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Glucocorticoids: Boon or Bane-An assessment of safety profiling of steroids in a tertiary care hospital

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ABSTRACT

Glucocorticoids are used in therapy empirically, but undesirable effects occur with large doses or prolonged administration. The aim of the study is to assess the pattern of adverse drug reactions of glucocorticoids in a tertiary care hospital. A retrospective analysis of adverse drug reactions (ADRs) following administration of glucocorticoids was conducted in the ADR monitoring center, Department of Pharmacology, Kasturba Medical College, Manipal. Clinical and treatment data were collected from the patient case records in the suspected adverse drug reaction reporting form as per the World Health Organization guidelines. ADRs were assessed for Causality, Preventability and Severity using WHO causality assessment scale, Modified Schumock and Thornton's scale and Hartwig's severity scale, respectively. 100 ADRs were observed in 85 patients, with 51% males and 49% females. Prednisolone (53%) was the most common drug responsible for ADRs, followed by betamethasone (9%) and dexamethasone (8%). Hyperglycemia (34%) was the most common ADR, followed by cutaneous adverse reactions (32%). Acne (20%) was common among them. Over 86% reactions were categorized "possible". Among ADRs (91%) treated, only 16 % recovered. About 39% of cases were "probably preventable". The majority of ADRs (72%) were moderate in "severity". Given the number and severity of side effects, the institution of glucocorticoids requires careful consideration of the relative risks and benefits in each patient.

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INTRODUCTION

Glucocorticoids (GC) perform essential and vital physiological functions in the body system. Glucocorticoids synthesized from the adrenal cortex are secreted under circumstances of stress, having a vital role in body growth and development, blood pressure control and regulation of carbohydrate, protein and fat metabolism (Ramamoorthy and Cidlowski, 2016). Synthetic analogues of glucocorticoids are therapeutically used for anti-inflammatory, anti-allergic, immunomodulatory and anti-malignant actions. They are the only group of drugs used empirically for a wide majority of illnesses. Having a physiological and pharmacological similarity to endogenous cortisol, they are used as replacement therapy in Addison's disease and congenital adrenal hyperplasia (Yasir *et al.*, 2020).

Glucocorticoids are potent inhibitors of inflammation and prescribed for chronic inflammatory diseases like asthma, chronic obstructive airway diseases, rheumatoid arthritis, skin disorders, inflammatory bowel disease, etc. They act by inducing gene transcription to co-activate or co-repress

genes by binding to the glucocorticoid receptor complex. They cause transactivation of genes like annexin-1, an inhibitor of NF-κB (IκB-α) coding for anti-inflammatory properties. They repress pro-inflammatory transcription factors like nuclear factor-kappa B and activator protein-1 (AP-1) and inhibit the production of cytokines, chemokines, arachidonic acid metabolites and adhesion molecules. In contrast, anti-inflammatory mediators often are up-regulated by glucocorticoids (Barnes, 2005). GC can regulate both innate and adaptive immunity, affects the activation and effect or functions of interleukins, interferons and T cells through manipulation of their transcriptional pathways. Their unparalleled immunosuppressive and anti-inflammatory activity, along with cost-effectiveness, makes these compounds a treatment of choice for the majority of autoimmune and anti-inflammatory disorders like Sarcoidosis, Sjogren syndrome, Graves' ophthalmopathy and prevention of rejection in organ transplant (Flammer and Rogatsky, 2011).

However, treatment of such conditions requires prolonged administration of large doses, which produces severe harmful effects. Long term administration of glucocorticoids is associated with adrenal insufficiency, osteoporosis, fracture, growth retardation, cutaneous changes and neuropsychiatric disturbances. Effect on carbohydrate, protein and fat metabolism causes changes such as weight gain, hyperglycemia and fat redistribution. Rarer complications such as proximal myopathy, gastric ulcers, posterior subcapsular cataract and retinopathy occur in a few patients, but certainly, if there is a predisposal risk (Gensler, 2013).

