

Title

Topical Corticosteroid Allergy: Results of sequential testing to a corticosteroid series in New Zealand

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Conflict of Interest

None to declare

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Abstract

Background

Our institution tests the European Baseline Series (EBS) and a steroid series sequentially in all patients presenting for patch testing. The rate of steroid sensitisation in New Zealand has not previously been documented.

Objectives

To investigate the rate of corticosteroid sensitisation and assess additional benefit of testing the full steroid series over the steroid allergy markers in the EBS.

Methods/Patients

Retrospective analysis of all patient demographics and patch test results over a 5-year period (2014 to 2019) was performed at a tertiary patch test clinic in Auckland, New Zealand.

Results

319 patients completed patch testing, with a sensitisation rate of 4.4% to ≥ 1 steroid. 79% of positive reactions were of current relevance. 11/14 steroid reactions were to tixocortol pivalate or budesonide. The 'number needed to test' to detect one additional case of steroid sensitisation by using the full steroid series over the EBS alone was 107.

Conclusions

Although steroid sensitisation was not uncommon in our population, the results suggest that sequential testing with the steroid markers (budesonide and tixocortol) in the standard series alone is adequate. The additional steroid series should be added if the steroid markers are positive or where there is a clinical suspicion of steroid allergy.

Main Text

1. Introduction

Corticosteroid creams and ointments are amongst the most commonly prescribed preparations in dermatology. Adverse reactions to steroids may be immunologic, such as immediate and delayed-type hypersensitivity, as well as non-immunologic adverse effects such as skin atrophy and striae (1). Delayed-type hypersensitivity to topical corticosteroids is particularly difficult to diagnose as the anti-inflammatory effect of the steroid can mask the inflammatory response and patch testing is usually required. In New Zealand a variety of topical corticosteroids are fully funded by the government agency PHARMAC, and therefore are available to patients at minimal cost for dispensing only (maximum NZ \$5 per item). Table 1 outlines funded steroid preparations and relative prescription numbers in recent years (2). The PHARMAC subsidy modifies which steroid preparations tend to be prescribed, with potential impact on sensitisation.

Patch testing in New Zealand is a limited service; only the most severe cases are accepted for testing and patients have a long period of symptomatology and treatment prior to testing (3). Both the chronicity of disease in the patch tested population and low cost of topical corticosteroids in New Zealand may contribute to increased steroid exposure and the potential risk of sensitisation. Due to this, it has been standard practice at our institution to routinely test a wide range of corticosteroids (the 'steroids series'), in addition to the steroid allergy markers in the EBS. Routine testing of the steroid series is not generally performed in New Zealand other than at our institution.

Corticosteroids are classified into three groups; nonmethylated and nonhalogenated molecules (group 1), halogenated molecules with a C₁₆/C₁₇ cis ketal/diol structure (group 2) and halogenated and C₁₆methylated molecules (group 3) (Table 2). Baeck and colleagues compared results of patch testing with molecular modelling of corticosteroids, and found patient reactions fitted into two distinct groups (4). For patients reacting only to group 1, molecule charge was important; whereas for patients reacting to groups 1, 2, and 3, the basic corticosteroid molecule structure determined sensitisation.

The reported prevalence of topical corticosteroid allergy amongst patients undergoing patch testing varies widely with reported prevalence rates of 0.5% to 4.9% (5-11). A 2004 study from Melbourne, Australia found 0.52% of patients had a positive reaction to five corticosteroids, suggesting high regional variability (11). A meta-analysis in children found steroid allergy in approximately 1% of those patch-tested (12). There is no data on topical corticosteroid allergy in New Zealand. The aim of this study was to investigate the rate of corticosteroid sensitisation in our population and assess the additional benefit of testing the steroid series over the steroid allergy markers in the EBS.

2. Methods

This study was a retrospective review of all patients patch tested at Auckland District Health Board over a five-year period. This is a tertiary service for patch testing and a central referral site for central Auckland (population 515,000) as well as the greater Auckland and Northland (populations 1,193,000 and 179,000 respectively) (13). Referrals are accepted from specialists only, predominantly dermatologists. Locality approval was granted from Auckland District Health Board Research Office.

Individuals were routinely patch tested to the EBS (30 allergens) and a steroid series (19 allergens) (14). Testing to additional series as indicated by the clinical presentation as well as patients' own products was routine. Patch testing was performed with commercial allergens in plastic chambers on adhesive hypoallergenic tape (Chemotechnique, Vellinge, Sweden.). Patches were removed on D2 and readings were recorded on D2 and D5 (2014 to 2017) or D7 (2018 to 2019) (15).

Population characteristics were described using the MOAHLFAP index (M = male, O = occupational, A = age, H = hands, L = legs, F = face, A = atopy P = positivity rate), in addition to patient ethnicity, and the primary pre- and post-patch test diagnosis (16). The rates of positive and relevant positive patch test reactions to the steroid allergy markers and individual steroids were recorded. Data was entered into an Microsoft excel spreadsheet and statistical analysis was performed using SPSS version 24 (IBM, Armonk, New York).

Reactions were assessed for clinical relevance and the researchers used this to find the prevalence of both topical corticosteroid sensitisation and allergy. For the EBS and steroid series, any positive reaction (+, ++ or +++) on the final reading was categorised as 'positive', while doubtful positive (?+), irritant (IR), and negative reactions were excluded. Reactions were graded in accordance with ESCD guidelines (15). The sensitisation rate within the patient population uses the denominator of the total number of patients tested and numerator of the number of patients with at least one positive reaction. Relevance was recorded as current, past or unknown.

3. Results

From January 2014 to July 2019, 327 individuals attended for patch testing and of these, 319 completed testing. Patient demographics are presented in Table 3. Atopic dermatitis was the most common predominant diagnosis (41% of pre-test diagnoses, 35% of post-test diagnoses), followed by allergic contact dermatitis (26% of pre-test diagnoses, 30% of post-test diagnoses). Ethnicity analysis showed New Zealand European as the largest group (61.4%), followed by Asian (24.8%), Māori (6.0%) and Pacific Peoples (6.0%). Compared to 2018 Census data, Asian patients are overrepresented while other groups, particularly Māori, are underrepresented despite the incidence of eczema being higher in Māori (17).

51% of patients had at least one positive reaction (n=164). The most frequently positive allergens from the EBS were nickel sulphate (20.1%), methylisothiazolinone/methylchloroisothiazolinone (7.8%), methylisothiazolinone (7.5%) fragrance mix I (7.2%), thiuram mix (6.9%), *Myroxylon perei* (6.3%) and p-Phenylenediamine (6.3%).

Corticosteroid reactions are summarised in Table 4. Eighty percent (256) were tested to their own products, which included a steroid in 145 cases. There were 27 positive reactions, and 23 relevant reactions to patients' own products. Of interest, no patients had a positive reaction to their own steroid creams and ointments. Fourteen patients were positive to ≥ 1 steroid, giving a sensitisation rate of 4.4%. Of the 14 cases, 7 reacted to more than one steroid, and 3 reacted to more than two steroids. 11 of the 14 positive steroid reactions were of current clinical relevance to the presenting dermatosis, making the rate of steroid allergy 4.1%, and two reactions were of past relevance. The cases that reacted to steroids on patch testing are summarised in Table 5. There were no significant differences in patient age, gender or ethnicity between the overall patch-tested population and those with steroid sensitisation.

The sensitisation rates for tixocortol and budesonide were both 1.9%. After the markers, the most frequently positive steroid allergens were hydrocortisone butyrate lipocream (0.9%), hydrocortisone butyrate ointment (0.6%), clobetasol cream (0.6%) and clobetasol ointment (0.6%). Several steroids had not produced a positive reaction in any of the patients tested over the five-year period. For those with steroid sensitisation, marker reactions occurred in 79% and the calculated “number needed to test” to detect one extra case of steroid sensitisation by testing the steroid series in addition to the EBS steroid markers was 107.

