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Immediate Hypersensitivity Reactions to Corticosteroids

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Patel A, Bahna SL:

Immediate hypersensitivity to corticosteroids.

Annals of Allergy, Asthma & Immunology 115:178,2015.

Immediate Hypersensitivity to Corticosteroids

Objectives

- Suspect corticosteroids as possible causes of allergy.
- Evaluate patients to identify the specific corticosteroid that may be the culprit of a hypersensitivity reaction.
- Prescribe safe substitutes for patients who have hypersensitivity to a corticosteroid.

General considerations in drug allergy

- The drug may have been taken before by the patient multiple times without reactions.
- The reaction may have not been previously reported about a drug that has been in the market for many years.
- The reaction may be due to a concurrent illness (infectious agent, tissue breakdown, autoimmunity) or food.
- The reaction may be caused by a particular formulation of the drug but not by another.
- The cause may not be the pharmacologically active drug, but rather a preservative, stabilizer, dye, or food protein.

Case Presentation (a)

- A woman with MS & acute optic neuritis received in the Neurology Dept 1 g IV methylprednisolone sodium succinate (MPSS) preceded with oral famotidine 20 mg & acetaminophen 650 mg.
- 50 min into the infusion, she developed generalized urticaria, periorbital edema & severe hoarseness.
- Infusion was stopped and she was treated with epinephrine 0.3 mg IM, famotidine 20 mg IV, loratadine 10 mg orally, oxygen, and 1 liter NS IV.
- Symptoms abated within 20 min.
- She was referred for evaluation of drug reaction; possibly to acetaminophen, famotidine, or MPSS.

Case Presentation (b)

- In the A/I Clinic, the history revealed that she previously received MPSS multiple times over the past 11 yr without any reaction.
- She also reported taking acetaminophen, famotidine & interferon- β 1 α after the anaphylactic reaction without any adverse effects.
- Therefore, MPSS was the most likely cause.
- PE: WNL
- ST with 6 CS preparations

Case Presentation (c)

Skin testing with 6 CS preparations

Steroid Preparation	SPT		Intradermal			
	Full strength		1:100		1:10	
	W/E mm	Score	W/E mm	Score	W/E mm	Score
MPSS (IV) 40mg/mL	3/20	3+	ND	ND	ND	ND
MPSS (IV) 125mg/ML	4/25	4+	ND	ND	ND	ND
Methylprednisolone (PO) 4mg/mL	0/0	0	0/0	0	0/0	0
Hydrocortisone (PO) 10mg/mL	0/0	0	0/0	0	0/0	0
Prednisone (PO) 10mg/mL	0/0	0	3/20	3+	ND	ND
Dexamethasone Na P (IV) 4mg/mL	0/0	0	0/0	0	0/0	0
Control	0/0	0	0/0	0	0/0	0
Histamine	3/15	3+	3/20	3+	ND	ND

Case Presentation (d)

Conclusion

- This patient showed sensitization (SPT +) to 2 preparations of methylprednisolone sodium succinate but not to methylprednisolone alone.
- Therefore her anaphylaxis seems to be to the succinate ester in MPSS.

Literature Search

Patel & Bahna:

Immediate hypersensitivity reactions to corticosteroids.

Ann Allergy Asthma Immunol 2015;115:178.