As a short term therapy, they are used for acute conditions like anaphylactic shock, allergic conditions, cerebral edema, pulmonary edema and fetal lung maturation. Although there is enough evidence on the toxicity of long term glucocorticoid exposure, shorter courses of steroids were presumed to have lesser adverse effects. However, population-based studies conducted have shown the shorter duration of glucocorticoid therapy are associated with adverse events such as thromboembolism, sepsis, fracture, mood changes and metabolic disturbances like hyperglycemia, hyperlipidemia (Richards, 2008; Buchman, 2001). These adverse effects may lead to deterioration of the patient's quality of life and can be life-threatening.

Currently, steroids are catching up with antibiotics as the most abused class of medications. Since they have been indicated for various conditions, the adverse effect occurring is often missed or sometimes ignored due to benefits they provide for the majority of chronic inflammatory conditions. Definitely prescription of glucocorticoids depends on the risk versus benefit ratio, but unwanted effects do occur with large doses or prolonged administration.

Hence, an attempt has been made in this study to analyze the clinical spectrum and the objectives clearly state to assess seriousness, outcome, causality, severity, and preventability of the glucocorticoid-induced ADRs.

MATERIALS AND METHODS

The aim of the study was to explore the pattern of adverse drug reactions occurring in patients receiving glucocorticoids therapy in a tertiary care hospital.

This study was conducted in the Department of Pharmacology, Kasturba Medical College Manipal, an established ADR monitoring centre (AMC) under the Pharmacovigilance Program of India (PvPI). Permission from the Institutional Ethical Committee of the hospital was obtained before the initiation of the study. It was a prospective observational study conducted from a period of June 2015 to May 2016. Enrolment criteria included all patients who developed adverse drug reactions following the administration of glucocorticoids irrespective of the diagnosis, route and duration. As part of Standard Operating Procedure, the adverse drug reaction data were collected from patient case records of Kasturba Hospital, Manipal and filled in the Suspected Adverse Drug Reaction Reporting forms and then uploaded in net-based software, "Vigiflow" for reporting to the National Coordinating Centre (NCC).

The data of the patients on glucocorticoids therapy (oral/ parenteral/ inhalational/ topical) and who developed adverse drug reactions were extracted from the filled ADR forms. The information of patients was summarized based on demographic characteristics like age, gender, diagnosis, details on adverse drug reactions like onset, pattern, action taken and outcome. Details of suspected drugs causing ADR, route and dose reduction and drug stoppage was analysed.

The causality of the adverse drug reaction was assessed by World Health Organization- Uppsala Monitoring Centre (WHO-UMC) assessment scale, which classifies suspected ADRs as certain, probable, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable (Uppsala, 2005). The severity of ADR was assessed by Modified Hartwig and Seigel scale, which was classified as mild, moderate and severe (Hartwig *et al.*, 1992). Evalua-

tion of chances of preventability of ADRs was done by using Modified Schumock and Thornton criteria which classifies ADRs as definitely preventable, probably preventable and not preventable (Schumock and Thornton, 1992).

Descriptive statistics was used to summarize and analyze the data on the occurrence and frequency of ADRs. The results of the study were entered into an excel sheet and individual percentages were calculated.

RESULTS

Age and gender

100 ADRs were seen in 85 patients. Out of these, 51 ADRs were in male patients and 49 ADRs were in female patients. The mean age for males was 49 years and females was 43 years, respectively.

Medical conditions

The prescribed glucocorticoids were used for various conditions like chronic respiratory, autoimmune, inflammatory and allergic conditions. The most common indication of glucocorticoids for use was in COPD patients (12%), followed by 11% of patients with idiopathic thrombocytopenic purpura [Table 1].

