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Skin testing for immediate hypersensitivity to corticosteroids – a case series and literature review

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Abstract

Background

Immediate hypersensitivity to corticosteroids is reported to occur with an incidence of 0.1%. The largest previous case series reporting corticosteroid skin testing has 7 patients.

Methods and Patients

We identified 23 patients (mean age 50 years, 65% female) from Auckland hospital who underwent skin testing for suspected corticosteroid hypersensitivity between July 2005 and April 2012. We performed a retrospective clinical case note review detailing clinical history of reaction, skin test results and subsequent management. Most patients (21/23) had a standard panel of testing with prednisolone, triamcinolone, methylprednisolone, hydrocortisone, and dexamethasone. Skin tests used a 10% steroid stock concentration for skin prick tests (SPT) and dilutions of 1:1000, 1:100 and 1:10, for subsequent intradermal testing. A wheal 3mm greater than the negative control was considered positive.

Results

A total of 23 patients were identified who had skin testing for suspected acute hypersensitivity to corticosteroids, 8 of which had a history of anaphylaxis. From 28 reactions (in 23 patients) the most common route of administration was intra-articular (13), followed by oral (7), intravenous (3) and other (5). Skin tests were positive in 8/23 patients and 7/8 of these patients had a history of corticosteroid associated anaphylaxis. Skin tests were positive at either the skin prick test or intradermal stages. There was evidence suggesting clinical and skin test cross-reactivity between corticosteroids in one patient. One patient had a positive skin test but negative oral challenge suggesting the skin test was false positive. Skin tests were negative in 15/23 patients. One patient had a negative prednisolone skin test and positive unblinded oral challenge, suggesting a false negative skin test.

Conclusions

Skin testing can provide sufficient evidence to diagnose allergy in patients with a clear history of immediate hypersensitivity to corticosteroids such as anaphylaxis. Both skin prick and intradermal tests should be used. There is evidence of cross-reactivity between steroids so a panel is recommended. False positive and false negative reactions do occur, however the frequency is unknown. Challenge remains the only definitive way to demonstrate a safe alternative to use.

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Accepted Article

Background

Immediate Hypersensitivity to Corticosteroids

Allergy to corticosteroids has been increasingly described in the literature over the last 30 years. Contact allergy to corticosteroids is well described and of varying incidence (0.5-5%)(1). It is important to distinguish contact delayed type reactions from immediate hypersensitivity, which is the focus of this study.

Immediate allergic reactions are less frequent. Evidence consists mostly of case reports, of which there are over 100 in the published literature(2). The reported incidence varies. One study of 213 children who had a total of 10000 doses of corticosteroids reported an incidence of allergic reaction as 0.1% most of which were immediate(14).

Almost all corticosteroids have been associated with immediate hypersensitivity, including methylprednisone, hydrocortisone, prednisone, prednisolone, triamcinolone, dexamethasone and betamethasone(9). Anaphylaxis has been associated with oral, intravenous and intra-articular administration(11) as well as inhalation(30). Intranasal glucocorticoid administration has been associated with acute urticaria(31), and contact urticaria has been described with corticosteroid creams(32).

The basic structure of most steroid hormones has three rings of six carbon atoms and one ring of five, the cyclopentanoperhydrophenanthrene nucleus. Variations in double bonds, methyl groups, acetonide bonds or halogenation influence the steroid properties such as solubility, cutaneous penetration and enzyme degradation. In contact dermatitis secondary to corticosteroids, cross-reaction patterns have been identified between structurally similar compounds. In immediate hypersensitivity however, there is insufficient data to demonstrate a pattern of cross-reactivity(7,20,25).

Corticosteroids may be coupled with an ester (eg succinate, phosphate, butyrate, aceponate) which can increase skin penetration or solubility depending on the ester and position attached. The succinate ester used to enhance solubility in parenteral preparations has been implicated in antigenicity in several immediate hypersensitivity case reports(5,6,26). In one case, skin tests and oral challenge to the succinate ester version of methylprednisone (Solumedrol) were positive, but both were negative to the unesterified (medrol) version(2).

