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Comparative study of adverse drug reactions of corticosteroids

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Abstract
Background: In Dermatology, corticosteroids (CSs) are widely prescribed in either topical or systemic formulations in various potencies to tailor therapy according to severity of the underlying condition, area of involvement, and patient's age. CSs, however, are associated with a number of serious adverse effects, particularly with long-term usage.
Aims: To study the relationship of adverse drug reactions (ADR) of long-term glucocorticoids (GC) with age, sex, smoking, alcoholism, underlying dermatologic conditions and co-existing medical disorders. To study CSs in relation to musculoskeletal system, metabolic & blood sugar levels and eye complications. To compare the ADR in cases on Oral mini pulse therapy (OMP) and Daily glucocorticoid (DGC) therapy groups.
Methods: This was a hospital based prospective study done on 130 patients on OMP or Daily glucocorticoid therapy for more than 1 month duration, over a period of 2 years.
Results: Cushingoid features and weight gain were observed in both groups. Bone changes, diabetes mellitus and hypertension were seen in patients on DGC therapy. Bone changes were seen in 17 (18.88%), Steroid induced Diabetes Mellitus (SDM) in 27(30%), Hypertension in 12(13.3%), Lipid abnormalities (in the form of raised cholesterol and triglyceride levels) in 7 (7.77%), Cataract in 12(13.33%) and glaucoma was seen in 1(1.11%) out of 90 patients on Daily glucocorticoid therapy.1 patient each out of 40 in the OMP group developed cataract and hypertension.
Conclusion: In conditions like vitiligo, alopecia areata and lichen planus particularly in children, it is preferable to give OMP. In pemphigus group of disorders while using daily GC therapy, continuous monitoring and ADR prevention measures should be considered for patient's benefit.

Keywords: Corticosteroids, glucocorticoid, lichen planus, pemphigus

Introduction
Adverse drug reactions (ADRs) are inevitable consequences of drug therapy, as no pharmacotherapeutic agent is completely free from noxious and unintended effects. They are major contributors for morbidity, mortality and hospitalization of the patients increasing the economic burden on the society. Though they are unavoidable accompaniments of pharmacotherapy, the reporting of ADR is poor and inadequate [1]. Healthcare systems rely mainly on the detection and, assessment and spontaneous reporting of suspected ADRs by health care professional [2]. Substantial under-reporting and selective reporting of ADRs are the major drawbacks of the commonly followed method of spontaneous reporting by healthcare professionals (HCP). Upto 57% of ADRs are unrecognized by attending physicians, leading to its inappropriate management [3]. The various factors frequently associated to inadequate ADR reporting by HCP are poor work place environment, increased work load, and no specific training in pharmacovigilance. The influence of attitudes responsible for the failure to recognize and report a recognized ADR as proposed by Inman include complacency that only safe drugs are allowed to the market, fear of possible involvement in litigations or investigations, guilt of having caused harm to the patient, ambition to compile and publish a personal case series, ignorance of requirements of reporting, hesitancy at the prospect of appearing ridiculous for reporting merely suspected ADR, indifference of HCP to suspected ADR, lethargy due to lack of interest or time, procrastination, no financial incentives [4, 5]. Patient direct reporting of ADR has been incorporated into the pharmacovigilance (PV) system in several countries. Patient direct reporting of ADR was qualitatively similar to HCP ADR report.

Nevertheless, patient reports gave detailed descriptions of suspected ADRs, recognized reactions to specific medicines and provided information useful for assessing causality. Patient reports often had richer narratives than those of HCPs and rarely provided irrelevant information or ambiguities. Patient reports often contained detailed information about the impact of the suspected ADR on the patient's life, thus providing insights that were comparatively rare in HCP reports [6].

Corticosteroids (CS) are the most frequently used class of highly potent anti-inflammatory and immunosuppressant agents in clinical practice for various clinical indications [7]. However, their long-term use is associated with serious side effects, which restrict their clinical utility [8, 9]. Even low dose CS treatment has been suggested to be not free from risks [10]. Moreover, cutaneous adverse effects have also been reported to occur even with prolonged treatment of topical CS.

CSs play a major role in the dermatologist's armamentarium. CSs have long been a mainstay of pharmacotherapy in a variety of disorders and conditions for the suppression of inflammation and of the immune system.

CSs are widely prescribed in dermatology however they are associated with a number of serious adverse events, particularly with long-term use. Safe and effective use of this class of agents, therefore, requires knowledge of their mechanism of action and potential complicating factors [4, 5]. GC show ever have proven to be the "archetypal double-edged sword of medicine."

