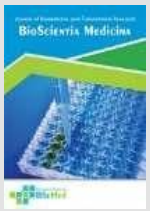
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Role of Corticosteroids in the Management of Drug Allergy: A Narrative Literature Review

Rivani Sintia Suratman[1]*, Rudy Afriant[2], Roza Mulyana[3], Saptino Miro[4], Deka Viotra[5]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[3]Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[5]Division of Kidney and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
Anti-inflammatory drugs
Corticosteroid
Drugs reaction
Hypersensitivity
Immunoglobulin E

***Corresponding author:**
Rivani Sintia Suratman

E-mail address:
rivanisuratman@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v7i2.773

A B S T R A C T

Drug allergy is an adverse drug reaction that occurs through an immune reaction that occurs through IgE or a rapid hypersensitivity reaction with various mechanisms and clinical presentations. One of the therapeutic modalities for drug allergies is corticosteroids. In allergic processes, corticosteroids can suppress the production and effects of humoral factors involved in the inflammatory response, inhibit the migration of leukocytes to sites of inflammation, and interfere with the function of endothelial cells, granulocytes, mast cells, and fibroblasts. This literature review aimed to describe the role of corticosteroids in the management of drug allergies. Corticosteroids are used very widely in the treatment of various allergic diseases because of their strong anti-inflammatory properties. Corticosteroids inhibit the synthesis of a number of cytokines, such as the interleukins IL-1 to IL-6, tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF). In conclusion, corticosteroids are one of the therapeutic modalities in various manifestations of drug allergies. Every drug allergy gets the anti-inflammatory effects of corticosteroids with different choices, routes, and doses for each manifestation.

1. Introduction

Drug allergy is an adverse drug reaction involving an immunological mechanism.[1] Adverse reactions caused by drugs are a major hazard in medical practice and are responsible for morbidity. Drug allergic reactions can be divided into predictable and unpredictable reactions.[2] Predictable reactions, including drug toxicity, drug interactions, and dose-dependent side effects, can be related to the pharmacological mechanism of the drug. In contrast, adverse reactions are dose-independent, often unrelated to the pharmacological mechanisms of the drug, and occur in susceptible patients. Unexpected reactions include idiosyncratic, hypersensitivity, and pseudoallergic reactions. Pseudoallergic reactions mimic allergic reactions but lack an immunological

mechanism involved.[3]

One of the therapeutic modalities for drug allergies is corticosteroids. In allergic processes, corticosteroids can suppress the production and effects of humoral factors involved in the inflammatory response, inhibit the migration of leukocytes to sites of inflammation, and interfere with the function of endothelial cells, granulocytes, mast cells, and fibroblasts.[4] Some research shows that corticosteroids can cause thinning of the mast cells in the skin. Corticosteroids reduce eosinophilia in asthmatic patients and also reduce T-cell proliferation, and induce T-cell apoptosis. In addition, several cytokines are directly affected by corticosteroids, including IL-1, tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, and IL-8. Several studies provide recommendations for the use of corticosteroids in the treatment of various manifestations of drug allergies ranging from mild to severe and life-threatening manifestations. The choice and recommended dose of corticosteroids differ at each level of severity, and it is necessary to pay attention to the time and duration of corticosteroid administration. Pros and cons of using corticosteroids have also been reported by several studies, especially regarding the side effects of using corticosteroids.[5,6] This literature review aimed to describe the role of corticosteroids in the management of drug allergies.

Definition and mechanism of drug allergy

Drug allergy is an adverse drug reaction that occurs through an immune reaction that occurs through IgE or a rapid hypersensitivity reaction with various mechanisms and clinical presentations.[7,8] Drug allergic reactions can be divided into predictable and unpredictable reactions. Predictable reactions include drug toxicity, drug interactions, and dose-dependent adverse effects, as well as being linked to the pharmacological mechanism of the drug. Adverse reactions are dose-independent, often unrelated to the pharmacological mechanisms of the drug, and occur in susceptible patients.