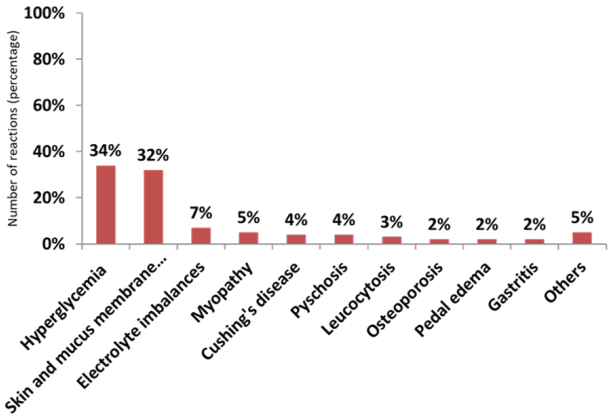

Figure 1: Pattern of adverse drug reactions

Suspected glucocorticoids causing ADR

Prednisolone was the most common glucocorticoid causing adverse drug reaction in 47% of cases, followed by a topical corticosteroids in 18% of cases. Out of which betamethasone was the most common one [Table 2].

Route of administration

Out of the total number of adverse drug reactions that occurred with glucocorticoids, 60% of them were administered through oral route, 17% was through topical application and 14% was given intravenously. In addition, inhalational route (7%) and intramuscular route (2%) was employed in few patients.

The pattern of adverse drug reactions

The most common clinical presentation of an adverse drug reaction to glucocorticoids was hyperglycemia, with 34% of cases having high blood sugars. This was followed by skin and mucous membrane changes in 32% of cases, such as acne (17%), stria albicans and telangiectasia (4%), atrophic dermatitis (3%), erythematous rash (3%), oral candidiasis (3%) and depigmentation (2%). Electrolyte imbalances presented as hypokalemia (6%) and hyponatremia (1%). The other group (5%) of adverse drug reactions included cases of glaucoma, myopia, hypothalamus-pituitary suppression, bone marrow suppression and hypertension [Figure 1].

Time for the occurrence of adverse drug reactions

The majority of the adverse drug reactions to glucocorticoids occurred in long term use (62%). Short term use for less than 1-month duration was seen in 38% of cases [Table 3].

Intervention

Multiple strategies were involved in treating the adverse drug reactions. Specific treatment were given in 46% of them, also in 23% of the patients with drug stoppage and 7% of patients with dose reduction. Among all, 10% of them required no intervention for ADRs [Table 4].

Causality assessment of suspected adverse drug reactions

According to the WHO-UMC scale for causality assessment, the majority (79%) of them were categorized as possible and 21% cases as probable ADRs.

Preventability of the reactions

According to the Modified Schumock and Thornton preventability score, 54% of the ADRs were not preventable, whereas 39% of ADRs were probably preventable and 7% were definitely preventable [Table 5].

The severity of the reactions

According to Hartwig and Siegel scale of severity assessment, the ADRs were classified into different levels as mild, moderate and severe. The majority of the ADRs, 72%, were moderate in nature, whereas the others, 20% were severe and 8% were mild in nature [Table 6].

Outcome at the time of reporting

The majority of the reactions were recovering (42%) at the time of reporting, while in 36% of

Table 1: List of medical conditions prescribed with glucocorticoids

Area of medicine	Indications
Pulmonary (23)	Chronic obstructive pulmonary disease (12), Hypersensitive pneumonitis (4), Bronchial asthma (5), Idiopathic pulmonary fibrosis (2)
Rheumatology (15)	Rheumatoid arthritis (8), Systemic lupus erythematosus (5), Sjogren's syndrome (1), Connective tissue disease (1)
Haematology (14)	Idiopathic thrombocytopenic purpura (11), Autoimmune haemolytic anaemia (2), Vasculitis (1)
Inflammatory (12)	Glomerulonephritis (3), Nephrotic syndrome (2) Chronic kidney disease (4), Chronic inflammatory demyelinating polyneuropathy (1), Arthritis (1), Pelvic inflammatory disease (1)
Dermatology (11)	Dermatitis (3), Pigmentation (2), Acne (1), Xerosis (3), Bullous pemphigoid (1), Eczema (1)
Allergy (8)	Anaphylaxis (3), Contact dermatitis (3), Urticaria (2).
Infections (4)	Hansen's disease (2), Genital tuberculosis (1), Disseminated tuberculosis (1)
Replacement therapy (4)	Acute adrenal insufficiency (2), Chronic heart failure (1), Road traffic accident/shock (1)
Malignancies (3)	T-cell lymphoma (1), Anaplastic sarcoma (1), Astrocytoma (1)
Ocular conditions (3)	Macular oedema (2), Optic neuropathy (1)
Unknown (3)	Not mentioned

