THE STABILITY OF HYDROCORTISONE-21-ACETATE IN AQUEOUS SOLUTION

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During solubility determinations of hydrocortisone-21-acetate in a number of aqueous vehicles we found that the corticosteroid ester was undergoing hydrolytic degradation. The chemical instability of corticosteroid esters has led to a number of reports (Jensen & Lamb 1964; Oesterling & Gustafson 1970; Yip & Li Wan Po 1979) but none have specifically investigated the stability of hydrocortisone-21-acetate in aqueous solution.

Consequently,a stability-indicating HPLC assay was developed. The technique employs 5 µm ODS-Hypersil in a 100 x 5 mm column, the mobile liquid being methanol/water (60:40 % v/v) at a flow-rate of 1 ml min^{-1}. The separation was monitored at 245 nm using a sensitivity of 0.2 AUFS. Under these conditions hydrocortisone -21-acetate (capacity factor, k', 7.9) was well resolved from hydrocortisone-17-acetate (6.7) and hydrocortisone (4.9) and the analysis time was 7 min. The degradation products of hydrocortisone (Das Gupta 1978) and the buffer constituents used in the stability study were shown not to interfere.

The stability solutions were prepared by adding 100 µl methanolic solution of hydrocortisone-21-acetate (0.8 mg ml^{-1}) to a mixture of Clark and Lubs' buffer (9 ml) and water (1 ml). The ionic strength was maintained constant by the addition of potassium chloride. The solutions were stored at 30 $\pm$ 1°C and aliquots (50 µl) were withdrawn periodically and assayed by HPLC. The residual content of hydrocortisone-21-acetate was estimated using an external standard since peak height was linearly related to the weight of hydrocortisone-21-acetate injected over the range 0.1 - 0.8 µg and passed through the origin.

The decrease in the concentration of hydrocortisone-21-acetate was found to be first-order down to about 25% residual hydrocortisone-21-acetate and the degradation rate to be dependent on pH, as shown in the table. The pH of maximum stability was found to be approximately 4.5.

pH	rate constant/hr^{-1}
1.6	5.6×10^{-3}
2.2	1.9×10^{-3}
3.3	6.5×10^{-4}
4.4	1.7×10^{-4}
5.2	4.1×10^{-3}
6.2	3.3×10^{-2}
7.1	1.0×10^{-2}
7.8	1.5×10^{-1}
9.1	2.3×10^{0}

Although hydrocortisone was formed as the major degradation product, a second component, hydrocortisone-17-acetate, was also found to be rapidly produced albeit in only small amounts. The formation of hydrocortisone-17-acetate decreased with decrease in pH and became undetectable in solutions below pH 4.0. Data obtained at pH 9.1 suggest that hydrocortisone-17-acetate exists in equilibrium with the 21-acetate but that hydrolysis to hydrocortisone probably occurs directly from the 21-acetate. This is supported by the fact that at pH 9.1 the 17-acetate rapidly undergoes intramolecular rearrangement to the 21-acetate.

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