

Review Article

Corticosteroid cross-reactions: an alternative view

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An alternative view of corticosteroid cross-reactivity is proposed, based on 2 immune recognition sites on the corticosteroid molecule, 1 influenced by C 6/9 substitution and 1 by C 16/17 substitution. A case report is adduced in support of such a hypothesis.

Key words: corticosteroid; cross-reaction; allergic contact dermatitis; tixocortol pivalate; hydrocortisone; budesonide; medicaments; structure-activity relationships. © Munksgaard, 2000.

Accepted for publication 9 August 1999

Cross-reactions occur between chemicals with similar structures. However, structure is not the only determinant of whether such a reaction will occur (1, 2). On the skin, penetration of the allergen determines whether the immune system will be exposed, and if the substance is a prohaptens, its susceptibility to metabolism or degradation determines whether antigen is formed.

Metabolism and Degradation

The available evidence suggests that with corticosteroids, the allergen is not the steroid itself but a degradation product. Metabolism and degradation within the skin might therefore be a factor that influences the development of a cross-reaction. It has been suggested that corticosteroids degrade to a reactive corticosteroid-glyoxal that then reacts with arginine (Fig. 1) to form antigen (3, 4). Clinically, it has been shown that positive patch test reactions to corticosteroid are correlated with patch test reactions to the corresponding corticosteroid-glyoxal (5, 6). This suggests that the corticosteroid-glyoxal degradation product is involved in corticosteroid allergy. In vitro, the amount of degradation product, which subsequently reacted with arginine, has been shown to vary between corticosteroids and to be correlated with the frequency of allergic reactions to a steroid (7).

The corticosteroid-glyoxal is formed on the C17 side chain (Fig. 2). Alterations to this chain might therefore affect whether corticosteroid-glyoxal is

formed. For practical purposes, the main alterations to this side-chain occur at the C21 position. In the skin, an esterase rapidly splits any ester from the molecule, resulting in a C21 hydroxyl group. *In vivo*, it has been estimated that within 5 h, 80% in rats, and 50% in dogs, of topically applied hydrocortisone-17-butyrate-21-propionate

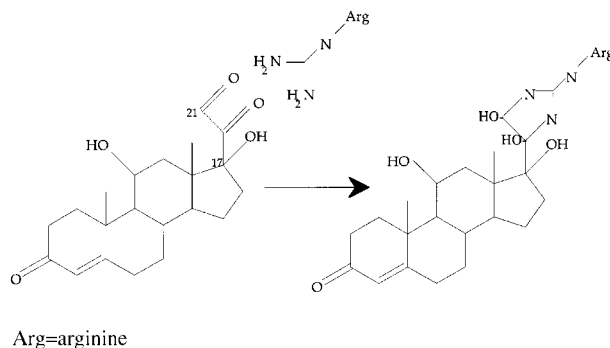


Fig. 1. Possible reaction of steroid-glyoxal with the guanidino group of arginine.

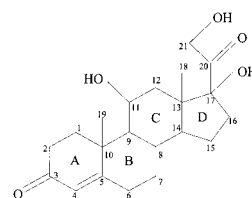


Fig. 2. Nomenclature of hydrocortisone.