Table 2: List of prescribed glucocorticoids suspected to cause adverse drug reactions

Glucocorticoids	Adverse drug reactions (No. of reactions)
Short-acting	
Hydrocortisone	7
Intermediate-acting	
Prednisolone	47
Methylprednisolone	12
Deflazocort	2
Long-acting	
Dexamethasone	7
Inhalational	
Budesonide	7
Topical	[18]
Betamethasone	9
Clobetasol	4
Beclomethasone	2
Mometasone	2
Fluticasone	1

Table 3: Time taken for the occurrence of adverse drug reactions

Time period	Incidence of adverse drug reactions
Less than 1 month	38%
1 month-6 months	29%
More than 6 months-1 year	13%
More than 1 year	11%
More than 10 years	9%

Table 4: Means of intervention to manage ADRs

Action taken for the adverse drug reaction	Adverse drug reactions (%)
Specific treatment	46%
Drug stopped + specific treatment	23%
Drug stopped + without specific treatment	5%
Dose reduced	9%
Dose reduced + specific treatment	7%
No intervention	10%

Table 5: Modified Schumock and Thornton preventability scoring of ADRs

Preventability Criteria	Adverse drug reactions (%)
Definitely preventable	7
Probably preventable	39
Not preventable	54

Table 6: Hartwig and Siegel scale of severity assessment of ADRs

Severity	Adverse drug reactions (%)
Mild 1,2	8
Moderate 3,4,5	72
Severe 6,7	20

them, the reaction continued and only 17% of them fully recovered from the adverse drug reaction. There was no fatality, and the outcome of 5% was unknown due to a lost to follow-up.

DISCUSSION

Adverse drug reactions, as defined by World Health Organization (WHO), is "a response to a medicinal product which is noxious, unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function". The under-reporting of adverse drug reactions is a major problem worldwide, and the possible attributes include shortage of time, limited awareness, insufficient knowledge on reporting process in terms of who, when and how to report (Gurmesa and Dedefo, 2016; Dweik *et al.*, 2017).

Pharmacovigilance (PV), is a program initiated by the WHO in detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of the drugs. The main aim of the Pharmacovigilance Program of India (PvPI) is to strengthen the process of reporting by familiarizing the process and providing clarity in reporting ADRs (Rajgopal *et al.*, 2016). There are numerous studies on the analysis of ADRs of drugs in various field of medicine; however, there are only a few published reports on adverse drug reactions and safety profile of patients receiving glucocorticoid therapy. There is a need to strengthen the database of these ADRs so as patients who are on therapy can relate to them and possibly prevent them (Vivekanantham *et al.*, 2019).

This study was a retrospective analysis of 100 adverse drug reactions following administration of glucocorticoids in 85 patients. Males and females were equally affected. There was no gender difference in the incidence of ADRs, also seen in other similar studies (Venkatasubbaiah *et al.*, 2018; Paradkar, 2019). It was also observed that adults were the ones who were most affected (71.26%, 76.6%) in both the above studies, identical to the finding where the mean age was 49 and 43 years for males and females, respectively. Glucocorticoids were prescribed for pulmonary, rheumatological and inflammatory diseases.

However, the most common indication was COPD (12%), ITP (11%) and rheumatoid arthritis (8%). A drug utilization study revealed majority of patients (66%) were prescribed steroids for respiratory illness (Balasubramanian *et al.*, 2019). This study was conducted in a tertiary care hospital and across various departments and has captured almost all the diagnoses where glucocorticoids have been prescribed.