The currently accepted concept of drug allergy mechanism is the hapten concept, the pro-hapten concept, and the p-i concept. The pro-hapten concept states that drugs with insufficiently large molecules, such as penicillins, sulfonamides, muscle relaxants cephalosporins, thiopental, antituberculosis drugs, cisplatin, and quinidine need to bind to carrier proteins in order to induce a specific immune response.[9] While the pro-hapten concept illustrates that there are some drugs that are non-reactive and need to be converted first through metabolic processes, both with enzymes and non-enzymes, to become reactive forms, for example, in allergies to sulfamethoxazole drugs. Meanwhile, based on the p-i concept itself, it was found that some drugs can have pharmacological interactions with T-cell receptors or major histocompatibility complex (MCH) molecules in the form of reversible bonds other than covalent bonds, which can activate T cells.[13]

Drug reactions themselves are influenced by various risk factors. Previous studies have mentioned risk factors that can affect drug reactions, including the type of drug, molecular drug weight, drug chemistry, treatment regimen, host factors, atopic, certain diseases, disorders metabolism, and environment. Drugs with a high molecular weight are more likely to elicit an immune reaction. Administration of oral, intravenous, intramuscular, subcutaneous, and topical regimens, respectively, causes increased allergy induction. Young age and female gender increase the trend of drug allergy.[8] The division of drug reactions according to the mechanism is classified in Table 1.

Drug allergy diagnosis

When there is a suspicion of the emergence of a drug allergic reaction, a history of the use of recently used drugs and the relationship between the time of drug use and the appearance of symptoms should be asked. Drug allergy usually appears after a second exposure because this reaction requires memory (sensitivity), and other possible causes of clinical manifestations have been excluded.[7-9] According to the

American Academy of Allergy, the most common clinical manifestations of drug allergies are skin organs.[10] Although skin reactions are the most common physical manifestation of drug-induced allergic reactions, many other organ systems may be involved, such as the renal, hepatic, and haematological systems. Multi-organ reactions can also occur and include anaphylaxis, drug rash with eosinophilia and systemic symptoms (DRESS), serum sickness, drug-induced lupus erythematosus (DILE), and vasculitis.[11]

Table 1. Mechanism of drug reaction.

Drug allergic reaction		
Proven/strongly suspected	**Probable**	**Pseudoallergies**
Antibioticsβ-lactams (penicillins, cephalosporins, monobactams, carbapenems) Insulin Chymopapain Streptokinase Heterologous tetanus serum (Toxoid-tetanus/Diphtheria-Td) Latex New biological agents (measles, mumps, MMR, egg-origin vaccines)	Quinolones Sulfonamides Dilantin Protamine Muscle relaxant Local anesthesia Chemotherapy Transfusion Hemodialysis	Opiates Aspirin and NSAIDs heparin Additive ACE inhibitor Plasma protein solution Gelatin-based replacement solution Tartrazine Contrast

Supporting examinations in patients with drug allergies are necessary to establish the diagnosis. Important tests include skin tests for rapid hypersensitivity reactions (IgE), patch tests, provocation tests or dosing tests, RAST tests, drug-specific IgG or IgM measurements, measurements of complement activation, measurements of the release of histamine or other mediators from basophils.[12,13]

The mechanism of action of corticosteroids in allergy

Corticosteroids are used very widely in the treatment of various allergic diseases because of its strong anti-inflammatory properties. Corticosteroids inhibit the synthesis of a number of cytokines, such as interleukins IL-1 to IL-6, tumor necrosis factor-α (TNF-α), dan granulocyte-macrophage colony-stimulating factor (GM-CSF). Corticosteroids also inhibit the synthesis of chemokine IL-8, regulated on activation of normal T cell expressed and secreted (RANTES), eotaxin, macrophage inflammatory protein-1α (MIP-1α), dan monocyte chemoattractant protein-1.[12,13]

Free corticosteroids are small molecules and are lipophilic, easily diffuse through the cell membrane into the cytoplasm, and bind to glucocorticoid receptors. The glucocorticoid-corticosteroid receptor complex works by modifying activity transcription, which causes a decrease in the expression of pro-inflammatory molecules and cells such as Langerhans cells, lymphocytes, mast cells, basophils, eosinophils, accompanied by an increase in the expression of anti-inflammatory molecules and β-adrenergic receptors.[9]

Clinical use of corticosteroids in drug allergy

Exanthema

Exanthema drug eruptions are the most common manifestation of mild drug reactions, especially in children, and occur in 1-5% of cases of first drug exposure. This rash is marked with macula developing erythema in papules 1-5 mm in diameter and may coalesce into plaques. Complaints may be accompanied by pruritus and mild fever. Exanthema management is by administering topical corticosteroids, emollients, and oral antihistamines. The choice of topical corticosteroids, in this case, is hydrocortisone cream 1% or betamethasone lotion 0.05% 2-3 times a day. Topical steroids are chosen for exanthema because they are relatively safe, have few side effects, and are inexpensive.[13]