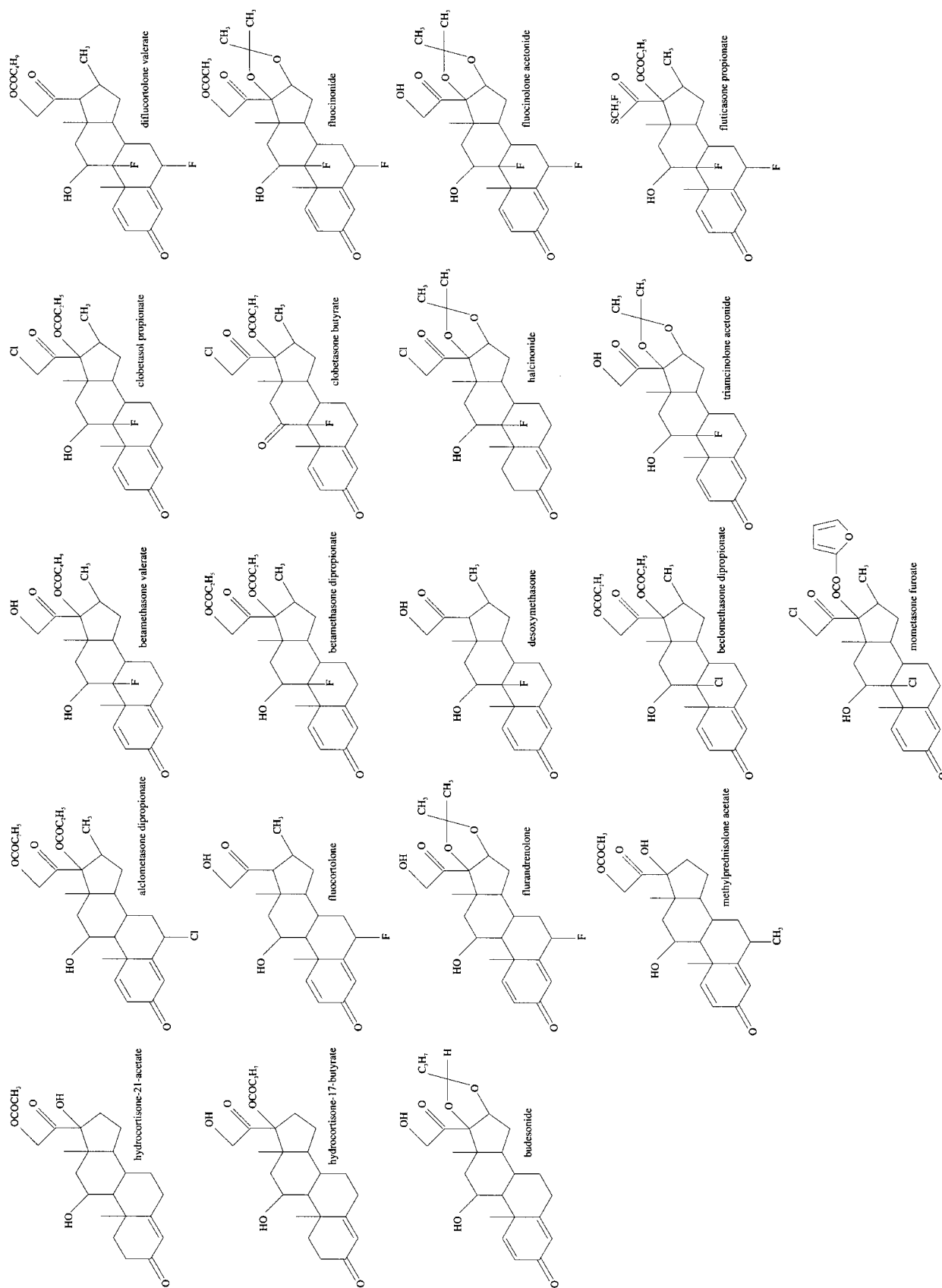


Fig. 3. Structures of corticosteroids on the UK market.

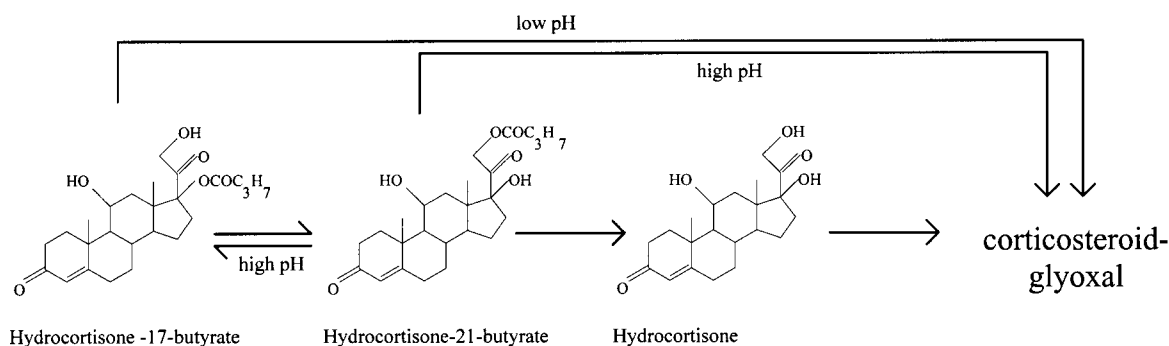


Fig. 4. Rearrangement of the C₁₇ ester of hydrocortisone.

had been metabolized or degraded by keratinocytes of the epidermis (8). The degradation rate of the C21 esters has been shown to be unaffected by the length of the carbon chain for unbranched chain dicarboxylic acids of 4 or more carbons (9). For the carboxylic acids, esters with between 3 and 10 carbon chains were >60% hydrolysed within 30 min (10). Therefore, for most of the corticosteroids currently available on the UK market (Fig. 3) one would not expect the C21 ester to affect the development of a cross-reaction. This is in accordance with our previous statistical analyses (11, 12).

There is no information available on degradation if C21 is not hydroxylated or esterified. In consequence, corticosteroids substituted with chlorine (clobetasol propionate, clobetasone butyrate, mometasone furoate and halcinonide) or with a truncated side chain (fluticasone propionate) may behave differently.

A review (13) has suggested that substitutions to the carbon rings also influence the rate of degradation, the presence of C11=O enhancing degradation whilst C16 β-methyl and C17-H stabilized the molecule. It was suggested that the latter occurred through interference with metal-corticosteroid complex formation that involved the C₁₇ hydroxyl group. We previously found that C6, C9 halogenation was highly significant, and possibly, the major determinant in determining cross-reaction patterns. It is possible that this influence is through stabilization of the corticosteroid. Structurally, these atoms occupy a similar volume to a hydrogen atom and do not affect the shape of the molecule (14). *In vitro*, these substituted corticosteroids formed less antigen than unsubstituted molecules (7).