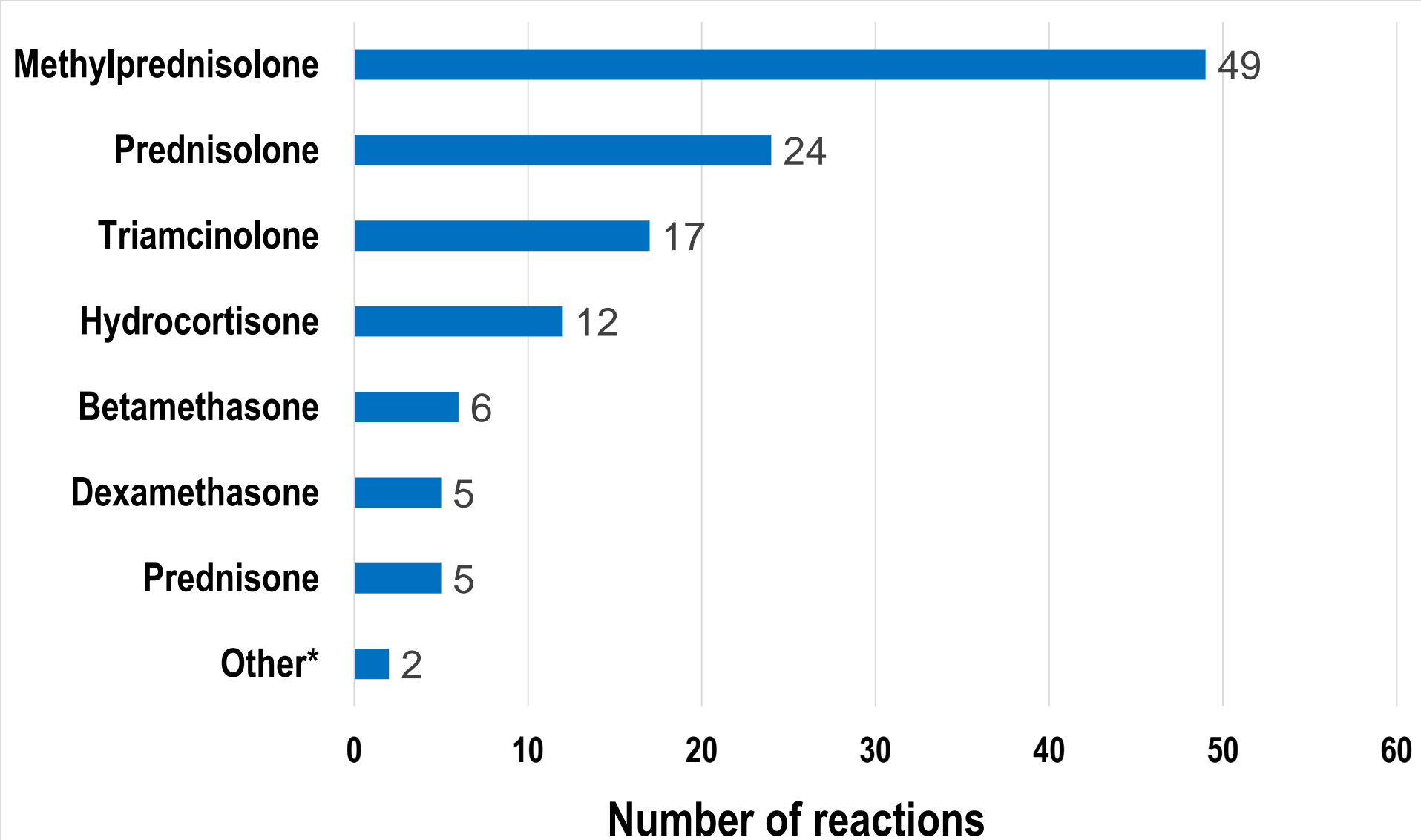
- PubMed search for English publications over 11 yr (Jan 1, 2004 to Dec 31, 2014). Only reports of immediate hypersensitivity reactions that occurred <24 hr after administration of a CS were included.
- 48 articles fulfilled the criteria, reporting:
 - 120 reactions in 106 patients,
 - 55 M & 51 F,
 - 2 - 90 yr of age.

Table 1. Immediate hypersensitivity to corticosteroids in 106 patients according to route of administration

(Patel & Bahna: Ann Allergy Asthma Immunol 2015; 115:178)

Route	Manifestation (& reported frequency)	No. of reactions	No. of pts
Intravenous	Anaphylaxis (33), urticaria/angioedema (11), bronchospasm/dyspnea (5), rash (4)	53 (44.2%)	48
Intramuscular	Anaphylaxis (5), urticaria/angioedema (1)	6 (5.0%)	6
Intraarticular	Anaphylaxis (14)	14 (11.7%)	14
Oral	Urticaria/angioedema (15), anaphylaxis (11), rash (3), bronchospasm/dyspnea (1), flushing (1)	31 (25.8%)	27
Intralesional	Anaphylaxis (2), urticaria/angioedema (1)	3 (2.5%)	3
Topical	Anaphylaxis (2), urticaria/angioedema (1)	3 (2.5%)	3
Epidural	Anaphylaxis (1)	1 (0.8%)	1
Inhalation	Anaphylaxis (1)	1 (0.8%)	1
Iontophoresis	Rash (1)	1 (0.8%)	1
Unknown	Anaphylaxis (4), urticaria/angioedema (3)	7 (5.8%)	7
	Total^a	120	111

^aOne pt had reactions by 3 routes , and 3 pts each had reactions by 2 routes. Three patients had >1 manifestation on separate occasions.