The excipient carboxymethylcellulose (which is a suspending agent in parenteral preparations) has been the only positive reaction on skin testing in at least 18 described cases(24). A similar problem has been reported with carboxymethylcellulose in radiocontrast media(3). Two patients with severe cow's milk allergy had immediate allergic reactions with Solumedrol, and subsequent skin testing was only positive to B-lactoglobulin contaminating lactose in the steroid preparation(10).

The authors of some case reports have described acute reactions to corticosteroids that are postulated to be non-IgE mediated. These include pseudo-allergic reactions similar to those with acetylsalicylic acid through cyclooxygenase blockade(16,17),

alpha-adrenergic blockade and negative inotropic effect with rapid intravenous infusion(11,18), and direct stimulation of mast cells to release histamine(23).

Flushing/erythema has been reported as a side effect of triamcinolone intra-articular injections with an incidence of 40% in one case series of 100 patients. It was more common in women($p<0.01$), with a mean time of onset at 19 hours after injections, and lasting an average of 48 hours (range 6 – 96 hrs). This recurred again on repeat triamcinolone injections in the majority who were rechallenged(27). Facial flushing and/or generalised erythema has also been reported in a case series of 12 patients with triamcinolone epidural injections, occurring at a similar timeframe. In one patient this occurred with methylprednisone as well(28). Flushing occurred in 13/81 patients(13%) with lumbar epidural injections of methylprednisone or Betamethsone acetate/Betamethsone sodium phosphate(29).

Testing for suspected glucocorticoid immediate hypersensitivity

With over 100 cases of glucocorticoid immediate hypersensitivity published, a number have had positive skin tests, both skin prick and intradermal(6,13,14,21). *In vitro* specific IgE testing has not been performed in most, however it has been positive in several cases(2). Specific IgE tests have often been negative however, potentially due to the hapten nature of corticosteroids or difficulties with solubility requiring conjugation in the testing(19,20).

Currently the largest case series of skin testing for corticosteroid associated immediate hypersensitivity has been reported by Venturini et al. From 7 patients with clinical presentations suggestive of acute hypersensitivity, 6 had positive STs. Three reacted to methylprednisone, two to carboxymethylcellulose and one to triamcinolone. Skin tests were positive at either the skin prick or intradermal stages. One patient had a negative ST but a positive oral challenge, suggesting that false negative STs do occur(21). De Sousa et al reported skin testing to 4 children presenting with corticosteroid associated anaphylaxis and all four were positive to the implicated steroid(30).

There have been a few reported cases of corticosteroid skin testing in “healthy controls” with no history of corticosteroid allergy. In one study, five healthy controls had skin prick testing (but not intradermal injections) to a panel of prednisolone, methylprednisolone, betamethasone, hydrocortisone, dexamethasone and triamcinolone. These were negative for all five(20). Of ten atopic and ten non-atopic controls in another study, all twenty were negative(21). Another study included 10 atopic control patients and all were negative to skin prick and intradermal testing with prednisolone glycolate, methylprednisolone sodium succinate, hydrocortisone sodium succinate, dexamethasone phosphate and oral betamethasone(30). This suggests a relatively low-rate of false positive results.

Due to the small numbers in these case series, the sensitivity and specificity of corticosteroid skin testing is unknown and therefore negative skin testing or specific IgE does not rule out the possibility of allergy. Challenge provocation testing remains the gold standard for confirming or refuting immediate hypersensitivity to corticosteroids.

Aim

To describe our experience with corticosteroid skin testing at Auckland City Hospital, and interpret this with reference to previous literature on the subject.

Methods

All corticosteroid skin tests performed at Auckland City Hospital are prospectively recorded in a database. Cases between July 2005 and April 2012 were identified from this database. A retrospective review of the clinical notes was performed by one author (AB). Information extracted included the clinical history of symptoms associated with corticosteroid exposure, other potential causative drugs/agents involved, skin testing results, and subsequent management advice given to the patient.