4. Discussion

The rate of topical corticosteroid allergy in our population (4.1%) is in line with internationally reported rates. A multi-centre European study found sensitivity ranging from 2.0 to 2.5%, a British study found clinical allergy in 1.9%, and a Dutch study found 4.4% versus 1.5% of patients were sensitised in Leuven and Amsterdam respectively (6) (7) (9). There is no prior New Zealand data for comparison however our rate is significantly higher than that reported from Australia (0.52%) (11). Results may vary due to local prescribing patterns, diverse patch testing populations, different patch test series and patch testing methodologies.

Dermatoses affecting the legs such as ulcers and stasis dermatitis are known to be associated with a higher rate of corticosteroid allergy; our population has a low rate of leg dermatoses. However, the literature shows no clear relationship between higher rates of sensitisation and MOAHLFAP characteristics for other centres. A study at two U.K. sites (Oxfordshire and Manchester) found lower rates of steroid allergy in patients at the Oxfordshire site (2.5% versus 8.6%), despite higher rates of leg dermatitis at that centre (6). The authors propose this may be related to prescribing patterns amongst dermatologists at the two sites.

History of atopic dermatitis is another risk factor for steroid sensitisation due to long term use of medicaments. Our steroid sensitised patients had chronic dermatoses and concurrent allergens found on patch testing. Notably, our population has a high rate of atopy at 65.8% compared with 30% in the Australian study, which may somewhat explain their lower steroid sensitisation rate (11).

Our institution has adopted sequential testing to topical corticosteroids due to the theoretical increase in steroid exposure and sensitisation in our population. However, we found all of the steroids were positive in less than 1% of patients with the exception of the markers tixocortol and budesonide. Allergens with a sensitisation rate between 0.5% and 1% may be considered for sequential testing especially if they are of particular relevance or importance (15) (18). In our patients, steroids positive in more than 0.5% of patients were hydrocortisone butyrate cream and ointment, hydrocortisone and clobetasol propionate cream and ointment. Hydrocortisone butyrate and hydrocortisone are both group 1 corticosteroids, and this group also contains the markers tixocortol pivalate and budesonide. In New Zealand, hydrocortisone butyrate is the most common topical corticosteroid prescribed and hydrocortisone can be purchased in pharmacies without prescription. Therefore, our results correlate somewhat with New Zealand steroid prescribing patterns (Table 1).

Wilkinson and Jones found the major determinants of corticosteroid sensitisation to be corticosteroid usage, and ability of the steroid to bind arginine (19). Group 3 steroids such as betamethasone valerate and clobetasol propionate bind arginine to a lesser degree than hydrocortisone and hydrocortisone-17-butyrate and therefore have less potential for sensitisation. However, prescribing habits and chronic use also impact sensitisation rates. Clobetasol is fully funded and easily available in New Zealand. Of the three patients who did not react to markers in our study, two reacted to

clobetasol ointment and clobetasol cream only. In a study of 3,699 patients tested to a steroid series, in addition to the Spanish baseline series, 61.5% of patients who reacted to the additional steroid series did not react to a steroid marker (20). The authors conclude that consideration should be given to updating the corticosteroid screening markers to include group 3 steroids.

Other studies have found steroid markers perform well in detecting corticosteroid allergy. A combination of tixocortol pivalate and budesonide detected 91.3% of corticosteroid-allergic subjects in a 1995 U.K. study (10). Testing tixocortol pivalate and budesonide in ethanol generally detects patients with hydrocortisone and budesonide allergy respectively, but other corticosteroids have displayed both false positive and false negative reactions (21-23). According to Baeck's classification, screening markers in group 1 seems logical; patients with allergy to group 2 and/or 3 are often co-sensitised to group 1 (4). If the markers are positive, further testing with the full steroid series is then helpful in characterising the pattern of sensitisation.

This study has a number of limitations. Firstly, the recommendation for corticosteroid patch testing is that a reading should be taken on D6 or D7, as earlier readings may underestimate corticosteroid allergy by 1/3rd (11). Due to change in clinic staffing, the final reading in our centre changed from D5 to D7 in 2018. As a late reading was not routinely done in our clinic prior to 2018, corticosteroid sensitisation may have been underestimated. Therefore, while our results represent our 'real world' patch testing experience, the diagnostic accuracy of testing may be impacted and this should be considered when interpreting results. Due to dermatology workforce shortage and reduced access to patch testing it is likely corticosteroid allergy is underdiagnosed in our region.

The results of this study are taken from a tertiary referral centre, which biases to patients with chronic and severe dermatoses. The retrospective design meant data was collected from clinical notes, which led to difficulty in some cases interpreting relevance of steroid reactions. As none of our cases reacted to their own steroid preparations, determining relevance was more difficult. Relevance in our cases was determined by the supervising dermatologist if the patient gave a history of using a comparable steroid preparation at the time the dermatosis was active (in a distribution in keeping with the presenting dermatosis). Due to the time lag between referral and performing patch testing (average 4-6 months), it is common that patients no longer have access to their own products for testing.

Another constraint is that our steroid series includes both steroid allergens, and proprietary creams and ointments. Allergy to components of the vehicles were tested for but cannot be excluded in all cases, which may lead to a falsely high rate of sensitisation. It has been suggested that ethanol is a better vehicle for testing steroid allergens (petrolatum was used in the present study) with reduced false negative rates and earlier reactions (24). However, ethanol has issues with irritancy and more rapid allergen degradation (25). This project has been an opportunity to examine our methods for diagnosing steroid allergy and make improvements for future practice.

In summary, we report a steroid sensitisation rate of 4.4% and allergy rate of 4.1% in a New Zealand tertiary referral population. Testing with the steroid markers budesonide and tixocortol is appropriate in our population, but routine sequential testing with the full steroid series is unnecessary. Patients should be tested with their own topical steroid preparations, and the steroid series may be added if the markers are positive or there is clinical suspicion of steroid allergy. Given local prescribing patterns, hydrocortisone, hydrocortisone butyrate, and clobetasol propionate are important steroids; and interventions to address prescribing of steroids with higher sensitising potential should be considered in New Zealand. Risk stratification and positive testing to steroid markers should be used to select patients for additional testing with an extended steroid series.

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Tables

Table 1. Topical Corticosteroid preparations in New Zealand (2)

Corticosteroid Preparation	Number of Prescriptions (2018)
Hydrocortisone butyrate 0.1% - lipocream, ointment, milk emulsion and scalp preparation	194130
Hydrocortisone 1% - cream	139094
Clobetasol propionate 0.05% - cream, ointment and scalp preparation	86345
Betamethasone valerate 0.1% - cream, ointment, lotion and scalp preparation	78100
Mometasone furoate 0.1% - cream, ointment and lotion	72085
Methylprednisolone aceponate 0.1% - cream and ointment	28011
Triamcinolone acetonide 0.02% - cream and ointment	21176
Betamethasone dipropionate 0.05% - cream and ointment	8411

Table 2. Classification of corticosteroids according to Baeck et al. (4).

Corticosteroid Class	Example class members
1	Budesonide, hydrocortisone, hydrocortisone 17-butyrate, methylprednisolone aceponate, prednisone, tixocortol pivalate, triamcinolone
2	Desonide, amcinonide, halcinonide
3	Betamethasone, betamethasone 17-valerate, betamethasone dipronionate, clobetasol propionate, dexamethasone

Table 3. Clinical characteristics of patients patch tested at Auckland City Hospital between 2014 and 2019 (n=319).

Characteristic	Frequency	Percentage
Male	108	33.9%
Occupational cause	26	8.2%
Atopy	210	65.8%
Site of Dermatitis:		
Hands	85	26.6%
Face	70	20.6%
Legs	3	0.9%
Age > 40 years†	183	57.4%
Positivity rate (≥ 1 positive reaction)	164	51.4%

†Mean age = 45 (standard deviation 16.9)

Table 4. Reactions to Steroid Series and Own Products in patients patch-tested at Auckland City Hospital from 2014 to 2019 (n=319).

