INFLUENCE OF SIDE CHAIN ON ENZYME INHIBITORY ACTIVITY OF SOME HYDROCORTISONE ESTERS

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Psoriasis is characterised by a greatly enhanced epidermal cell production. The increased metabolic and proliferative activity has been demonstrated by enhanced levels of several of the enzymes involved in energy metabolism. Antipsoriatic agents such as methotrexate, azathioprine and corticoseroids have been shown to inhibit the activity of glucose-6 phosphate dehydrogenase (i.e. inhibit the pentose phosphate pathway), (Raab and Gmeiner 1975a,b). Marked differences in activity between esters of corticosteroids have indicated that the esterified forms have biochemical activity and are not merely transport forms (Raab and Gmeiner 1975b, 1976).

Several straight chain esters (C_2 to C_{14}) of hydrocortisone were incubated with glucose-6 phosphate dehydrogenase (E.C. 1.1.49; G-6 PDH) pure from yeast, at 37°C in 0.05M triethanolamine pH 7.5 buffer containing 0.005M ethylenediamine tetraacetate. Enzyme assays were performed at 25°C by monitoring the absorbance of the reduced coenzyme, NADPH, at 340nm after the addition of glucose-6 phosphate and NADP. Following incubation for periods up to one hour the inhibition of the glucose-6 phosphate dehydrogenase activity was compared with the control. After incubation, samples were also analysed by HPLC to assess any hydrolysis which might have occurred.

The hydrocortisone esters, corticosteroids of possible dermatological significance, were found to exhibit significant inhibitory activity on the pentose phosphate metabolic pathway.

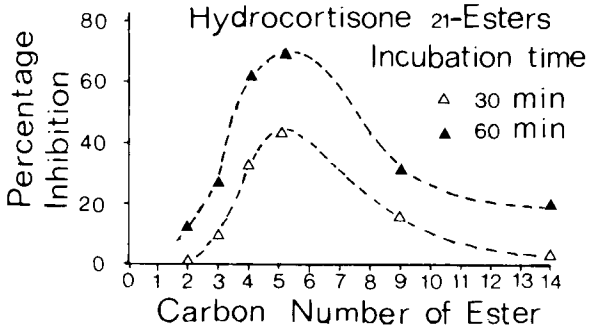

Fig.1
The influence of side chain on inhibition of activity of glucose-6-phosphate dehydrogenase.

The HPLC studies were unable to show that hydrolysis had occurred with any of the corticosteroids during the incubation period, indicating inherent activity of the esters. This was important since hydrocortisone itself showed high inhibitory activity.

The results are comparable with those of Schlagel (1971) who showed a progressive increase in topical anti-inflammatory activity with increase in ester side chain with an optimum ester chain length of about five or six. The low anti-inflammatory activity of hydrocortisone and the longer chain esters may be due to poor topical bioavailability rather than low inherent activity. This enzyme inhibition assay may provide a means of differentiating between the two and offer a useful in vitro assay for topical corticosteroid activity.

Raab W.P. and Gmeiner B.M. (1975a) Arch.Derm.Res. 253, 77
Raab W.P. and Gmeiner B.M. (1975b) ibid. 253, 113
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