A standard panel of testing was most frequently used, see table 1 below:

	SPT(10%)	Intradermal 1:1000	Intradermal 1:100	Intradermal 1:10
Prednisolone (Redipred)	0.67mg/ml	0.067mg/ml	0.067mg/ml	0.67 mg/ml
Triamcinolone (Kenacort)	4mg/ml	0.04mg/ml	0.4mg/ml	4mg/ml
Methylprednisone (Depomedrol)	4mg/ml	0.04mg/ml	0.4mg/ml	4mg/ml
Hydrocortisone (Solu-cortef)	5mg/ml	0.05mg/ml	0.5mg/ml	5mg/ml
Dexamethasone	0.4mg/ml	0.004mg/ml	0.04mg/ml	0.4mg/ml
Negative control	Saline (0.9%)	Saline(0.9%)		
Positive control	Histamine			

A wheal 3mm greater than the negative control was considered as positive. Injection volume was standardised at 0.02ml. If a skin test result was positive to a particular corticosteroid, skin testing continued to other corticosteroids as per the protocol. Patients were tested with lignocaine, chlorhexidine and other agents if indicated by the clinical history.

Five cases were excluded due to insufficient information in the clinical notes. Twelve cases with perioperative allergic reactions were also excluded as they had a large number of co-administered medications such as anaesthetics, analgesics, and antibiotics. These cases were only tested to dexamethasone and all were negative. These are summarised in Appendix 1.

The study design was reviewed by the Health and Disability Ethics Committee of the New Zealand Ministry of Health, and was confirmed as meeting the criteria for an audit and therefore not requiring further ethical review.

Results

A total of 23 patients were included, (mean age 50 years, 65% female). Clinical presentations were with anaphylaxis(8), acute urticaria/rash and/or acute angioedema(4), presyncope(2), acute flushing(2) delayed flushing(3) and other delayed or miscellaneous reactions(4).

Of these, 21 had skin testing to a full panel of five corticosteroids, while 2 had skin testing limited to the agent implicated in the clinical history. From 28 reactions (in 23 patients) the most common route of administration was intra-articular (13), followed by oral (7), intravenous (3) and other (5).

There were positive skin test results in 8/23 patients (Table 1). Most (7/8) of these patients had a history of corticosteroid associated anaphylaxis. Five of these patients had clinically reacted in association with intra-articular triamcinolone injections, whereas one patient clinically reacted to a rotator cuff injection of methylprednisone. Initial positive results occurred at either skin prick (n=2) or intradermal stages (n=6). There were no systemic reactions to the skin testing. Management advice for patients with a positive skin test generally consisted of avoiding the steroid associated with a positive skin test result.

One patient, (number 6) had a positive ST to prednisolone (oral liquid) but had no history of using this steroid, and had a subsequent negative prednisone(tablet) oral challenge, so we consider this evidence of a false positive skin test. Furthermore, the positive skin test to prednisolone in patient 1 from the excluded anaesthetic group(Appendix 1) may be another example of a false positive result.

These results are below:

Table 2 :Positive Steroid Skin Tests

Age	Steroid/ route	Other drugs	Symptoms and time of onset	SPT	Intraderm.	Negative tests	Management / challenge
167M	Tr intra-articular	Lign	Ax, H, U immediate	-ve	Tr (0.04mg/ml)	Pr MPr Hct Dex Lign	Avoid Tr
252M	Tr intra-articular	Lign	Ax H, Ang, SOB	Tr (4mg/ml)	-ve (TrNT)	Pr MPr Hct Dex Lign	Avoid Tr
351F	Tr intra-articular	Lign	Ax 30 minutes	-ve	Tr (0.04mg/ml)	Pr MPr Hct Dex Latex, chlorhex, Lign	Avoid Tr
437M	Tr intra-articular	Lign	Ax , U, SOB immediate	Tr (4mg/ml)	-ve (TrNT)	Pr MPr Hct Dex Latex, Lign	Avoid Tr
590F	Tr intra-articular	Lign	Ax	-ve	Tr (0.04mg/ml)	Pr MPr Hct Dex Lign	Avoid Tr,

