

Cross-reactivity patterns to budesonide

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Allergic contact dermatitis from topical corticosteroids is not uncommon. Budesonide has been included in the European standard series as a marker for corticosteroid allergy, though little is known of its cross-reactivity with other corticosteroids. Twelve patients previously positive to budesonide on patch testing were given further patch and intradermal tests to a range of corticosteroids. Six patients previously negative to budesonide on patch testing were used as a control group. Budesonide cross-reacts with hydrocortisone-21-sodium phosphate and triamcinolone acetonide. Patients positive to budesonide should therefore avoid hydrocortisone and triamcinolone acetonide. Patch testing, unfortunately, is an inaccurate method of determining cross-reactivity patterns among corticosteroids.

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Patch tests have been shown to be inferior to intradermal tests at detecting corticosteroid allergy (1). Budesonide has been included in the European standard series as it is thought to be a good marker for other corticosteroid allergies. Despite this, the cross-reaction patterns of budesonide have not been accurately determined by intradermal testing. In this study, we therefore set out to define accurately the cross-reaction patterns of budesonide with certain other corticosteroids using intradermal tests.

A number of structural factors are thought important in determining the allergenicity and cross-reaction pattern of a corticosteroid molecule. No single factor can predict all the patterns seen, so it seems likely that in any one molecule several regions in its structure are important.

In 1980, Bundgaard suggested that, *in vivo*, the C-17 side chain of the corticosteroid molecule (Fig. 1) underwent oxidative degeneration to form a steroid glyoxal (2). The steroid glyoxal then bound to an arginine moiety of a serum protein forming a hapten protein complex, in which the steroid glyoxal was presented as the allergen. This theory is supported by the following observations:

- glyoxals are potent allergens (2);
- positive patch tests to corticosteroids correlated with the corresponding steroid-glyoxal (3, 4);

- the degree to which a corticosteroid binds to arginine appears to be a marker of its allergenicity (5).

Coopman et al. analysed the results of patch tests to a range of corticosteroids and used these to subdivide corticosteroids into 4 groups (A, B, C and D) based on the D-ring of the molecule (Fig. 1) (6). Corticosteroids within each group have the ability to cross-react with one another. This classification was later supported by spatial analysis, which showed that molecules within each group had a

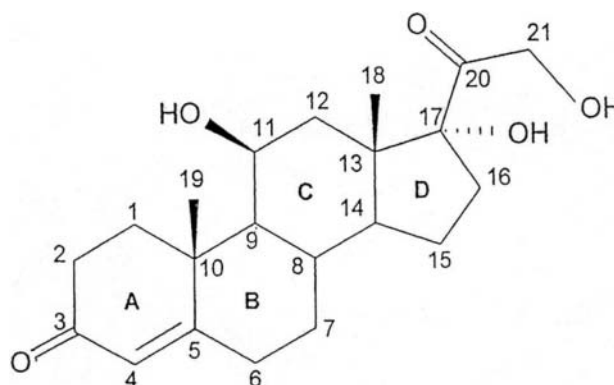


Fig. 1. Molecular structure of hydrocortisone demonstrating the 4-ring structure of corticosteroids (A, B, C, D).

Table 1. Results of patch and i.d. tests in patients previously shown to be allergic to budesonide

Budesonide		Hydrocortisone		Triamcinolone		Tixocortol		Methyl-prednisolone	
patch	i.d.	patch	i.d.	patch	i.d.	patch	i.d.	patch	i.d.
+	+	NT	+	—	+	—	NT	NT	—
+	+	NT	+	—	—	+	NT	NT	—
+	+	NT	—	—	+	—	NT	NT	—
+	+	NT	+	—	—	—	NT	NT	—
+	+	NT	—	—	—	+	NT	NT	—
—	+	NT	+	—	—	—	NT	NT	—
—	+	NT	+	+	+	—	NT	NT	—
—	+	NT	—	—	+	+	NT	NT	+
—	+	NT	+	—	+	—	NT	NT	—
—	+	NT	+	—	+	—	NT	NT	—
—	+	NT	—	—	—	—	NT	NT	—
—	+	NT	—	—	—	—	NT	NT	—

Table 2. Results of patch and intradermal tests in the control group

Budesonide		Hydrocortisone		Triamcinolone		Tixocortol		Methyl-prednisolone	
patch	i.d.	patch	i.d.	patch	i.d.	patch	i.d.	patch	i.d.
—	—	NT	—	—	—	—	NT	NT	—
—	—	NT	—	—	—	—	NT	NT	—
—	—	NT	—	—	—	+	NT	NT	—
—	—	NT	—	—	—	—	NT	NT	—
—	—	NT	—	—	—	—	NT	NT	—
—	—	NT	—	—	—	—	NT	NT	—

similar spatial structure and that the spatial structure was significantly different between groups (7). Work done more recently has conflicted with this classification and Wilkinson has suggested that substitutions at the C-6/9 and C-16/17 sites are important (8).

Most patients have been exposed to at least one corticosteroid in their lifetime. This makes the determination of cross-reactivity difficult. Patients are often unsure which steroids they have used in the past, thus it is often difficult to determine whether a reaction is a true cross-reaction or whether the patient has been previously sensitized. We searched the hospital and general practice records of each patient to try and form an accurate picture of the corticosteroids each patient had previously met.