Steroid/Own Allergen Tested	Positive	Relevant positive	Sensitisation rate	Relevant/positive %
<i>Own substances</i>	30	20	9.4%	66.7%
Budesonide 0.01% pet	6	6	1.9%	100.0%
Tixocortol-21-pivalate 0.1% pet	6	5	1.9%	83.3%
Hydrocortisone butyrate lipocream 0.1% (as is)	3	3	0.9%	100.0%
Hydrocortisone 1.0% pet	2	2	0.6%	100.0%
Clobetasol ointment 0.05% (as is)	2	1	0.6%	50.0%
Clobetasol cream 0.05% (as is)	2	1	0.6%	50.0%
Hydrocortisone butyrate ointment 0.1% (as is)	2	2	0.6%	100.0%
Betamethasone-17 valerate 0.12% pet	1	-	0.3%	0.0%
Hydrocortisone-17-butyrate 0.1% pet	1	1	0.3%	100.0%
Triamcinolone acetonide cream 0.02% (as is)	1	1	0.3%	100.0%
Methylprednisolone aceponate ointment 0.1% (as is)	1	1	0.3%	100.0%
Clobetasol-17-propionate 0.25% pet	-	-	0.0%	0.0%
Triamcinolone acetonide 0.1% pet	-	-	0.0%	0.0%
Prednisolone 1.0% pet	-	-	0.0%	0.0%
Betamethasone valerate ointment 0.1% (as is)	-	-	0.0%	0.0%
Betamethasone valerate cream 0.1% (as is)	-	-	0.0%	0.0%
Mometasone furoate ointment 0.1% (as is)	-	-	0.0%	0.0%
Mometasone furoate cream 0.1% (as is)	-	-	0.0%	0.0%
Methylprednisolone aceponate cream 0.1% (as is)	-	-	0.0%	0.0%
Betamethasone dipropionate ointment 0.05% (as is)	-	-	0.0%	0.0%
Betamethasone dipropionate cream 0.05% (as is)	-	-	0.0%	0.0%
<i>Patient's own topical steroid</i>	-	-	0.0%	0.0%
Number of patients with ≥ 1 steroid reaction	14 (4.4%)	11(3.4%)	4.4%	85.7%

Table 5. Summary of clinical data of patients with reaction to tested corticosteroids

Case	Age at testing	Ethnicity	Gender	Atopy	Clinical Diagnosis and Localisation	Reaction to marker	Positive Steroid Reactions	Relevance	Other positive reactions
1	55	Pasifika	Female	No	Allergic contact dermatitis (hands)	Yes	Budesonide, Tixocortol-21-pivalate, Hydrocortisone-17-butyrate, Hydrocortisone butyrate lipocream 0.1%, Hydrocortisone butyrate ointment 0.1%	Yes	Fragrance mix I, 2-Methoxy-6-n-pentyl-4-bezoquinone
2	17	Asian	Female	Yes	Atopic dermatitis (hands)	No	Betamethasone-17 valerate	Unknown – no previous use of steroid in this class	-
3	65	Asian	Female	No	Allergic contact dermatitis (hands)	No	Clobetasol ointment 0.05%, Clobetasol cream 0.05%	Past relevance	Thiuram mix, Fragrance mix I
4	39	Asian	Male	Yes	Atopic dermatitis (generalised)	No	Clobetasol ointment 0.05%, Clobetasol cream 0.05%	Yes	Thiuram mix
5	57	Asian	Female	No	Allergic contact dermatitis (generalised)	Yes	Budesonide	Yes – exposure to triamcinolone and mometasone	Potassium dichromate, Cobalt chloride, Nickel sulphate, Colophonium, Lanolin alcohol, <i>Myroxylon Pereirae</i> , Fragrance mix I
6	49	Asian	Male	Yes	Allergic contact dermatitis (hands)	Yes	Budesonide, Hydrocortisone butyrate lipocream 0.1%	Yes	-
7	53	Asian	Female	No	Allergic contact dermatitis (generalised)	Yes	Budesonide	Yes – exposure to triamcinolone and hydrocortisone 17-butyrate	4-Phenylenediamine base
8	55	Pasifika	Female	No	Allergic contact dermatitis (hands)	Yes	Tixocortol-21-pivalate	Yes	Neomycin sulphate, Nickel sulphate
9	52	European/ Pākehā	Female	Yes	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Yes	Colophonium, <i>Myroxylon Pereirae</i> , Fragrance Mix I, 2-Methoxy-6-n-pentyl-4-bezoquinone
10	41	European/ Pākehā	Female	No	Allergic contact dermatitis (palmoplantar)	Yes	Budesonide, Hydrocortisone, Hydrocortisone butyrate lipocream 0.1%, Hydrocortisone butyrate ointment 0.1%	Yes	-
11	23	European/ Pākehā	Female	Yes	Allergic contact dermatitis (face)	Yes	Tixocortol-21-pivalate, Hydrocortisone, Triamcinolone acetonide cream 0.02%	Yes	Nickel sulphate, <i>Myroxylon Pereirae</i>
12	64	European/ Pākehā	Male	Yes	Allergic contact dermatitis (generalised)	Yes	Budesonide, Methylprednisolone aceponate ointment 0.1%	Yes	<i>Myroxylon Pereirae</i>
13	62	European/ Pākehā	Female	No	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Past relevance	Neomycin sulphate, Nickel sulphate
14	56	Asian	Female	Yes	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Yes	4-Phenylenediamine base, Neomycin sulphate

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Conclusions

Although steroid sensitisation was not uncommon in our population, the results suggest that sequential testing with the steroid markers (budesonide and tixocortol) in the standard series alone is adequate. The additional steroid series should be added if the steroid markers are positive or where there is a clinical suspicion of steroid allergy.

Main Text

1. Introduction

Corticosteroid creams and ointments are amongst the most commonly prescribed preparations in dermatology. Adverse reactions to steroids may be immunologic, such as immediate and delayed-type hypersensitivity, as well as non-immunologic adverse effects such as skin atrophy and striae (1). Delayed-type hypersensitivity to topical corticosteroids is particularly difficult to diagnose as the anti-inflammatory effect of the steroid can mask the inflammatory response and patch testing is usually required. In New Zealand a variety of topical corticosteroids are fully funded by the government agency PHARMAC, and therefore are available to patients at minimal cost for dispensing only (maximum NZ \$5 per item). Table 1 outlines funded steroid preparations and relative prescription numbers in recent years (2). The PHARMAC subsidy modifies which steroid preparations tend to be prescribed, with potential impact on sensitisation.

Patch testing in New Zealand is a limited service; only the most severe cases are accepted for testing and patients have a long period of symptomatology and treatment prior to testing (3). Both the chronicity of disease in the patch tested population and low cost of topical corticosteroids in New Zealand may contribute to increased steroid exposure and the potential risk of sensitisation. Due to this, it has been standard practice at our institution to routinely test a wide range of corticosteroids (the 'steroids series'), in addition to the steroid allergy markers in the EBS. Routine testing of the steroid series is not generally performed in New Zealand other than at our institution.

Corticosteroids are classified into three groups; nonmethylated and nonhalogenated molecules (group 1), halogenated molecules with a C₁₆/C₁₇ cis ketal/diol structure (group 2) and halogenated and C₁₆methylated molecules (group 3) (Table 2). Baeck and colleagues compared results of patch testing with molecular modelling of corticosteroids, and found patient reactions fitted into two distinct groups (4). For patients reacting only to group 1, molecule charge was important; whereas for patients reacting to groups 1, 2, and 3, the basic corticosteroid molecule structure determined sensitisation.