6 5 3 M	MPr to rotator cuff	Li gn	Ax	-ve	Pr (0.67mg/ml)	Tr MPr Hct Dex Lign	Oral Pr challenge negative
7 6 5 F	1-Pr oral 2- Hct skin cream		1-Ax 2-U acute	-ve	Pr (0.067mg/ml) Hct(0.5mg/ml) at 18hrs (both -ve at 15 mins)	Tr MPr Dex	Dex challenge negative, Avoid Pr and Hct
8 6 2 F	Unknow n steroid intracul ar		Ang 2 hours	-ve	Pr (0.067mg/ml)	Tr MPr Hct Dex Lign	Avoid Pr

Pr = prednisolone = redipred

H=hypotension

Ang=Angioedema

Dex = dexamethasone

Lign = Lignocaine

-ve = Negative

MPr = methylprednisone = Depomedrol

Tr = triamcinolone = Kenacort

NT = not tested

U=Urticaria

SOB=Shortness of breath

Chlorhex = chlorhexidene

Hct = hydrocortisone

Ax = anaphylaxis

ST results were negative in 15/23 patients (see Table 2). Only one of these patients(patient 9) presented with anaphylaxis, with the remainder having acute urticaria or angioedema(3), presyncope(2), acute flushing(2), delayed flushing(3) and other delayed or miscellaneous reactions(4). Six patients were offered a supervised corticosteroid challenge. Three patients refused, while 2 patients had negative challenges. One patient(patient 10) had a challenge considered positive, precipitating acute urticaria suggesting a false negative skin test. It is however worthy of note that this patient had a past history chronic urticaria, that was quiescent at the time.

Table 3. Negative Steroid Skin Prick Tests By Indication

Acute urticaria/Angioedema/Anx							
A g e	Steroid/ro ute	Other drugs	Symptoms	SPT	Intr ad.	Negative tests	Management plan / challenge
9 2 M	Pr oral		Anx - Acute U, Ang, abdo pain dyspnoea	-ve	-ve	Pr	Oral challenge offered – not attended
1 0 2 4 F	Pr oral IV Hct		Acute U and Ang PHx chronic U and Ang	-ve	-ve	Pr Tr MPr Hct Dex	Oral Pr challenge – U at 2 hours Avoid Pr and Hct
1 1 5 3 F	1-IV MPr 2-IV Hct 3-Dex po		1-Rash 15 mins 2-rash immediate 3- rash	-ve	-ve	Pr Tr MPr Hct Dex	Use Pr
1 2 3 4 F	Pr oral	Hair dye - dermatit is	Ang 30 minutes	-ve	-ve	Pr Tr MPr Hct Dex	Oral Pr challenge negative
Presyncope							
1 3 7 9 M	Unk intrarticular	Lign	Presyncope 5 minutes	-ve	-ve	Pr Tr MPr Hct Dex Lign	Diagnosed as vasovagal
1 4 5 9 M	MPr tendon injection	Lign	Presyncope	-ve	-ve	Pr Tr MPr Hct Dex Lign	Diagnosed not allergic
Flushing							
1 5	Beclometh asone nasal	Doxycy cline	Acute itch flushing	-ve	-ve	Beclomethasone	Beclomethasone challenge negative.

20F	spray						Diagnosed doxycycline allergic
1687F	Pr oral		Acute facial flushing	-ve	-ve	Pr Tr MPr Hct Dex	Oral challenge offered - refused
1762F	MPr and Tr intrarticular	Lign	Flushing 1-3 days	-ve	-ve	Pr Tr MPr Hct Dex Lign	Diagnosed not allergic
1843F	MPr oral		Flushing for 1 week	-ve	-ve	Pr Tr MPr Hct Dex Latex	Avoid MPr, use Hct
1941F	MPr intrarticular		Flushing for 1 week	-ve	-ve	Pr Tr MPr Hct Dex Latex	Use Tr Dex or Hct