Cross-reaction Patterns

Once antigen has formed, structure would then be expected to have the major influence on the development of cross-reactions. To date, the C16/17 substitutions have been clearly demonstrated to in-

fluence cross-reactivity. All groups agree on the importance of this site on the steroid D ring (11, 12, 14, 15). Different isomeric forms of budesonide have been shown to resemble both the acetonide structure and C17 esters, explaining why budesonide is such a good patch test screen (14). At least 90% of individuals with a reaction on patch testing to budesonide are allergic to another corticosteroid. This is true of 50% of those allergic to tixocortol pivalate, the other proposed marker of corticosteroid allergy (16).

It needs to be remembered that because of degradation and metabolism, further molecules may be formed from a topically applied corticosteroid (17). This may result in a cross-reaction to a degradation product but not to the parent compound, i.e., hydrocortisone-17-butyrate may cross-react with hydrocortisone after loss of the C17 ester (Fig. 4).

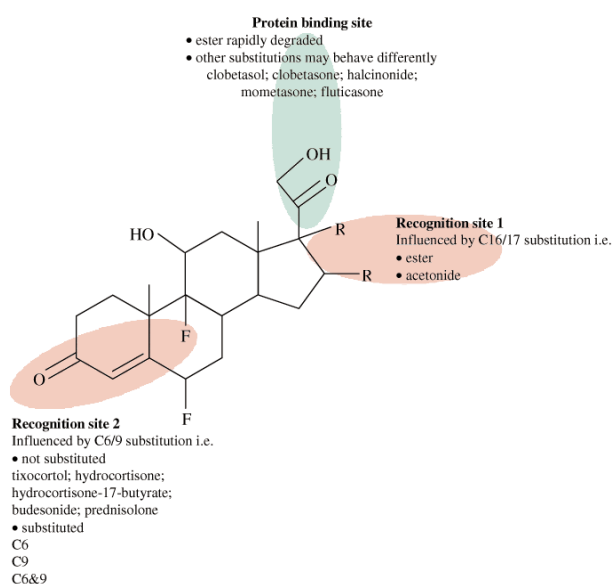


Fig. 5. Representation of factors influencing corticosteroid cross-reactions.

The currently quoted classification of corticosteroid cross-reactions was derived from a descriptive analysis (15). Whilst some of this has proven correct, other components of the classification are open to question based on the chemical and clinical data given above. A structural analysis was unable to provide support for the existence of group C in this classification (14).

Some groups have questioned whether the classification adequately explains the range of cross-reaction patterns seen (18, 19). My experience has been similar and is exemplified by this case report.

Case report

A 35-year-old medical practitioner was referred for patch testing with a history of rosacea aggravated by contact with medicaments. Past medical history was unremarkable. Patch tests to a standard, medicament and facial series were all negative. She returned at 2 weeks with a solitary delayed reaction. Further tests produced reactions at day 2 (++) and 4 (++) to both tixocortol pivalate (1% pet.) and budesonide (1% eth.). There were no reactions to betamethasone valerate, clobetasol propionate and clobetasone butyrate (all 1% eth.), which are included in our standard series. On further questioning, she denied previous use of any topical or systemic steroid. The patient declined further testing to our steroid series.

Comment

The appearance of a solitary late reaction and subsequent reactions to 2 topical corticosteroids was suggestive of sensitization to one and cross-reaction to the other. It is difficult to explain this, as tixocortol pivalate is in group A and budesonide group B. There is no degradative/metabolic pathway that would produce a common molecule. This suggests that the carbon rings may be recognized by the immune system, as the steroid A-D rings are similar between the 2 molecules. Experimentally-induced antibodies to the steroid structure have been used as a basis for radioimmunoassay techniques (20), although this may not necessarily reflect the antigen recognition pattern of the T-cell receptor.

Structurally (14), it is then difficult to explain why the patient did not also react to betamethasone-17-valerate. Fluorine has a similar volume to hydrogen and so in terms of size and shape of the carbon rings, betamethasone and budesonide are identical. We previously found the substitutions on the carbon rings to have a significant influence on cross-reactions and explained this by

charge differences (21). Although they are the same size, hydrogen is relatively electro-positive and fluorine electro-negative.

If this is true, the implication is that there is more than 1 site of immune recognition on the corticosteroid molecule. In my view, this may provide a better explanation of the cross-reaction patterns seen. If one accepts this hypothesis, a summary of factors influencing corticosteroid cross-reactions is illustrated in Fig. 5.

Acknowledgement

I am grateful to Dr. Michael Beck for his comments on an earlier draft of this paper.

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