Urticaria

Urticaria is characterized by nodules resulting from swelling of the dermis and/or angioedema. Urticaria is divided into acute urticaria and chronic urticaria (lasting more than 6 weeks). Drug-induced urticaria is usually acute, rarely chronic. Giving recommendations on corticosteroids in patients with chronic urticaria, namely systemic corticosteroids, prednisone 20 mg per day, or methylprednisolone 16 mg per day with gradual tapering. Prolonged use of daily corticosteroids, parenteral corticosteroids, or dexamethasone should be avoided. Angioedema of the face or tongue can be treated with 60 mg of prednisone, with 40 mg given the next day. Treatment can then be discontinued, or an alternative day dosing schedule can be continued.[14,15]

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

SJS-TEN is a severe idiosyncratic reaction characterized by extensive necrosis and shedding of the epidermis, usually precipitated by drugs. There is usually prodromal malaise and fever, followed by rapid onset of erythematous or purpuric macules and plaques that progress to necrosis and epidermal sloughing. SJS and TEN are considered to be on the same disease spectrum, differing only in how much of the skin surface is affected.

Systemic corticosteroids and immunosuppressive therapy have been used in the management of SJS/TEN, although evidence supporting their use is lacking.[16] The role of systemic corticosteroids in the treatment of SJS-TEN is still controversial. One study showed that treatment of SJS with corticosteroids may be associated with significant side effects and prolonged recovery.[17] In particular, the study showed that patients who received systemic corticosteroids (compared to supportive care) had a longer hospital stay and more complications than those who were not treated with corticosteroids. On the other hand, several studies support the administration of corticosteroids in SJS-TEN. A study by Kardaun et al. stated that the negative opinion of the use of corticosteroids might be because they are often given too late, in too low a dose, and for too long a period of time.[18] Another study found that the use of systemic corticosteroids in SJS showed better outcomes without increased complications and found SJS to be a corticosteroid-responsive condition with rapid recovery.[19] Regardless of the dose or route of administration, it is clear that proponents of using systemic corticosteroids argue for administration early in the course of the disease. The researchers recommend using high-dose corticosteroids given for a short time and tapering off appropriately. SJS-TEN is treated with a choice of prednisone 0.5-1 mg/kg/day, methylprednisolone 1 mg/kg/day for 3 days, or dexamethasone 1.5 mg/kg for 3 consecutive days.

Drug rash with eosinophilia and systemic symptoms (DRESS)

DRESS syndrome is a severe idiosyncratic drug reaction characterized by generalized skin eruption, eosinophilia, lymphadenopathy, and end-organ damage, usually 2 to 6 weeks after initiation of the offending drug. Systemic corticosteroid therapy for DRESS syndrome is currently the most widely accepted and used treatment. Significant improvement in clinical symptoms and laboratory abnormalities is often seen within days of starting steroid therapy.[20]

Early administration of systemic steroids is generally recommended for all cases of DRESS syndrome. Systemic steroid therapy should be started with a minimum dose equivalent to 1.0 mg/kg/day of prednisone. Gradual reduction over 3 to 6 months after clinical and laboratory stabilization is recommended to avoid relapse. There is often a significant improvement in symptoms and laboratory abnormalities within days of starting steroid treatment. In cases where there is no improvement or exacerbation of symptoms with oral corticosteroids or significant visceral involvement, the patient can be treated with intravenous methylprednisolone. Pulse methylprednisolone 30 mg/kg intravenously for 3 days may be given. During this time, complete blood

cell counts, liver function tests, lymph nodes, and other organ-specific laboratory tests should be monitored carefully to detect potential relapse, and steroid doses should be adjusted accordingly. Significant skin and systemic symptoms have been reported following accidental discontinuation or rapid reduction of corticosteroid doses. Although steroid therapy is generally effective in the acute setting, its effect on the long-term course of the disease is unknown.

Anaphylactic shock

Anaphylaxis is a serious, generalized, or systemic acute immunological reaction that begins rapidly and may be fatal or life-threatening. Based on available data from international studies, the lifetime prevalence of anaphylaxis has been estimated at 0.05 to 2%, with estimates of incidence ranging from 10 to 20 per 100,000 population per year. The incidence of anaphylaxis is also reported to be increasing worldwide.[21]

Currently, the mainstay of therapy recommended in the event of anaphylaxis is epinephrine, given intramuscularly or intravenously. Second-line therapy in the event of anaphylaxis includes corticosteroids, H1 and H2 antihistamines, and bronchodilators. British, European, Australia, Canada, and the World Allergy Organization recommend glucocorticoids as second-line or adjuvant therapy after initial treatment with adrenaline. However, there is no strong evidence to support this practice. Prednisolone, methylprednisolone, dexamethasone, and hydrocortisone were given orally, intravenously, or intramuscularly are recommended in different guidelines. This therapy is given as a single dose or continued for several days. The therapeutic dose of corticosteroids in anaphylactic shock is prednisone 1 mg/kg, methylprednisolone 1-2 mg/kg, or hydrocortisone 200 mg with slow boluses.