Distribution of total immediate hypersensitivity reactions to corticosteroids according to the implicated preparation.

(Patel & Bahna: Ann Allergy Asthma Immunol 2015; 115:178)

Table 2. Manifestations & the causative corticosteroids reported in 106 patients (Patel & Bahna: Ann Allergy Asthma Immunol 2015; 115:178)

Manifestation	Corticosteroid preparations (frequency)	M:F	Age yr (median)	No. of Rxns	Pts #
Anaphylaxis	Methylprednisolone (30), triamcinolone (14), prednisolone (13), hydrocortisone (6), betamethasone (6), dexamethasone (1), fluticasone/salmeterol (1), mometasone (1), prednisone (1)	38:26	2-90 (26)	73 (60.8%)	67
Urticaria/ angioedema	Methylprednisolone (13), prednisolone (7), hydrocortisone (5) triamcinolone (3), dexamethasone (2), prednisone (2)	9:19	2-78 (29)	32 (26.7%)	29
Bronchospasm /dyspnea	Methylprednisolone (3), prednisolone (3)	3:0	8-64 (26)	6 (5.0%)	6
Rash	Methylprednisolone (3), dexamethasone (2), prednisone (2), hydrocortisone (1)	4:2	3-53 (10)	8 (6.7%)	6
Flushing	Prednisolone (1)	0:1	87	1(0.8%)	1
	Total^a	54:48		120	109

^aAge unknown in 4 females & 2 males of which 2 had anaphylaxis, 1 had anaphylaxis & urticaria, and 3 had bronchospasm. 3 patients had more than 1 manifestation on separate occasions.

Table 3. Inactive ingredients implicated in immediate hypersensitivity to corticosteroids in 34 cases (32%)

(Patel & Bahna: Ann Allergy Asthma Immunol 2015; 115:178)

Implicated ester or excipient	Corticosteroid preparation	Manifestations	Rxns #	Pts #
Succinate ester	Methylprednisolone (7), hydrocortisone (3), prednisolone (2)	Anaphylaxis (7), urticaria/angio (4), dyspnea (1)	12 (35.3%)	12
Lactose	Methylprednisolone (10)	Anaphylaxis (8), urticaria/angio (2)	10 (29.4%)	10
Carboxy-methylcellulose	Triamcinolone (7)	Anaphylaxis (7)	7 (20.6%)	7
Polyethylene glycol	Methylprednisolone (2), betamethasone (2), mometasone (1)	Anaphylaxis (5)	5 (14.7%)	5


Lactose-containing asthma medications

Preparation	Active ingredients	Lactose content
Advair Diskus	Fluticasone/salmeterol	12.5 mg/blister
Asmanex Twisthaler	Mometasone	Small amounts
Breo Ellipta	Fluticasone/vilanterol	24.7mg/bliste
Flovent Diskus	Fluticasone	12.5 mg/blister
Foradil Aerolizer	Formoterol	25 mg/capsule
Pulmicort Flexhaler	Budesonide	Not indicated
Serevent Diskus	Salmeterol	12.5 mg/blister
Solu-Medrol <u>40mg/ml</u> injectable	Methylprednisolone succinate <u>40 mg/ml</u>	25 mg/1 ml vial
Accolate tablet	Zafirlukast	Not indicated
Singulair tablet	Montelukast 10 mg	Not indicated
Deltasone tablet	Prednisone	Not indicated
Millipred tablet	Prednisolone	Not indicated

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Milk allergy through a particular injectable corticosteroid

(Eda et al: Allergol Intl 2009; 58:137)

Two milk-allergic children developed generalized urticaria following IM dose of a particular formulation of Solu-Medrol.

Case 1: An 8-yr-o girl with asthma, AD & milk allergy.

Presented to ED with acute asthma, partial response to β 2-agonist inhalation. Solu-Medrol IM 0.75ml of 40 mg/ml was followed by generalized urticaria.

Case 2: A 3-mo-o boy presented to ED with urticaria on the neck, did not improve after a dose of oral hydroxyzine. Has history of allergy to milk (& other foods). In ED, Solu-Medrol IM 0.5ml of 40mg/ml was followed by generalized urticaria.