The most commonly prescribed glucocorticoids were prednisolone (47%) and methylprednisolone (12%) and the majority of them was administered orally. A similar presentation was observed in another study (Dweik *et al.*, 2017). A cohort analysis of 11 different corticosteroid related adverse events studies revealed oral prednisolone being strongly associated with infections, gastrointestinal, neuropsychiatric, ocular, cardiovascular, metabolic, and bone-related complications (Bloechliger *et al.*, 2018).

Metabolic and endocrine disturbances are mostly hyperglycemia, osteoporosis, dyslipidemia, central obesity, and adrenal suppression. Even though corticosteroids precipitate hyperglycemia in diabetics, the incidence of hyperglycemia in patients without prior history of diabetes can go up to 46% (Liu *et al.*, 2014). Our findings showed that hyperglycemia was the most common adverse drug reaction with corticosteroid use in 34% of the cases. A meta-analysis showed that the long-term incidence of glucocorticoid-induced hyperglycemia was 32.3% and diabetes was 18.6% in nondiabetic patients who received glucocorticoid treatment (Liu *et al.*, 2014). Corticosteroids increase endogenous glucose production by expression of the nuclear receptor peroxisome proliferator-activated receptor α, enhance the effects of other counter-regulatory hormones glucagon and epinephrine, reduce peripheral glucose uptake into muscle and adipose tissue. Also, they inhibit the production and secretion of insulin from pancreatic β-cells, thereby leading to insulin resistance (Tamez-Pérez, 2015).

The second common ADRs included those affecting skin and mucous membrane occurring in 32% of cases. In this study, acne (17%), stria albicans, telangiectasia, atrophic dermatitis, erythematous rash and depigmentation were the commonly reported ADRs. These cutaneous ADRs were seen with the use of topical corticosteroids (18%), most commonly was betamethasone and clobetasol. A cross-sectional analysis of skin changes in 100 patients seen predominantly with betamethasone, had the highest incidence of acneiform eruptions (56%) (Kannan *et al.*, 2015).

Even when a study was conducted across various departments, topical steroids were the most common drug (betamethasone sodium phosphate, 23.13%) where the majority of the reported ADRs were acne (18.03%) (Lihite *et al.*, 2017).

The occurrence of adverse effects of glucocorticoids parallels the therapeutic effects, which to an extent cannot be avoided. But by predicting the time of occurrence, it is possible to anticipate the potential side effects and take necessary measures to prevent them. The incidence of adverse drug reactions in patients taking short term steroids for less than 1 month was 38%, similar to a study with 21.1% incidence taking short term oral corticosteroids defined as less than 30 days' duration (Waljee *et al.*, 2017). Long term glucocorticoid use was seen in 62% of cases. Another study with incidence rates of short term therapy (42.6) and long term use (57.4%) of glucocorticoids correlated the type of ADR with a time of occurrence (Paradkar, 2019).

The timely intervention will reduce the long term consequences of ADRs on the patients. Specific treatment was given in 76% of the patients; few of them required drug stoppage (23%) and dose reduction (7%). Acute episodes of hyperglycemia were corrected with insulin; however, long term hyperglycemia was treated with oral antidiabetic agents like metformin. Untreated hyperglycemia due to steroids increased the risk of developing diabetes mellitus. Among the oral antidiabetics, the mechanism of action of metformin counteracts the effects of glucocorticoids by enhancing insulin sensitivity and reducing gluconeogenesis (Wallace and Metzger, 2018).

Acute episodes of psychosis required atypical antipsychotics and drug discontinuation, whereas effects like hypertension and gastritis were treated with amlodipine and proton pump inhibitors with just dose reduction. Cutaneous adverse events were treated with antihistamines and topical emollients. Timely implementation of adjunctive therapy significantly prevents, minimizes common as well as disabling complications of glucocorticoid therapy (Aulakh and Singh, 2008; Moghadam-Kia and Werth, 2010).