The reported prevalence of topical corticosteroid allergy amongst patients undergoing patch testing varies widely with reported prevalence rates of 0.5% to 4.9% (5-11). A 2004 study from Melbourne, Australia found 0.52% of patients had a positive reaction to five corticosteroids, suggesting high regional variability (11). A meta-analysis in children found steroid allergy in approximately 1% of those patch-tested (12). There is no data on topical corticosteroid allergy in New Zealand. The aim of this study was to investigate the rate of corticosteroid sensitisation in our population and assess the additional benefit of testing the steroid series over the steroid allergy markers in the EBS.

2. Methods

This study was a retrospective review of all patients patch tested at Auckland District Health Board over a five-year period. This is a tertiary service for patch testing and a central referral site for central Auckland (population 515,000) as well as the greater Auckland and Northland (populations 1,193,000 and 179,000 respectively) (13). Referrals are accepted from specialists only, predominantly dermatologists. Locality approval was granted from Auckland District Health Board Research Office.

Individuals were routinely patch tested to the EBS (30 allergens) and a steroid series (19 allergens) (14). Testing to additional series as indicated by the clinical presentation as well as patients' own products was routine. Patch testing was performed with commercial allergens in plastic chambers on adhesive hypoallergenic tape (Chemotechnique, *Vellinge, Sweden*). Patches were removed on D2 and readings were recorded on D2 and D5 (2014 to 2017) or D7 (2018 to 2019) (15).

Population characteristics were described using the MOAHLFAP index (M = male, O = occupational, A = age, H = hands, L = legs, F = face, A = atopy P = positivity rate), in addition to patient ethnicity, and the primary pre- and post-patch test diagnosis (16). The rates of positive and relevant positive patch test reactions to the steroid allergy markers and individual steroids were recorded. Data was entered into an Microsoft excel spreadsheet and statistical analysis was performed using SPSS version 24 (IBM, *Armonk, New York*).

Reactions were assessed for clinical relevance and the researchers used this to find the prevalence of both topical corticosteroid sensitisation and allergy. For the EBS and steroid series, any positive reaction (+, ++ or +++) on the final reading was categorised as 'positive', while doubtful positive (?+), irritant (IR), and negative reactions were excluded. Reactions were graded in accordance with ESCD guidelines (15). The sensitisation rate within the patient population uses the denominator of the total number of patients tested and numerator of the number of patients with at least one positive reaction. Relevance was recorded as current, past or unknown.

3. Results

From January 2014 to July 2019, 327 individuals attended for patch testing and of these, 319 completed testing. Patient demographics are presented in Table 3. Atopic dermatitis was the most common predominant diagnosis (41% of pre-test diagnoses, 35% of post-test diagnoses), followed by allergic contact dermatitis (26% of pre-test diagnoses, 30% of post-test diagnoses). Ethnicity analysis showed New Zealand European as the largest group (61.4%), followed by Asian (24.8%), Māori (6.0%) and Pacific Peoples (6.0%). Compared to 2018 Census data, Asian patients are overrepresented while other groups, particularly Māori, are underrepresented despite the incidence of eczema being higher in Māori (17).

51% of patients had at least one positive reaction (n=164). The most frequently positive allergens from the EBS were nickel sulphate (20.1%), methylisothiazolinone/methylchlorisothiazolinone (7.8%), methylisothiazolinone (7.5%) fragrance mix I (7.2%), thiuram mix (6.9%), *Myroxylon perei* (6.3%) and p-Phenylenediamine (6.3%).

Corticosteroid reactions are summarised in Table 4. Eighty percent (256) were tested to their own products, which included a steroid in 145 cases. There were 27 positive reactions, and 23 relevant reactions to patients' own products. Of interest, no patients had a positive reaction to their own steroid creams and ointments. Fourteen patients were positive to ≥ 1 steroid, giving a sensitisation rate of 4.4%. Of the 14 cases, 7 reacted to more than one steroid, and 3 reacted to more than two steroids. 11 of the 14 positive steroid reactions were of current clinical relevance to the presenting dermatosis, making the rate of steroid allergy 4.1%, and two reactions were of past relevance. The cases that reacted to steroids on patch testing are summarised in Table 5. There were no significant differences in patient age, gender or ethnicity between the overall patch-tested population and those with steroid sensitisation.

The sensitisation rates for tixocortol and budesonide were both 1.9%. After the markers, the most frequently positive steroid allergens were hydrocortisone butyrate lipocream (0.9%), hydrocortisone butyrate ointment (0.6%), clobetasol cream (0.6%) and clobetasol ointment (0.6%). Several steroids had not produced a positive reaction in any of the patients tested over the five-year period. For those with steroid sensitisation, marker reactions occurred in 79% and the calculated “number needed to test” to detect one extra case of steroid sensitisation by testing the steroid series in addition to the EBS steroid markers was 107.

4. Discussion

The rate of topical corticosteroid allergy in our population (4.1%) is in line with internationally reported rates. A multi-centre European study found sensitivity ranging from 2.0 to 2.5%, a British study found clinical allergy in 1.9%, and a Dutch study found 4.4% versus 1.5% of patients were sensitised in Leuven and Amsterdam respectively (6) (7) (9). There is no prior New Zealand data for comparison however our rate is significantly higher than that reported from Australia (0.52%) (11). Results may vary due to local prescribing patterns, diverse patch testing populations, different patch test series and patch testing methodologies.

Dermatoses affecting the legs such as ulcers and stasis dermatitis are known to be associated with a higher rate of corticosteroid allergy; our population has a low rate of leg dermatoses. However, the literature shows no clear relationship between higher rates of sensitisation and MOAHLFAP characteristics for other centres. A study at two U.K. sites (Oxfordshire and Manchester) found lower rates of steroid allergy in patients at the Oxfordshire site (2.5% versus 8.6%), despite higher rates of leg dermatitis at that centre (6). The authors propose this may be related to prescribing patterns amongst dermatologists at the two sites.

History of atopic dermatitis is another risk factor for steroid sensitisation due to long term use of medicaments. Our steroid sensitised patients had chronic dermatoses and concurrent allergens found on patch testing. Notably, our population has a high rate of atopy at 65.8% compared with 30% in the Australian study, which may somewhat explain their lower steroid sensitisation rate (11).

Our institution has adopted sequential testing to topical corticosteroids due to the theoretical increase in steroid exposure and sensitisation in our population. However, we found all of the steroids were positive in less than 1% of patients with the exception of the markers tixocortol and budesonide. Allergens with a sensitisation rate between 0.5% and 1% may be considered for sequential testing especially if they are of particular relevance or importance (15) (18). In our patients, steroids positive in more than 0.5% of patients were hydrocortisone butyrate cream and ointment, hydrocortisone and clobetasol propionate cream and ointment. Hydrocortisone butyrate and hydrocortisone are both group 1 corticosteroids, and this group also contains the markers tixocortol pivalate and budesonide. In New Zealand, hydrocortisone butyrate is the most common topical corticosteroid prescribed and hydrocortisone can be purchased in pharmacies without prescription. Therefore, our results correlate somewhat with New Zealand steroid prescribing patterns (Table 1).

Wilkinson and Jones found the major determinants of corticosteroid sensitisation to be corticosteroid usage, and ability of the steroid to bind arginine (19). Group 3 steroids such as betamethasone valerate and clobetasol propionate bind arginine to a lesser degree than hydrocortisone and hydrocortisone-17-butyrate and therefore have less potential for sensitisation. However, prescribing habits and chronic use also impact sensitisation rates. Clobetasol is fully funded and easily available in New Zealand. Of the three patients who did not react to markers in our study, two reacted to

clobetasol ointment and clobetasol cream only. In a study of 3,699 patients tested to a steroid series, in addition to the Spanish baseline series, 61.5% of patients who reacted to the additional steroid series did not react to a steroid marker (20). The authors conclude that consideration should be given to updating the corticosteroid screening markers to include group 3 steroids.