Milk allergy through a particular injectable corticosteroid

(Eda et al: Allergol Intl 2009; 58:137)

Evaluation

- SPT strongly positive to milk (& few other foods).
- SPT with 5 injectable corticosteroid preparations :
Positive in both cases only to Solu-Medrol 40mg/ml.
Negative to Solu-Medrol 125mg/ml, Decadron, Solu-Cortef & Prednisolone.
- Only Solu-Medrol 40mg/ml contained lactose & has β -lactoglobulin 112 ng/ml.

Allergy to milk protein in IV corticosteroid (a)

(Savvatanos et al: Allergy 2011: 66:983)

Two children (9 & 7 yr) with a history of severe milk allergy presented to ED with acute asthma exacerbation. Anaphylaxis followed IM Solu-Medrol.

Case 1: Received nebulized salbutamol & IV 40 mg methylprednisolone, but wheezing deteriorated. Both medications were repeated, but within minutes he collapsed with hypotension, cyanosis & respiratory arrest.

Case 2: Similarly, received nebulized salbutamol & IV 40 mg methyl prednisolone, but his wheezing worsened & developed urticaria, vomiting & hypotension.

Allergy to milk protein in IV corticosteroid (b)

(Savvatanos et al: Allergy 2011: 66:983)

Skin testing with 7 different corticosteroid preparations:

- Both patients showed **positive ST only to Solu-Medrol 40mg/ml** (methyl-prednisolone succinate containing lactose) but not to Solu-Medrol 125mg/ml (methyl-prednisolone succinate without lactose) .
- Both patients tolerated 125mg of the non-lactose containing preparation.
- ELISA assay detected traces of milk protein 2.0–3.5 ppm in all 5 batches tested of the implicated product (*Solu-Medrol 40 mg, Pfizer*).

Pathogenesis of corticosteroids immediate hypersensitivity

Mechanism is not clear; proposed:

- IgE-mediated in most cases
- Non-IgE-mediated
- Cardiotoxicity from rapid infusion of large doses (>500 mg over <1 hr)

Diagnosis of corticosteroids immediate hypersensitivity

- History of development or worsening of reaction following CS administration.
- Check the label for the active & inactive ingredients in the implicated preparation.
- Past history of a reaction to an ingredient in that preparation.
- Skin testing: SPT & if negative do ID tests.
- Confirmation with graded challenge.

Corticosteroids used for skin testing (& concentration)*

(Angel-Pereira et al: JACI in Practice 2014, 2:346)

Corticosteroid	SPT mg/mL	ID 1/100 (mg/mL)	ID 1/10 (mg/mL)
Methylprednisolone sodium hemisuccinate	40	0.4	4
Methylprednisolone (unesterified, Urbason)	40	NP	NP
Betamethasone	6	0.06	0.6
Dexamethasone	4	0.04	0.4
Triamcinolone	40	0.4	4
Prednisolone (Estilona oral suspension)	13.3	NP	NP
Prednisone	30	NP	NP
Hydrocortisone sodium phosphate	100	1	10

ID, Intradermal; *NP*, not performed (available only for oral use).

Estilona, Sonphar; S.L. Barcelona, Spain.

*for drugs that are available only as tablet form, general recommendations described on the literature were followed,⁹ “For skin prick tests and patch tests of drugs that are only available as insoluble tablet, form, the tablet can be grind and diluted with 0.9% NaCl or petrolatum.”

Conclusion (a)

- Relative to their world-wide common use for many diseases, corticosteroids seem to rarely cause immediate hypersensitivity, but probably they are markedly missed , particularly since they are the major therapy for allergy.
- Immediate hypersensitivity CS reactions can occur at any age. The estimated prevalence is 0.1-0.3%, compared to 0.5-5% for allergic contact dermatitis.
- Any CS can cause hypersensitivity & by any route. methylprednisolone followed by prednisolone are the most common.

Conclusion (b)

- The culprit can be the pharmacologically-active molecule or an excipient such as succinate ester, phosphate ester, polyethylene glycol, carboxymethylcellulose, or benzyl alcohol .
- ST with multiple preparations, supplemented with graded challenge testing, would identify alternative safe preparations.
- Desensitisation is rarely needed.

THE END

Thank You