2. Conclusion

Corticosteroids are one of the therapeutic modalities in various manifestations of drug allergies. Every drug allergy gets the anti-inflammatory effects of corticosteroids with different choices, routes, and doses for each manifestation.

3. References

1. Liebhart J, Dobek R, Małolepszy J. The prevalence of allergic diseases in Poland- the results of the pmsead study in relation to gender differences. Adv Clin Exp Med. 2014; 23(5): 757-62.
2. Gamboa PM. The epidemiology of drug allergy-related consultations in Spanish Allergology Services: Alergológica-2005. J Investig Allergol Clin Immunol. 2009; 19(2): 45-50.
3. England RW, Ho TC, Napoli DC, Quinn JM. Inpatient consultation ofallergy/immunology in a tertiary care setting. Ann Allergy Asthma Immunol. 2003; 90(4): 393-7.
4. Newton R, Shah S, Altonsy MO. Glucocorticoid and cytokine crosstalk: feedback, feedforward, and co-regulatory interactions determine repression or resistance. J Biol Chem 2017; 292: 7163–72.
5. Vandewalle J, Luypaert A, De Bosscher K. Therapeutic mechanisms of glucocorticoids. Trends Endocrinol Metab 2018; 29: 42–54.
6. Warrington R, Silviu-Dan F. Drug allergy. Allergy Asthma Clin Immunol. 2011; 7(Suppl 1): S10.
7. Khan DA, Solensky R: Drug allergy. J Allergy Clin Immunol. 2010; 125(2 Suppl 2): S126-37.
8. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions - new concepts.Clin Exp Allergy. 2007; 37(7): 989-99.
9. McKenna JK, Leiferman KM. Dermatologic drug reactions. Immunol Allergy Clin North Am. 2004; 24(3): 399–423.
10. Joint Task Force on Practice Parameters; American Academy of allergy, asthma and immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy

Asthma Immunol. 2010; 105(4): 259-73.
11. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005; 209(2): 123–9.
12. Crisafulli G, Franceschini F, Caimmi S, Bottau P, Liotti L, Saretta F, et al. Mild cutaneous reaction to drug. Acta Biomed. 2019; 90(3): 36-43.
13. Trubiano JA, Soria A, Torres MJ, Trauntmann A. Treating through of drug-associated exanthem in drug allergy management: Current Evidence and Clinical Aspects. J Allergy Clin Immunol Pract. 2021;1-10.
14. Barniol C, Dehours E, Mallet J, Houze-Cerfon CH, Lauque D, Charpentier S. Levocetirizine and prednisone are not superior to levocetirizine alone for the treatment of acute urticaria: a randomized double-blind clinical trial. Ann Emerg Med. 2017; 1-7.
15. Kaplan AP. Chronic urticaria and angioedema. N Eng J Med. 2002; 346(3): 175-9.
16. Auyeung J, Lee M. Successful treatment of Stevens-Johnson syndrome with cyclosporine and corticosteroid. Can J Hosp Pharm. 2018; 71(4): 272-5.
17. Yeung AK, Goldman RD. Use of steroids for erythema multiform in children. Can Fam Physician. 2005; 51(11): 1481-3
18. Kardaun S, Jonkman M. Dexamethasone pulse therapy for Stevens-Johnson syndrome/ toxic epidermal necrolysis. Acta Derm Venerol. 2007; 87: 144-8.
19. Patterson R, Dykewick MS, Gonzalzles A. Erythema multiforme and Steven Johnson Syndrome. Descriptive and therapeutic controversy. Chest. 1990; 98: 331-6.
20. Husein Z, Reddy BY, Schwartz RA. DRESS syndrome. Part II: Management and Therapeutic. J Am Acad Dermatol. 2013; 68(5): 709.e1-e9.
21. Liyanage CK, Galappatthy P, Seneviratne SL. Corticosteroids in management of anaphylaxis; a systematic review of evidence. Eur Ann Allergy Clin Immunol. 2017; 49(5): 196-207.