Other studies have found steroid markers perform well in detecting corticosteroid allergy. A combination of tixocortol pivalate and budesonide detected 91.3% of corticosteroid-allergic subjects in a 1995 U.K. study (10). Testing tixocortol pivalate and budesonide in ethanol generally detects patients with hydrocortisone and budesonide allergy respectively, but other corticosteroids have displayed both false positive and false negative reactions (21-23). According to Baeck's classification, screening markers in group 1 seems logical; patients with allergy to group 2 and/or 3 are often co-sensitised to group 1 (4). If the markers are positive, further testing with the full steroid series is then helpful in characterising the pattern of sensitisation.

This study has a number of limitations. Firstly, the recommendation for corticosteroid patch testing is that a reading should be taken on D6 or D7, as earlier readings may underestimate corticosteroid allergy by 1/3rd (11). Due to change in clinic staffing, the final reading in our centre changed from D5 to D7 in 2018. As a late reading was not routinely done in our clinic prior to 2018, corticosteroid sensitisation may have been underestimated. Therefore, while our results represent our 'real world' patch testing experience, the diagnostic accuracy of testing may be impacted and this should be considered when interpreting results. Due to dermatology workforce shortage and reduced access to patch testing it is likely corticosteroid allergy is underdiagnosed in our region.

The results of this study are taken from a tertiary referral centre, which biases to patients with chronic and severe dermatoses. The retrospective design meant data was collected from clinical notes, which led to difficulty in some cases interpreting relevance of steroid reactions. As none of our cases reacted to their own steroid preparations, determining relevance was more difficult. Relevance in our cases was determined by the supervising dermatologist if the patient gave a history of using a comparable steroid preparation at the time the dermatosis was active (in a distribution in keeping with the presenting dermatosis). Due to the time lag between referral and performing patch testing (average 4-6 months), it is common that patients no longer have access to their own products for testing.

Another constraint is that our steroid series includes both steroid allergens, and proprietary creams and ointments. Allergy to components of the vehicles were tested for but cannot be excluded in all cases, which may lead to a falsely high rate of sensitisation. It has been suggested that ethanol is a better vehicle for testing steroid allergens (petrolatum was used in the present study) with reduced false negative rates and earlier reactions (24). However, ethanol has issues with irritancy and more rapid allergen degradation (25). This project has been an opportunity to examine our methods for diagnosing steroid allergy and make improvements for future practice.

In summary, we report a steroid sensitisation rate of 4.4% and allergy rate of 4.1% in a New Zealand tertiary referral population. Testing with the steroid markers budesonide and tixocortol is appropriate in our population, but routine sequential testing with the full steroid series is unnecessary. Patients should be tested with their own topical steroid preparations, and the steroid series may be added if the markers are positive or there is clinical suspicion of steroid allergy. Given local prescribing patterns, hydrocortisone, hydrocortisone butyrate, and clobetasol propionate are important steroids; and interventions to address prescribing of steroids with higher sensitising potential should be considered in New Zealand. Risk stratification and positive testing to steroid markers should be used to select patients for additional testing with an extended steroid series.

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Tables

Table 1. Topical Corticosteroid preparations in New Zealand (2)

Corticosteroid Preparation	Number of Prescriptions (2018)
Hydrocortisone butyrate 0.1% - lipocream, ointment, milk emulsion and scalp preparation	194130
Hydrocortisone 1% - cream	139094
Clobetasol propionate 0.05% - cream, ointment and scalp preparation	86345
Betamethasone valerate 0.1% - cream, ointment, lotion and scalp preparation	78100
Mometasone furoate 0.1% - cream, ointment and lotion	72085
Methylprednisolone aceponate 0.1% - cream and ointment	28011
Triamcinolone acetonide 0.02% - cream and ointment	21176
Betamethasone dipropionate 0.05% - cream and ointment	8411

Table 2. Classification of corticosteroids according to Baeck et al. (4).

Corticosteroid Class	Example class members
1	Budesonide, hydrocortisone, hydrocortisone 17-butyrate, methylprednisolone aceponate, prednisone, tixocortol pivalate, triamcinolone
2	Desonide, amcinonide, halcinonide
3	Betamethasone, betamethasone 17-valerate, betamethasone dipronionate, clobetasol propionate, dexamethasone

Table 3. Clinical characteristics of patients patch tested at Auckland City Hospital between 2014 and 2019 (n=319).

Characteristic	Frequency	Percentage
Male	108	33.9%
Occupational cause	26	8.2%
Atopy	210	65.8%
Site of Dermatitis:		
Hands	85	26.6%
Face	70	20.6%
Legs	3	0.9%
Age > 40 years†	183	57.4%
Positivity rate (≥ 1 positive reaction)	164	51.4%

†Mean age = 45 (standard deviation 16.9)

Table 4. Reactions to Steroid Series and Own Products in patients patch-tested at Auckland City Hospital from 2014 to 2019 (n=319).

Steroid/Own Allergen Tested	Positive	Relevant positive	Sensitisation rate	Relevant/positive %
<i>Own substances</i>	30	20	9.4%	66.7%
Budesonide 0.01% pet	6	6	1.9%	100.0%
Tixocortol-21-pivalate 0.1% pet	6	5	1.9%	83.3%
Hydrocortisone butyrate lipocream 0.1% (as is)	3	3	0.9%	100.0%
Hydrocortisone 1.0% pet	2	2	0.6%	100.0%
Clobetasol ointment 0.05% (as is)	2	1	0.6%	50.0%
Clobetasol cream 0.05% (as is)	2	1	0.6%	50.0%
Hydrocortisone butyrate ointment 0.1% (as is)	2	2	0.6%	100.0%
Betamethasone-17 valerate 0.12% pet	1	-	0.3%	0.0%
Hydrocortisone-17-butyrate 0.1% pet	1	1	0.3%	100.0%
Triamcinolone acetonide cream 0.02% (as is)	1	1	0.3%	100.0%
Methylprednisolone aceponate ointment 0.1% (as is)	1	1	0.3%	100.0%
Clobetasol-17-propionate 0.25% pet	-	-	0.0%	0.0%
Triamcinolone acetonide 0.1% pet	-	-	0.0%	0.0%
Prednisolone 1.0% pet	-	-	0.0%	0.0%
Betamethasone valerate ointment 0.1% (as is)	-	-	0.0%	0.0%
Betamethasone valerate cream 0.1% (as is)	-	-	0.0%	0.0%
Mometasone furoate ointment 0.1% (as is)	-	-	0.0%	0.0%
Mometasone furoate cream 0.1% (as is)	-	-	0.0%	0.0%
Methylprednisolone aceponate cream 0.1% (as is)	-	-	0.0%	0.0%
Betamethasone dipropionate ointment 0.05% (as is)	-	-	0.0%	0.0%
Betamethasone dipropionate cream 0.05% (as is)	-	-	0.0%	0.0%
<i>Patient's own topical steroid</i>	-	-	0.0%	0.0%
Number of patients with ≥ 1 steroid reaction	14 (4.4%)	11(3.4%)	4.4%	85.7%

Table 5. Summary of clinical data of patients with reaction to tested corticosteroids