Patients and Methods

12 patients previously positive to 0.01% budesonide in petrolatum (pet.) were subject to further patch tests, using Finn Chambers applied for 2 days, with 0.01% budesonide, 1% alclomethasone-17-21-dipropionate, 1% betamethasone-17-valerate, 1% clobetasol-17-propionate, 1% hydrocortisone-17-butyrate, 0.1% tixocortol-21-pivalate and 1% triamcinolone acetonide. All agents, except hydrocortisone-17-butyrate, were dispersed in petrolatum. The vehicle used for hydrocortisone-17-

butyrate was ethanol. The patients were then given 0.1 mL intradermal (i.d.) injections of 0.025% budesonide, 0.4% dexamethasone, 10% hydrocortisone-21-sodium phosphate, 4% methyl-prednisolone and 4% triamcinolone acetonide. A 0.1-mL i.d. injection of normal saline was used as an in-patient control. The steroids chosen for intradermal injection were determined by the availability of sterile commercial products. All sites were read at 15 min, D2 and D4 using the ICDRG guidelines (9). The same procedure was repeated with a control group of 6 patients previously found negative to budesonide on patch testing.

Results

Tables 1 and 2 show the results of patch and i.d. tests in the budesonide allergic and control groups, respectively. No positive reactions were seen with alclomethasone, betamethasone, clobetasol, dexamethasone or hydrocortisone-17-butyrate.

Discussion

Of the 12 patients positive to intradermal budesonide, 7 were positive to i.d. hydrocortisone-21-sodium phosphate, 6 were positive to triamcinolone acetonide and 1 was positive to methyl-prednisolone. None of the control group, all of whom

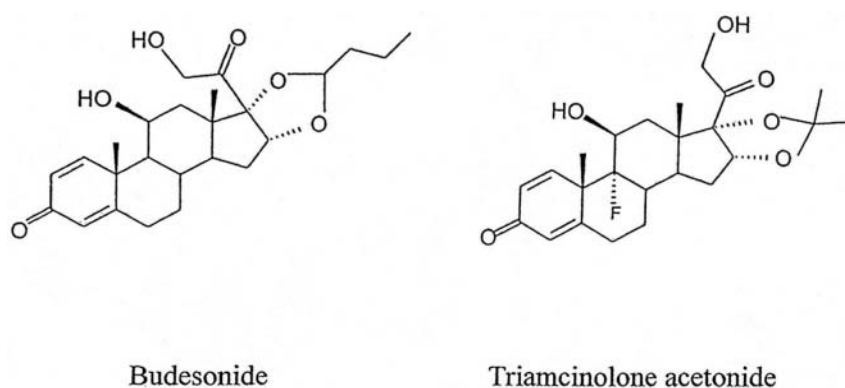


Fig. 2. Molecular structures of budesonide and triamcinolone acetonide.

were negative to budesonide, showed a positive reaction to hydrocortisone-21-sodium phosphate or triamcinolone acetonide. Our results suggest budesonide cross-reacts with both hydrocortisone-21-sodium phosphate and triamcinolone acetonide. None of the patients had previously been exposed to triamcinolone and so the results are likely to represent a true cross-reaction. Conversely, all the patients had been exposed to hydrocortisone in the past and so some of the positive reactions to this compound might represent earlier sensitization. A larger study would be needed to see if there is a cross-reaction between methyl-prednisolone and budesonide.

Budesonide and triamcinolone share a similar structure (Fig. 2) and using the Coopman et al. classification a cross-reaction would be expected as they both belong to Group B. However this classification is contradicted by the observation that hydrocortisone-21-sodium phosphate and budesonide cross-react, as the former belongs to Group A and the latter to group B. The discrepancies between our results and Coopman et al.'s classification may be because their observations were based on patch tests, which are less reliable than i.d. tests. Hydrocortisone and budesonide have a high affinity for arginine (4); as a result they would be expected to form allergenic steroid glyoxal-protein complexes readily.

The patch test results corresponded poorly with the results from the i.d. tests, supporting earlier observations that patch tests are a poor marker for steroid allergy (8).

Of 6 positive tests to i.d. triamcinolone, only 1 was predicted by patch testing. Patch testing with 1% triamcinolone has been shown to give a higher rate of false-negatives than using concentrations 1000–10,000 less (10). The accuracy of our patch tests might have been improved using a lower concentration of triamcinolone.

Tixocortol is normally regarded as an excellent marker for hydrocortisone, but in our series only

2 of 8 patients positive to i.d. hydrocortisone were positive to tixocortol on patch testing. This may be because our population was not representative of the general population attending for patch tests.

Only 5 of 12 patients previously positive to budesonide on patch testing were positive on re-test, despite all being positive on i.d. testing. Variation in patch test reactivity with time has been described in the past (11, 12).

In conclusion, we have demonstrated that budesonide cross-reacts with hydrocortisone-21-sodium phosphate and triamcinolone acetonide. C-21 substitutions are known not to affect allergenicity (13) and so one can assume that budesonide would also cross-react with hydrocortisone-21-acetate, hydrocortisone-21-butyrate and hydrocortisone-21-succinate. The possibility of a cross-reaction with methyl-prednisolone also exists; however, a larger study would be needed to determine this.

Patients with a positive patch test to budesonide should avoid hydrocortisone and triamcinolone acetonide. Our results support earlier observations that patch tests have a high false-negative rate when testing for corticosteroid allergy.

Our study was limited by its small size. The range of corticosteroids used for i.d. tests was determined by the availability of sterile commercial products. The commercial preparations used contained excipients, which were not controlled for. It would be helpful to subject a wider range of corticosteroids to i.d. tests and to use preparations without excipients.

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