Delayed/Miscellaneous

2027M	Tr intrarticular		U- 2 days later	-ve	-ve	Pr Tr MPr Hct Dex Lign	Avoid Tr,
2158F	MPr Intrarticular	Lign	Subjective facial swelling no objective Ang	-ve	-ve	Pr Tr MPr Hct Dex Lign Latex	Avoid MPr, challenge refused
2240F	Unk Epidural injection	Lign	Raised BP vomiting, high anxiety	-ve	-ve	Pr Tr MPr Hct Dex Lign Latex	Diagnosed not allergic
2343F	Unk intrarticular		Acute swelling injection site	-ve	-ve	Pr Tr MPr Hct Dex	Give Pr and antihistamine prior

Pr = Prednisolone
Dex = Dexamethasone

Tr = Triamcinolone
Ang = Angioedema

U = Urticaria
MPr = Methylprednisone

Hct = Hydrocortisone
Chlorhex = Chlorhexidene

Anx = Anaphylaxis

Lign = lignocaine

-ve = Negative

Unk = Unknown steroid

Discussion

A number of points are evident from our case series:

Firstly, most patients with positive skin tests had a history of anaphylaxis associated with corticosteroid exposure(7/8). Furthermore, most patients presenting with corticosteroid associated anaphylaxis had positive skin tests(7/8). Therefore, in the setting of a clear clinical history such as anaphylaxis, skin testing can provide sufficient information for a diagnosis of corticosteroid associated immediate hypersensitivity. De Sousa et al. had similar findings with positive skin tests in all of their 4 reported children with corticosteroid associated anaphylaxis(30). For patients with acute urticaria and/or acute angioedema in our study, 1 out of 4 had a positive skin test result suggesting some clinical utility for skin testing with this indication as well.

Skin tests were negative in all patients presenting with presyncope, flushing, and delayed or miscellaneous reactions. This suggests that corticosteroid skin testing has less value with these clinical indications, however our numbers are too small to definitively comment on this, and we recommend testing be considered on a case-by-case basis.

To our knowledge this is the first case series detailing skin tests in patients with corticosteroid associated flushing. Skin tests were notably negative in all five patients. Onset of flushing was delayed (24 hours) in 3 of our patients and lasted several days which is similar to other case series(27,28,29). The timeframe and negative skin tests do not favour an IgE mediated mechanism for delayed flushing/erythema with corticosteroids, however again numbers are too low for definitive comment. This inference should not be extended to include acute onset flushing, which could have a different aetiology.

Several technical points with the skin testing were noted:

Firstly, corticosteroid skin testing can give positive results at either skin prick or intradermal stages, therefore both should be performed. This is similar to the findings of Venturini et al(21).

Secondly, false positive skin tests do occur as seen in patient 6. False negative skin tests may occur, with patient 10 being a possible example. Venturini et al also identified a false negative skin test in their series(21). We feel this is an important point that should be borne in mind when making clinical decisions after a negative corticosteroid skin test. A large number of patients in our case series had no restrictions placed on future corticosteroid use on the basis of negative skin tests however the rate of false negative skin tests is unknown.

We provide further evidence of cross-reactivity in immediate hypersensitivity to corticosteroids, both in terms of clinical reaction, and on skin testing, as evidenced by patient 7 with hydrocortisone and prednisone. A full panel of corticosteroid skin testing is therefore recommended to look for other positive results.

As discussed in our literature review, immediate hypersensitivity to excipients and components of the medication other than the steroid itself has been described, so testing should use the exact brand of steroid associated with clinical reaction. We did not test with individual components however this is an option. Testing for alternative causative agents often associated with corticosteroid administration such as chlorhexidene, lignocaine and latex should always be considered and performed when relevant.

We elected to exclude patients with perioperative reactions. These consisted of 12 patients all of whom had dexamethasone at the time of induction in conjunction with multiple other co-administered agents (eg anaesthetics, antibiotics and analgesics) and we speculate this reflects a lower pre-test probability for corticosteroid associated hypersensitivity, due to the presence of numerous alternative potential causative agents.