Case	Age at testing	Ethnicity	Gender	Atopy	Clinical Diagnosis and Localisation	Reaction to marker	Positive Steroid Reactions	Relevance	Other positive reactions
1	55	Pasifika	Female	No	Allergic contact dermatitis (hands)	Yes	Budesonide, Tixocortol-21-pivalate, Hydrocortisone-17-butyrate, Hydrocortisone butyrate lipocream 0.1%, Hydrocortisone butyrate ointment 0.1%	Yes	Fragrance mix I, 2-Methoxy-6-n-pentyl-4-bezoquinone
2	17	Asian	Female	Yes	Atopic dermatitis (hands)	No	Betamethasone-17 valerate	Unknown – no previous use of steroid in this class	-
3	65	Asian	Female	No	Allergic contact dermatitis (hands)	No	Clobetasol ointment 0.05%, Clobetasol cream 0.05%	Past relevance	Thiuram mix, Fragrance mix I
4	39	Asian	Male	Yes	Atopic dermatitis (generalised)	No	Clobetasol ointment 0.05%, Clobetasol cream 0.05%	Yes	Thiuram mix
5	57	Asian	Female	No	Allergic contact dermatitis (generalised)	Yes	Budesonide	Yes – exposure to triamcinolone and mometasone	Potassium dichromate, Cobalt chloride, Nickel sulphate, Colophonium, Lanolin alcohol, <i>Myroxylon Pereirae</i> , Fragrance mix I
6	49	Asian	Male	Yes	Allergic contact dermatitis (hands)	Yes	Budesonide, Hydrocortisone butyrate lipocream 0.1%	Yes	-
7	53	Asian	Female	No	Allergic contact dermatitis (generalised)	Yes	Budesonide	Yes – exposure to triamcinolone and hydrocortisone 17-butyrate	4-Phenylenediamine base
8	55	Pasifika	Female	No	Allergic contact dermatitis (hands)	Yes	Tixocortol-21-pivalate	Yes	Neomycin sulphate, Nickel sulphate
9	52	European/ Pākehā	Female	Yes	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Yes	Colophonium, <i>Myroxylon Pereirae</i> , Fragrance Mix I, 2-Methoxy-6-n-pentyl-4-bezoquinone
10	41	European/ Pākehā	Female	No	Allergic contact dermatitis (palmoplantar)	Yes	Budesonide, Hydrocortisone, Hydrocortisone butyrate lipocream 0.1%, Hydrocortisone butyrate ointment 0.1%	Yes	-
11	23	European/ Pākehā	Female	Yes	Allergic contact dermatitis (face)	Yes	Tixocortol-21-pivalate, Hydrocortisone, Triamcinolone acetonide cream 0.02%	Yes	Nickel sulphate, <i>Myroxylon Pereirae</i>
12	64	European/ Pākehā	Male	Yes	Allergic contact dermatitis (generalised)	Yes	Budesonide, Methylprednisolone aceponate ointment 0.1%	Yes	<i>Myroxylon Pereirae</i>
13	62	European/ Pākehā	Female	No	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Past relevance	Neomycin sulphate, Nickel sulphate
14	56	Asian	Female	Yes	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Yes	4-Phenylenediamine base, Neomycin sulphate

Title

Topical Corticosteroid Allergy: Results of sequential testing to a corticosteroid series in New Zealand

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Conflict of Interest

None to declare

Abstract

Background

Our institution tests the European Baseline Series (EBS) and a steroid series sequentially in all patients presenting for patch testing. The rate of steroid sensitisation in New Zealand has not previously been documented.

Objectives

To investigate the rate of corticosteroid sensitisation and assess additional benefit of testing the full steroid series over the steroid allergy markers in the EBS.

Methods/Patients

Retrospective analysis of all patient demographics and patch test results over a 5-year period (2014 to 2019) was performed at a tertiary patch test clinic in Auckland, New Zealand.

Results

319 patients completed patch testing, with a sensitisation rate of 4.4% to ≥ 1 steroid. 79% of positive reactions were of current relevance. 11/14 steroid reactions were to tixocortol pivalate or budesonide. The 'number needed to test' to detect one additional case of steroid sensitisation by using the full steroid series over the EBS alone was 107.

Conclusions

Although steroid sensitisation was not uncommon in our population, the results suggest that sequential testing with the steroid markers (budesonide and tixocortol) in the standard series alone is adequate. The additional steroid series should be added if the steroid markers are positive or where there is a clinical suspicion of steroid allergy.

Main Text

1. Introduction

Corticosteroid creams and ointments are amongst the most commonly prescribed preparations in dermatology. Adverse reactions to steroids may be immunologic, such as immediate and delayed-type hypersensitivity, as well as non-immunologic adverse effects such as skin atrophy and striae (1). Delayed-type hypersensitivity to topical corticosteroids is particularly difficult to diagnose as the anti-inflammatory effect of the steroid can mask the inflammatory response and patch testing is usually required. In New Zealand a variety of topical corticosteroids are fully funded by the government agency PHARMAC, and therefore are available to patients at minimal cost for dispensing only (maximum NZ \$5 per item). Table 1 outlines funded steroid preparations and relative prescription numbers in recent years (2). The PHARMAC subsidy modifies which steroid preparations tend to be prescribed, with potential impact on sensitisation.

Patch testing in New Zealand is a limited service; only the most severe cases are accepted for testing and patients have a long period of symptomatology and treatment prior to testing (3). Both the chronicity of disease in the patch tested population and low cost of topical corticosteroids in New Zealand may contribute to increased steroid exposure and the potential risk of sensitisation. Due to this, it has been standard practice at our institution to routinely test a wide range of corticosteroids (the 'steroids series'), in addition to the steroid allergy markers in the EBS. Routine testing of the steroid series is not generally performed in New Zealand other than at our institution.

Corticosteroids are classified into three groups; nonmethylated and nonhalogenated molecules (group 1), halogenated molecules with a C₁₆/C₁₇ cis ketal/diol structure (group 2) and halogenated and C₁₆methylated molecules (group 3) (Table 2). Baeck and colleagues compared results of patch testing with molecular modelling of corticosteroids, and found patient reactions fitted into two distinct groups (4). For patients reacting only to group 1, molecule charge was important; whereas for patients reacting to groups 1, 2, and 3, the basic corticosteroid molecule structure determined sensitisation.

The reported prevalence of topical corticosteroid allergy amongst patients undergoing patch testing varies widely with reported prevalence rates of 0.5% to 4.9% (5-11). A 2004 study from Melbourne, Australia found 0.52% of patients had a positive reaction to five corticosteroids, suggesting high regional variability (11). A meta-analysis in children found steroid allergy in approximately 1% of those patch-tested (12). There is no data on topical corticosteroid allergy in New Zealand. The aim of this study was to investigate the rate of corticosteroid sensitisation in our population and assess the additional benefit of testing the steroid series over the steroid allergy markers in the EBS.

2. Methods

This study was a retrospective review of all patients patch tested at Auckland District Health Board over a five-year period. This is a tertiary service for patch testing and a central referral site for central Auckland (population 515,000) as well as the greater Auckland and Northland (populations 1,193,000 and 179,000 respectively) (13). Referrals are accepted from specialists only, predominantly dermatologists. Locality approval was granted from Auckland District Health Board Research Office.

Individuals were routinely patch tested to the EBS (30 allergens) and a steroid series (19 allergens) (14). Testing to additional series as indicated by the clinical presentation as well as patients' own products was routine. Patch testing was performed with commercial allergens in plastic chambers on adhesive hypoallergenic tape (Chemotechnique, *Vellinge, Sweden*). Patches were removed on D2 and readings were recorded on D2 and D5 (2014 to 2017) or D7 (2018 to 2019) (15).

Population characteristics were described using the MOAHLFAP index (M = male, O = occupational, A = age, H = hands, L = legs, F = face, A = atopy P = positivity rate), in addition to patient ethnicity, and the primary pre- and post-patch test diagnosis (16). The rates of positive and relevant positive patch test reactions to the steroid allergy markers and individual steroids were recorded. Data was entered into an Microsoft excel spreadsheet and statistical analysis was performed using SPSS version 24 (IBM, *Armonk, New York*).

Reactions were assessed for clinical relevance and the researchers used this to find the prevalence of both topical corticosteroid sensitisation and allergy. For the EBS and steroid series, any positive reaction (+, ++ or +++) on the final reading was categorised as 'positive', while doubtful positive (?+), irritant (IR), and negative reactions were excluded. Reactions were graded in accordance with ESCD guidelines (15). The sensitisation rate within the patient population uses the denominator of the total number of patients tested and numerator of the number of patients with at least one positive reaction. Relevance was recorded as current, past or unknown.

