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# 5alpha-Tetrahydrocorticosterone: A Novel Topical Anti-inflammatory Agent With Improved Therapeutic Index

DE Livingstone, C Sykes, L Hollis, BR Walker, R Andrew. Univeristy of Edinburgh, Edinburgh, UK

Topical steroids are the mainstay of treatment of inflammatory skin conditions such as eczema, but their use is limited by negative effects on skin integrity. Furthermore, chronic topical treatment is sometimes associated with systemic effects on metabolic function. There is therefore a need for novel steroid treatments with dissociated anti-inflammatory vs metabolic effects. We have previously identified 5alpha-tetrahydrocorticosterone (5aTHB) as a novel glucocorticoid receptor ligand(1) which displays dissociated effects in vitro(2). The aim here was to determine the anti-inflammatory efficacy of 5aTHB in vivo, along with effects on skin thickness, in comparison with the most commonly used topical steroid, hydrocortisone (HC).

Anti-inflammatory efficacy was determined in adult male C57Bl6 mice. Inflammation was stimulated by topical treatment with croton oil to the right ear (300ug in 95:5 ethanol:isopropylmyristate) and swelling assessed at cull after 24 hr by ear weight vs untreated ear. Dose-responses to 5aTHB and hydrocortisone (0-100ug) were determined by co-administration of steroid with croton oil, and IC50 calculated by curve fitting of %maximal inflammation (n=6-12/dose). To ascertain the effect of 5aTHB on skin thickness, 5aTHB or HC (0,25,100,200ug in 95:5 ethanol:isopropylmyristate) was applied to the right ear of mice daily for 4wks (n=6/group). Doses were selected following dose response studies as efficacious (25ug), high therapeutic (100ug) and pharmacological (200ug). Body weight and ear skin thickness (by foil thickness gauge) were measured biweekly. Mice were killed by approved method; treated and control ears were weighed, adrenals weighed, and plasma insulin analysed by ELISA. Data are mean±SEM, *$p<0.05$, **$p<0.01$.

The anti-inflammatory IC50s for 5aTHB and HC were 23.3 and 12.7ug respectively. Comparison of 15ug and 25ug doses of steroid on % maximum inflammation showed equivalent efficacy between 5aTHB and HC: 15ug; 26.4±9.7 vs 27.8±5.9%, $p=0.8$ and 25ug; 13.5±7.4 vs 16.9±11.4%, $p=0.9$. Daily treatment with HC caused significant ear skin thinning by day 6, with maximum effect by day 13: 20±3*, 22±2* and 17±2*% thinning at 25, 100 and 200ug HC respectively. HC dose-dependently reduced ear weight (at cull) by 23%** 39%** and 43**%. By contrast, 5aTHB treatment resulted in only slight and transient skin thinning, which fully recovered by day13, and there was no difference in ear weight at cull ($p>0.1$ at all doses). HC exhibited systemic effects, evident in reduced weight of the contralateral (untreated) ear at the two higher doses (33%** and 41%**), and reduced body weight at all doses ($p<0.001$). The two higher doses of HC also reduced adrenal mass (by 50%** and 42%**), and increased plasma insulin (by 3.5 ** and 5.2**fold) indicating systemic effects on HPA axis activity and glucose metabolism respectively. All these metabolic effects were absent at even the highest dose of 5aTHB ($p>0.2$ for all comparisons).

In summary, 5aTHB is equivalently efficacious to HC in the croton oil mouse model

of skin inflammation. Crucially, chronic 5aTHB treatment does not result in the negative skin or metabolic effects associated with hydrocortisone and therefore may prove to be a novel anti-inflammatory agent with improved therapeutic index.

1) McInnes et al,(2004),JBC;279,22908-12. 2) Yang et al,(2011),BJP;164,1661-71.