised by Pluta and Morgan (1986). Maximum stability appears to occur at around pH 7.5–8.0. Degradation accelerates rapidly below pH 7.0 and above pH 8.5. Manufacturers in the U.S.A. have recommended the addition of buffers to acidic infusions (such as 5% glucose) used to deliver erythromycin, in order to raise the pH to above 5.5. Sodium bicarbonate 8.4% is recommended (Data Sheet Compendium, 1991/2). The addition of a buffering agent to 0.9% sodium chloride might be beneficial in order to ensure reduced batch-to-batch variations in degradation rates because it would reduce pH variations due to differences in erythromycin concentration and

Correspondence: M.C. Allwood, Medicines Research Unit, Institute of Health and Community Studies, Derbyshire College of Higher Education, Mickleover, Derby, U.K.

batches of infusion vehicle. A buffer would also reduce changes in pH during storage.

Studies were therefore undertaken to determine a more reliable method for formulating Erythromycin IV infusions with extended shelf lives. The use of a buffer would appear to be the most effective method of achieving this goal, since pH is the major influence on variations in degradation rates of different solutions.

The aims of the study were to examine the effects of pH on the degradation of erythromycin lactobionate and to assess the stability of bicarbonate-buffered 0.9% sodium chloride pH 7.5–8.0 on the stability of commonly used concentrations of Erythromycin IV Lactobionate Injection (Abbott).

The Materials used were as previously described (Allwood, 1990). In addition, sodium bicarbonate 8.4% was obtained from Kendall Laboratories Ltd (Basingstoke) and Sorensen's phosphate buffer was prepared using 0.1 M solutions of potassium dihydrogen phosphate and disodium hydrogen phosphate solutions (Analar grade).

The methods were as follows. To assess the effect of pH on erythromycin stability, 25 ml of the appropriate phosphate buffer was measured accurately into each 50 ml glass volumetric flask. A 1 g vial of Erythromycin Lactobionate IV was reconstituted in 20 ml Water for Injections. 2-ml aliquots, accurately measured, were transferred to each volumetric flask and the volume adjusted to 50 ml using 0.9% sodium chloride solution to give a solution containing 2 mg/ml erythromycin. After mixing, a small amount was removed for assay and pH measurement. All solutions were then stored at 5 ± 2°C. To assess the stability of bicarbonate-buffered erythromycin infusions, vials of Erythromycin Injection IV were reconstituted in 20 ml Water for Injections. Volumes of 10 ml were transferred to 100 ml Minibags, or of 20 ml to 250 ml Minibags of 0.9% sodium chloride injection using plastic syringes (Plastipak, B.D.). Four bags were prepared for each strength. Sodium bicarbonate 8.4% was added to two bags for each strength at a volume of 0.2 ml/100 ml 0.9% sodium chloride (this was determined by preliminary tests to be the amount of 8.4% sodium bicarbonate injection necessary to adjust the pH of Erythromycin Infusions to the pH range 7.5–8.0). After mixing, small samples were taken from each bag for analysis and pH measurement. Analysis was by stability-indicating HPLC as previously described. Standards were prepared by weighing accurately approx. 100 mg powder from the contents of a vial and dissolving in distilled water. The volume was adjusted to 20 ml in a volumetric flask. A new standard was prepared for each analysis interval.

The degradation of erythromycin 2 mg/ml in solutions buffered over the pH range approx. 6–7.5 was studied over a 40 day period. Degradation was approximately linear over this period. Approximate values for $t/95\%$ periods were calculated to be: at pH 5.88 (recorded after erythromycin addition), 1.4 days; at pH 6.38, 4.8 days; at pH 6.92, 22.5 days; and pH 7.50, > 40 days. Clearly, erythromycin is far less stable in solutions below pH 6.5–7.0. The pH of erythromycin infusions is influenced principally by erythromycin concentration and the pH of the saline diluent. The effect of adding erythromycin on the pH of saline was examined. Adding erythromycin caused the pH to increase. For example, the addition of 1 g Erythromycin Lactobionate IV to a 250 ml Minibag raised the pH from 5.56 to 7.08. It was also noted that the pH of different batches or sizes of 0.9% sodium chloride Minibags could vary within the approximate range pH 5–6. These variations are clearly able to affect the degradation rates of erythromycin and suggest the possible reason for variations between experiments already noted. The addition of a suitable buffer should enhance the stability of erythromycin and reduce variations between infusions. The degradation rates of erythromycin infusions recommended by the manufacturer, producing infusions containing between 500 (0.5 g in 100 ml bag) and 400 mg (1 g in 250 ml bag) erythromycin/100 ml infusion, were investigated in unbuffered and bicarbonate-buffered vehicles. Sufficient sodium bicarbonate was added to each bag of 0.9% sodium chloride to ensure a final pH in the range 7.5–8.0. Preliminary tests showed that the addition of 0.2 ml/100 ml infusion was optimum to achieve this adjustment. Analysis was performed over periods of up to approx. 2 months

TABLE 1

The degradation of Erythromycin Lactobionate IV infusions in saline Minibags during storage at 5°C

Regression analysis (experiment)	Unbuffered infusion			Buffered infusion		
	1 [a]	2	3	1	2	3
Slope (mg/day 1)	0.0091	0.0110	0.0084	0.0024	0.0024	0.0018
r	−0.984	−0.996	−0.817	−0.660	−0.886	−0.675
t/95% (days)	23.5	19.8	23.6	85.6	87.9	172.0

[a] Expts 1 and 2,500 mg in 100 ml; Expt 3,1 g in 250 ml.

with at least four test points/experiment. Data were subjected to regression analysis to calculate the rates of degradation for erythromycin in each pair of bags, from which *t*/95% values were derived. Changes in pH were also recorded.

Results for the degradation investigation are summarised in Table 1. The pH of most infusions was also monitored. Unbuffered solutions commenced at pH 7.15–7.25 but this fell during storage. In the first experiment, this fall was approx. 0.5 units after 48 days storage. A similar fall was recorded in the second experiment. In contrast, bicarbonate-buffered solutions commenced at around pH 7.7–7.8. A slight fall (less than 0.1 units) was observed in Expt 1 while no change occurred in Expt 2.

The results of the present study confirm the importance of pH in determining the stability of erythromycin in aqueous solutions. Even minor falls can substantially reduce the shelf life of erythromycin infusions. Since the optimum pH range appears to lie between 7.5 and 8.0, and since degradation is accompanied by falls in pH, buffering of infusion vehicles is clearly indicated to maximise shelf life. An appropriate buffer will both optimise pH for maximum stability and reduce falls in pH on storage due to degradation of drug or migration of carbon dioxide into the bags. This study indicates that the addition of 0.2% sodium bicarbonate 8.4% by volume is sufficient to optimise pH in the erythromycin concentration range normally used, and to buffer solutions of erythromycin during storage to maintain a relatively constant pH. The data indicate that buffered Erythromycin IV Lactobionate (Abbott), 500 mg in 100 ml 0.9% sodium chloride Minibags (Baxter) or 1 g in 250 ml, can be assigned a shelf life of up to 60 days storage at 5°C, based on calculated *t*/95% values. Unbuffered infusions containing equivalent concentrations of the drug should not be assigned shelf lives greater than 20 days to ensure all batches and concentrations retain greater than 95% of the added erythromycin.

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