3. Results

From January 2014 to July 2019, 327 individuals attended for patch testing and of these, 319 completed testing. Patient demographics are presented in Table 3. Atopic dermatitis was the most common predominant diagnosis (41% of pre-test diagnoses, 35% of post-test diagnoses), followed by allergic contact dermatitis (26% of pre-test diagnoses, 30% of post-test diagnoses). Ethnicity analysis showed New Zealand European as the largest group (61.4%), followed by Asian (24.8%), Māori (6.0%) and Pacific Peoples (6.0%). Compared to 2018 Census data, Asian patients are overrepresented while other groups, particularly Māori, are underrepresented despite the incidence of eczema being higher in Māori (17).

51% of patients had at least one positive reaction (n=164). The most frequently positive allergens from the EBS were nickel sulphate (20.1%), methylisothiazolinone/methylchlorisothiazolinone (7.8%), methylisothiazolinone (7.5%) fragrance mix I (7.2%), thiuram mix (6.9%), *Myroxylon pereirae* (6.3%) and p-Phenylenediamine (6.3%).

Corticosteroid reactions are summarised in Table 4. Eighty percent (256) were tested to their own products, which included a steroid in 145 cases. There were 27 positive reactions, and 23 relevant reactions to patients' own products. Of interest, no patients had a positive reaction to their own steroid creams and ointments. Fourteen patients were positive to ≥ 1 steroid, giving a sensitisation rate of 4.4%. Of the 14 cases, 7 reacted to more than one steroid, and 3 reacted to more than two steroids. 11 of the 14 positive steroid reactions were of current clinical relevance to the presenting dermatosis, making the rate of steroid allergy 4.1%, and two reactions were of past relevance. The cases that reacted to steroids on patch testing are summarised in Table 5. There were no significant differences in patient age, gender or ethnicity between the overall patch-tested population and those with steroid sensitisation.

The sensitisation rates for tixocortol and budesonide were both 1.9%. After the markers, the most frequently positive steroid allergens were hydrocortisone butyrate lipocream (0.9%), hydrocortisone butyrate ointment (0.6%), clobetasol cream (0.6%) and clobetasol ointment (0.6%). Several steroids had not produced a positive reaction in any of the patients tested over the five-year period. For those with steroid sensitisation, marker reactions occurred in 79% and the calculated “number needed to test” to detect one extra case of steroid sensitisation by testing the steroid series in addition to the EBS steroid markers was 107.

4. Discussion

The rate of topical corticosteroid allergy in our population (4.1%) is in line with internationally reported rates. A multi-centre European study found sensitivity ranging from 2.0 to 2.5%, a British study found clinical allergy in 1.9%, and a Dutch study found 4.4% versus 1.5% of patients were sensitised in Leuven and Amsterdam respectively (6) (7) (9). There is no prior New Zealand data for comparison however our rate is significantly higher than that reported from Australia (0.52%) (11). Results may vary due to local prescribing patterns, diverse patch testing populations, different patch test series and patch testing methodologies.

Dermatoses affecting the legs such as ulcers and stasis dermatitis are known to be associated with a higher rate of corticosteroid allergy; our population has a low rate of leg dermatoses. However, the literature shows no clear relationship between higher rates of sensitisation and MOAHLFAP characteristics for other centres. A study at two U.K. sites (Oxfordshire and Manchester) found lower rates of steroid allergy in patients at the Oxfordshire site (2.5% versus 8.6%), despite higher rates of leg dermatitis at that centre (6). The authors propose this may be related to prescribing patterns amongst dermatologists at the two sites.

History of atopic dermatitis is another risk factor for steroid sensitisation due to long term use of medicaments. Our steroid sensitised patients had chronic dermatoses and concurrent allergens found on patch testing. Notably, our population has a high rate of atopy at 65.8% compared with 30% in the Australian study, which may somewhat explain their lower steroid sensitisation rate (11).

Our institution has adopted sequential testing to topical corticosteroids due to the theoretical increase in steroid exposure and sensitisation in our population. However, we found all of the steroids were positive in less than 1% of patients with the exception of the markers tixocortol and budesonide. Allergens with a sensitisation rate between 0.5% and 1% may be considered for sequential testing especially if they are of particular relevance or importance (15) (18). In our patients, steroids positive in more than 0.5% of patients were hydrocortisone butyrate cream and ointment, hydrocortisone and clobetasol propionate cream and ointment. Hydrocortisone butyrate and hydrocortisone are both group 1 corticosteroids, and this group also contains the markers tixocortol pivalate and budesonide. In New Zealand, hydrocortisone butyrate is the most common topical corticosteroid prescribed and hydrocortisone can be purchased in pharmacies without prescription. Therefore, our results correlate somewhat with New Zealand steroid prescribing patterns (Table 1).

Wilkinson and Jones found the major determinants of corticosteroid sensitisation to be corticosteroid usage, and ability of the steroid to bind arginine (19). Group 3 steroids such as betamethasone valerate and clobetasol propionate bind arginine to a lesser degree than hydrocortisone and hydrocortisone-17-butyrate and therefore have less potential for sensitisation. However, prescribing habits and chronic use also impact sensitisation rates. Clobetasol is fully funded and easily available in New Zealand. Of the three patients who did not react to markers in our study, two reacted to

clobetasol ointment and clobetasol cream only. In a study of 3,699 patients tested to a steroid series, in addition to the Spanish baseline series, 61.5% of patients who reacted to the additional steroid series did not react to a steroid marker (20). The authors conclude that consideration should be given to updating the corticosteroid screening markers to include group 3 steroids.

Other studies have found steroid markers perform well in detecting corticosteroid allergy. A combination of tixocortol pivalate and budesonide detected 91.3% of corticosteroid-allergic subjects in a 1995 U.K. study (10). Testing tixocortol pivalate and budesonide in ethanol generally detects patients with hydrocortisone and budesonide allergy respectively, but other corticosteroids have displayed both false positive and false negative reactions (21-23). According to Baeck's classification, screening markers in group 1 seems logical; patients with allergy to group 2 and/or 3 are often co-sensitised to group 1 (4). If the markers are positive, further testing with the full steroid series is then helpful in characterising the pattern of sensitisation.

This study has a number of limitations. Firstly, the recommendation for corticosteroid patch testing is that a reading should be taken on D6 or D7, as earlier readings may underestimate corticosteroid allergy by 1/3rd (11). Due to change in clinic staffing, the final reading in our centre changed from D5 to D7 in 2018. As a late reading was not routinely done in our clinic prior to 2018, corticosteroid sensitisation may have been underestimated. Therefore, while our results represent our 'real world' patch testing experience, the diagnostic accuracy of testing may be impacted and this should be considered when interpreting results. Due to dermatology workforce shortage and reduced access to patch testing it is likely corticosteroid allergy is underdiagnosed in our region.

The results of this study are taken from a tertiary referral centre, which biases to patients with chronic and severe dermatoses. The retrospective design meant data was collected from clinical notes, which led to difficulty in some cases interpreting relevance of steroid reactions. As none of our cases reacted to their own steroid preparations, determining relevance was more difficult. Relevance in our cases was determined by the supervising dermatologist if the patient gave a history of using a comparable steroid preparation at the time the dermatosis was active (in a distribution in keeping with the presenting dermatosis). Due to the time lag between referral and performing patch testing (average 4-6 months), it is common that patients no longer have access to their own products for testing.

Another constraint is that our steroid series includes both steroid allergens, and proprietary creams and ointments. Allergy to components of the vehicles were tested for but cannot be excluded in all cases, which may lead to a falsely high rate of sensitisation. It has been suggested that ethanol is a better vehicle for testing steroid allergens (petrolatum was used in the present study) with reduced false negative rates and earlier reactions (24). However, ethanol has issues with irritancy and more rapid allergen degradation (25). This project has been an opportunity to examine our methods for diagnosing steroid allergy and make improvements for future practice.

