INFLUENCE OF SIDE CHAIN ON THE HYDROLYSIS OF SOME HYDROCORTISONE ESTERS

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The epidermal barrier normally functions as a protective layer. However, it is not chemically and biochemically inert but possesses metabolic activity including the ability to metabolise drugs and other foreign compounds (Pannatier et al 1978). The most extensive research on the biotransformation of steroids in the skin has centred on the sex hormones and on the metabolism of hydrocortisone and cortisone (Hsia et al 1965; Hsia and Ho 1966). Cutaneous enzymes have been found which can hydrolyse synthetic corticosteroid esters (Taüber and Toda 1976). However, it is still unclear whether hydrolysis is a necessary prerequisite to topical biological activity of corticocosteroid esters, i.e. that the ester group acts as a transport facilitating moiety. Indeed, there may be some evidence that certain esters resist metabolic degradation in the skin (Greaves 1971; Whitefield 1977). The degree and rate of hydrolysis of a series of straight chain esters of hydrocortisone have been investigated in vitro using HPLC. The steroid esters were incubated with hamster and guinea pig skin homogenates and the cleavage rates compared with those in vitro using pure carboxylesterase and human plasma. Rm chromatographic parameters (TLC) were used to assess the lipophilicity of the hydrocortisone congeners

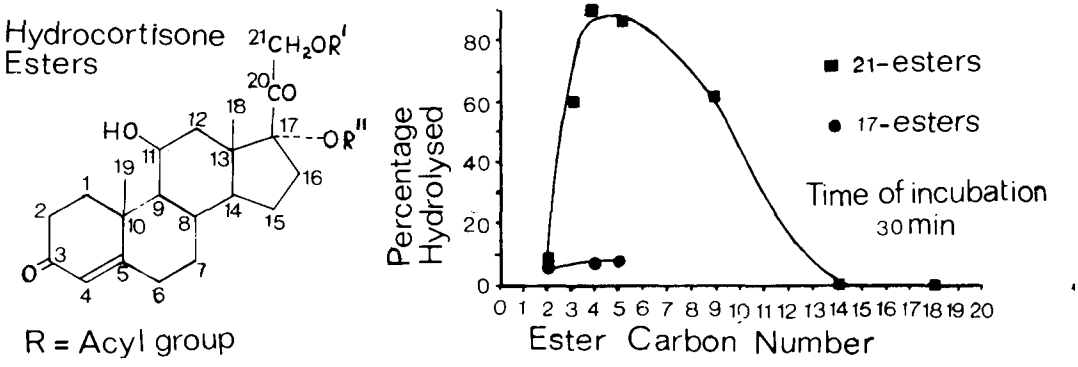

Fig.1 Influence of side chain enzymatic hydrolysis by carboxylesterase

The results presented show that the rates of ester cleavage vary with chain length and indicate a similar optimum carbon number for maximum hydrolysis rate. The sterically hindered 17-ester derivatives were found to be more slowly hydrolysed than their 21 isomers, as were the 17,21-diesters. These results support the suggestion that corticosteroids with substituents at carbon 17 are more resistant to metabolic degradation which may influence their topical potency. The longer chain C-21 esters such as the 21-tetradecanoate and 21-octadecanoate also showed very slow rates of hydrolysis which might suggest a more prolonged activity in vivo.

The lipo/hydrophilic balance and percutaneous penetration will depend upon the chain length of the ester function and whether this acts as a fixed or disposable moiety depends upon the ability of esterase enzymes to remove it. The relative contribution of lipophilicity and hydrolysis will influence the topical biological activity.

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