We have identified several potential weaknesses to our study. Firstly, it is retrospective. Secondly, clinicians were not blinded to skin test results which could potentially bias interpretation of patient's clinical histories. Finally, relatively few

patients underwent challenge testing after negative skin tests. This reflects the fact that many of our patients had clinical histories of reacting to corticosteroids given as intra-articular or intravenous preparations, so challenge provocation is difficult logistically. Nevertheless, a supervised challenge remains the only definitive test to prove tolerance of any given corticosteroid.

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Appendix 1 : Anaesthetic cases with corticosteroid skin tests

A g e	Ster oid/ rout e	Other drugs?	Symptoms and time of onset	SPT	Intraderm.	Negative tests	Management plan ?challenge
1 6 2 F	Dex IV	Induction agents	Ax, H, U, immediate	-ve	Pr (0.67mg/ml)	Tr MPr Hct Dex, induction agents (gelofusion positive)	Avoid gelofusion, no further advice on pred, didn't get pred in op.
2 6 6 F	Dex IV	Induction agents	5 minutes Bronchospasm	NT	-ve	Dex (induction agents negative)	Thought non-allergic,? Bronchospasm due to intubation
3 4 6 M	Dex IV	Induction agents	Anaphylaxis 5 mins	roc uro niu m posi tive	NT	Dex	Avoid suxamethonium, rocuronium
4 8 6 M	Dex IV	Induction agents	Rash 1 hour	chlo rhe x. posi tive	-ve	Latex, midazolam alfentanil Dex	Avoid chlorhex.
5 1 8 F	Dex IV	Induction agents	Rash 5 mins prior to Dex then angioedema, chest tightness 1 hr after	-ve	-ve	Fentanyl propofol, chlorhex latex parecoxib Dex	Awaiting penicillin challenge -rash actually began pre-op
6 4 4 F	Dex IV	Chlorhex, Latex, Penicillin Cephazolin Ondansetron Syntocin	Hypotension, vomiting, , post caesarian, Tryptase normal	-ve	-ve	Dex Latex Chlorhex, Ondansetron, Penicillin Cephazolin	High block, syntocin as cause
7 6 0 M	Dex IV	Dex, Anaesthetic agents, fentanyl, penicillin, cefoxitin	Bronchospasm post intubation, tryptase normal	-ve	-ve	Dex, Anaesthetic agents, fentanyl, penicillin, cefoxitin	Bronchospasm secondary to intubation
8	Dex	Dex	Hypotension 20	-ve	-ve	Dex Midazolam,	Chlorhex SPT and

7 0 M	IV	Midazolam, Anaesthetics, fentanyl cephazolin Chlorhex	minutes			Anaesthetics, fentanyl cephazolin	RAST positive, no restriction on Dex
9 6 0 M	Dex IV	Dex Anaesthetics, Cefoxitin, fentanyl chlorhex latex	Urticaria one day first operation, second operation urticaria one week	-ve	-ve	Dex Anaesthetics, Cefoxitin, fentanyl chlorhex latex	Unknown cause for rash
1 0 1 2 F	Dex IV	Dex Midaz Propofol fentanyl clonidine	Urticaria one day post-op	-ve	-ve	Dex Midaz Propofol fentanyl clonidine	No cause identified, no restrictions placed
1 1 9 F	Dex IV	Dex midaz propofol fentanyl cephazolin	Urticaria post operation 2 hours	-ve	-ve	Dex midaz propofol fentanyl latex chlorhex cephazolin	Antihistamine prior to operation, urticaria not evidence of significance
1 2 5 1 M	Dex IV	Dex midaz propofol fentanyl latex chlorhex cephazolin	Bronchospasm post induction	-ve	-ve	Dex midaz propofol fentanyl latex chlorhex cephazolin	Pretreat antihistamine

Dex = dexamethasone

Midaz = midazolam

Chlorhex = chlorhexidene