In summary, we report a steroid sensitisation rate of 4.4% and allergy rate of 4.1% in a New Zealand tertiary referral population. Testing with the steroid markers budesonide and tixocortol is appropriate in our population, but routine sequential testing with the full steroid series is unnecessary. Patients should be tested with their own topical steroid preparations, and the steroid series may be added if the markers are positive or there is clinical suspicion of steroid allergy. Given local prescribing patterns, hydrocortisone, hydrocortisone butyrate, and clobetasol propionate are important steroids; and interventions to address prescribing of steroids with higher sensitising potential should be considered in New Zealand. Risk stratification and positive testing to steroid markers should be used to select patients for additional testing with an extended steroid series.

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Tables

Table 1. Topical Corticosteroid preparations in New Zealand (2)

Corticosteroid Preparation	Number of Prescriptions (2018)
Hydrocortisone butyrate 0.1% - lipocream, ointment, milk emulsion and scalp preparation	194130
Hydrocortisone 1% - cream	139094
Clobetasol propionate 0.05% - cream, ointment and scalp preparation	86345
Betamethasone valerate 0.1% - cream, ointment, lotion and scalp preparation	78100
Mometasone furoate 0.1% - cream, ointment and lotion	72085
Methylprednisolone aceponate 0.1% - cream and ointment	28011
Triamcinolone acetonide 0.02% - cream and ointment	21176
Betamethasone dipropionate 0.05% - cream and ointment	8411

Table 2. Classification of corticosteroids according to Baeck et al. (4).

Corticosteroid Class	Example class members
1	Budesonide, hydrocortisone, hydrocortisone 17-butyrate, methylprednisolone aceponate, prednisone, tixocortol pivalate, triamcinolone
2	Desonide, amcinonide, halcinonide
3	Betamethasone, betamethasone 17-valerate, betamethasone dipronionate, clobetasol propionate, dexamethasone

Table 3. Clinical characteristics of patients patch tested at Auckland City Hospital between 2014 and 2019 (n=319).

Characteristic	Frequency	Percentage
Male	108	33.9%
Occupational cause	26	8.2%
Atopy	210	65.8%
Site of Dermatitis:		
Hands	85	26.6%
Face	70	20.6%
Legs	3	0.9%
Age > 40 years†	183	57.4%
Positivity rate (≥ 1 positive reaction)	164	51.4%

†Mean age = 45 (standard deviation 16.9)

Table 4. Reactions to Steroid Series and Own Products in patients patch-tested at Auckland City Hospital from 2014 to 2019 (n=319).

Steroid/Own Allergen Tested	Positive	Relevant positive	Sensitisation rate	Relevant/positive %
<i>Own substances</i>	30	20	9.4%	66.7%
Budesonide 0.01% pet	6	6	1.9%	100.0%
Tixocortol-21-pivalate 0.1% pet	6	5	1.9%	83.3%
Hydrocortisone butyrate lipocream 0.1% (as is)	3	3	0.9%	100.0%
Hydrocortisone 1.0% pet	2	2	0.6%	100.0%
Clobetasol ointment 0.05% (as is)	2	1	0.6%	50.0%
Clobetasol cream 0.05% (as is)	2	1	0.6%	50.0%
Hydrocortisone butyrate ointment 0.1% (as is)	2	2	0.6%	100.0%
Betamethasone-17 valerate 0.12% pet	1	-	0.3%	0.0%
Hydrocortisone-17-butyrate 0.1% pet	1	1	0.3%	100.0%
Triamcinolone acetonide cream 0.02% (as is)	1	1	0.3%	100.0%
Methylprednisolone aceponate ointment 0.1% (as is)	1	1	0.3%	100.0%
Clobetasol-17-propionate 0.25% pet	-	-	0.0%	0.0%
Triamcinolone acetonide 0.1% pet	-	-	0.0%	0.0%
Prednisolone 1.0% pet	-	-	0.0%	0.0%
Betamethasone valerate ointment 0.1% (as is)	-	-	0.0%	0.0%
Betamethasone valerate cream 0.1% (as is)	-	-	0.0%	0.0%
Mometasone furoate ointment 0.1% (as is)	-	-	0.0%	0.0%
Mometasone furoate cream 0.1% (as is)	-	-	0.0%	0.0%
Methylprednisolone aceponate cream 0.1% (as is)	-	-	0.0%	0.0%
Betamethasone dipropionate ointment 0.05% (as is)	-	-	0.0%	0.0%
Betamethasone dipropionate cream 0.05% (as is)	-	-	0.0%	0.0%
<i>Patient's own topical steroid</i>	-	-	0.0%	0.0%
Number of patients with ≥ 1 steroid reaction	14 (4.4%)	11(3.4%)	4.4%	85.7%

Table 5. Summary of clinical data of patients with reaction to tested corticosteroids

Case	Age at testing	Ethnicity	Gender	Atopy	Clinical Diagnosis and Localisation	Reaction to marker	Positive Steroid Reactions	Relevance	Other positive reactions
1	55	Pasifika	Female	No	Allergic contact dermatitis (hands)	Yes	Budesonide, Tixocortol-21-pivalate, Hydrocortisone-17-butyrate, Hydrocortisone butyrate lipocream 0.1%, Hydrocortisone butyrate ointment 0.1%	Yes	Fragrance mix I, 2-Methoxy-6-n-pentyl-4-bezoquinone
2	17	Asian	Female	Yes	Atopic dermatitis (hands)	No	Betamethasone-17 valerate	Unknown – no previous use of steroid in this class	-
3	65	Asian	Female	No	Allergic contact dermatitis (hands)	No	Clobetasol ointment 0.05%, Clobetasol cream 0.05%	Past relevance	Thiuram mix, Fragrance mix I
4	39	Asian	Male	Yes	Atopic dermatitis (generalised)	No	Clobetasol ointment 0.05%, Clobetasol cream 0.05%	Yes	Thiuram mix
5	57	Asian	Female	No	Allergic contact dermatitis (generalised)	Yes	Budesonide	Yes – exposure to triamcinolone and mometasone	Potassium dichromate, Cobalt chloride, Nickel sulphate, Colophonium, Lanolin alcohol, <i>Myroxylon Pereirae</i> , Fragrance mix I
6	49	Asian	Male	Yes	Allergic contact dermatitis (hands)	Yes	Budesonide, Hydrocortisone butyrate lipocream 0.1%	Yes	-
7	53	Asian	Female	No	Allergic contact dermatitis (generalised)	Yes	Budesonide	Yes – exposure to triamcinolone and hydrocortisone 17-butyrate	4-Phenylenediamine base
8	55	Pasifika	Female	No	Allergic contact dermatitis (hands)	Yes	Tixocortol-21-pivalate	Yes	Neomycin sulphate, Nickel sulphate
9	52	European/ Pākehā	Female	Yes	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Yes	Colophonium, <i>Myroxylon Pereirae</i> , Fragrance Mix I, 2-Methoxy-6-n-pentyl-4-bezoquinone
10	41	European/ Pākehā	Female	No	Allergic contact dermatitis (palmoplantar)	Yes	Budesonide, Hydrocortisone, Hydrocortisone butyrate lipocream 0.1%, Hydrocortisone butyrate ointment 0.1%	Yes	-
11	23	European/ Pākehā	Female	Yes	Allergic contact dermatitis (face)	Yes	Tixocortol-21-pivalate, Hydrocortisone, Triamcinolone acetonide cream 0.02%	Yes	Nickel sulphate, <i>Myroxylon Pereirae</i>
12	64	European/ Pākehā	Male	Yes	Allergic contact dermatitis (generalised)	Yes	Budesonide, Methylprednisolone aceponate ointment 0.1%	Yes	<i>Myroxylon Pereirae</i>
13	62	European/ Pākehā	Female	No	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Past relevance	Neomycin sulphate, Nickel sulphate
14	56	Asian	Female	Yes	Allergic contact dermatitis (generalised)	Yes	Tixocortol-21-pivalate	Yes	4-Phenylenediamine base, Neomycin sulphate