All the suspected adverse drug reactions were assessed for causality with the WHO-UMC scale. The causality association of the majority (79%) of ADRs to drugs were possible in nature. This can be attributed to alternative factors such as concomitant therapy, underlying disease and lack of re challenge that could have contributed to ADRs. This finding was similar to other observational studies analyzing the adverse effects of glucocorticoids. An important consideration in this study is when the modified Schumock and Thornton preventability score was applied, 54% of the ADRs were not preventable, and 39% could only be probably preventable. This could probably be explained by the underlying disease and comorbid conditions of the patient required prolonged therapy and drug accumulation.

A literature review on glucocorticoid induce adverse effects stated that only a few of the untoward effects

like osteoporosis, gastritis and, to some extent, infections could be prevented depending on dose, duration of therapy and patient factors. Conditions like hypertension, diabetes mellitus and neuropsychiatric changes could not be prevented and required regular treatment (Van der Goes, M. C., Strehl, C., Buttgereit, F., Bijlsma, J. W., Jacobs, J. W., 2016). This data could actually guide the clinicians in monitoring the adverse effects and that the medical conditions before or after the initiation of therapy are likely to stay and must be treated effectively (Liu *et al.*, 2013).

The Hartwig and Siegel scale of severity assessment depicted 72% of ADRs were moderate in nature, requiring intervention with antidote or discontinuation or change of drug therapy. Severe ADRs were 20% requiring intensive medication, prolonged hospitalization, or causing permanent harm to the patient. The severity of an ADR depicts the intensity of the drug therapy, which primarily depends on the dose and duration for steroids. An observational study with similar finding was observed with moderate severity assessment in 62% of the glucocorticoid adverse events (Aryal *et al.*, 2017).

The severity of glucocorticoid-induced harm could range from disturbing cosmetic changes, asymptomatic metabolic disturbances to life-threatening infections and can be perceived differently in patients (Alan and Alan, 2018). The intensity and severity can be reduced by taking preventive measures, appropriate therapy and treating the primary and comorbid illness. In terms of the outcome of the reaction, most of the patients were yet to recover from the adverse event and only 17% of them fully recovered from the adverse drug reactions during the study period.

The use of glucocorticoids is well established in inflammatory, allergic and autoimmune diseases. The side effects and complications of oral, parenteral and topical glucocorticoids are the major cause of iatrogenic illness. The distressing factor for the clinicians is adverse effects related to high dosages, or long duration of treatment that are not always assessed in clinical trials.

There is a paucity of data with respect to the use and complications of glucocorticoids in the patients with real-life scenario considering their comorbid illness, medications and underlying disease. Limitations of this study were concomitant drugs were not considered, no follow up and the dose of suspect medications were not studied owing to different dosage forms. Even though this study was conducted with few samples analyzing just 100 adverse drug reactions of glucocorticoids, the data obtained gave some important conclusions.

1. Hyperglycemia was the major adverse drug reaction among the patient, which stresses lifestyle modification as a preventive measure.
2. Complications is not always with long time administration. Even short courses of glucocorticoid therapy resulted in adverse effects.
3. The timely intervention will reduce the impact of events like psychosis, myopathy and electrolyte disturbances.
4. Over half of the reactions were not preventable, could be due to prolonged illness, comorbidity, multiple ADRs and polypharmacy.

CONCLUSION

It can be concluded that adverse events are going to be part of and in parallel to the therapeutic effects. It is just a question of balancing the risk and benefits of therapy. Few considerations when initiating glucocorticoid therapy would be to use low dose short-term medications with alternate-day dosing. Patients need to be screened for blood sugars, provided calcium and vitamin D supplements if necessary. Advice to prevent abrupt stoppage of steroids should be given. Risk and harm need to be informed to them. Counselling on choosing a healthy lifestyle, weight-bearing exercises, smoking cessation and reduction in alcohol consumption should be considered. Constant monitoring and follow-up with a structured approach is necessary to improve the use of glucocorticoid therapy and reduce the burden of its adverse effects.

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Conflict of Interest

The author declares no conflict of interest for this study.

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