In general, the risk of adverse effects of corticosteroids increases with the duration of therapy and frequency of administration. Side effects such as gastrointestinal intolerance, mood changes, nervousness, and insomnia can occur with short courses of corticosteroids [8]. It can cause various metabolic adverse effects like hyperglycemia, hypertension, cushingoid changes, etc.

A high index of suspicion is needed to catch adverse effects such as osteopenia, avascular necrosis and cataract as they are not visible clinically and may be missed.

Material and Methods

This was a hospital based prospective study done on 130 patients who attended the Dermatology OPD and were on systemic oral glucocorticoid (GC) therapy given on daily basis or in OMP therapy (for more than 1-month duration).

The patients on systemic oral GC therapy with minimum 6 months of follow up were recruited in the study. Daily glucocorticoid therapy comprised of daily administration of Prednisolone (1-2mg/kg/day) or Methylprednisolone whereas OMP therapy consisted of administering Betamethasone (0.1mg/kg) on two consecutive days per week. In both cases the dose was tapered according to clinical response.

Detailed history was taken which included demographic data, medical history and history regarding duration of treatment. They were repeated at fifteen days initially and then monthly. Thorough clinical examination was done including weight, Blood Pressure and Abdominal Girth. Ophthalmological examination and X-rays were carried out at baseline and 6 monthly thereafter. Baseline complete blood count, urine examination, fasting blood sugar, 2 hours post prandial blood sugar, serum creatinine, liver function test, serum cholesterol, chest X-ray, X-ray dorso-lumbar spine and pelvis with both hip joint were carried out and repeated as and when required. Other immunosuppressive therapies like cyclophosphamide, azathioprines etc. were given as steroid sparing agents. Pulse therapy was considered wherever possible.

Results

Out of 130 patients included in the study, 90 (69.23%) cases were on Daily glucocorticoid therapy and 40 (30.77%) were on OMP therapy. Out of 40 cases in OMP group, 20 were males and 20 were females. Out of 90 cases in Daily glucocorticoid therapy group, 40 were males and 50 were females.

15 (37.5%) out of 40 cases in OMP group and 29 (32.2%) out of 90 in Daily glucocorticoid therapy group were in the age group 31- 40 years. 34 (85%) out of 40 patients in OMP group and 60 (66.67%) out of 90 cases in Daily glucocorticoid therapy group were on treatment for 1-6 months at the time of inclusion. Mean duration of therapy was 5.2 months in OMP group whereas it was 7.88 months in the Daily glucocorticoid therapy group.

Most common indication for Daily glucocorticoid therapy was autoimmune vesiculobullous disorders like pemphigus vulgaris and its variants (40%) followed by lepra reactions (18.88%). On the other hand lichen planus constituted the most common indication (40%) followed by alopecia areata (25%) and vitiligo (17.5%) for OMP therapy. The various indications for which GC therapy of more than 1 month duration was given are shown in Table 1.

Table 1: Conditions for which GC therapy of more than 1 month duration was given: OMP vs. Daily glucocorticoid therapy

(n= 130)

Indication	OMP (n= 40) Number	Percent %	Daily GC (n=90) Number	Percent %
Lichen planus	16	40	4	4.4
Alopecia areata	10	25	1	1.1
Bullous pemphigoid	-	-	2	2.2
Vitiligo	7	17.5	-	-
Lepra Reactions	-	-	17	18.88
Airborne contact Dermatitis	-	-	2	2.2
Pemphigus group	5	12.5	36	40
Morphea	1	2.5	-	-
Photolichenoid eczema	1	2.5	-	-
Atopic Dermatitis	-	-	3	3.3
Photodermatitis	-	-	4	4.4
Vasculitis	-	-	3	3.3
MCTD/UCTD/SLE/SS/RA	-	-	14	15.55
Granuloma annulare	-	-	1	1.1
Disseminated eczema	-	-	3	3.3
Total	40	100	90	100

Bone and metabolic ADR seen in both groups are shown in Table 2. Side effects like bone changes and DM were seen only in patients on Daily glucocorticoid therapy. Maximum number of patients 29 (32.2%) on Daily glucocorticoid therapy were of age group 31-40 years, and pemphigus group of disorders was the major indication.

Cushingoid features and weight gain (based on weights taken on initiation and after 6 months of therapy) was observed in both groups, while 1 patient in OMP group suffered from hypertension.

Table 2: Bone and Metabolic ADR due to GC therapy: OMP vs. DGC Therapy

(n=130)

Sr. no.	ADR	OMP (n= 40)	Daily GC (n=90)
1	Bone changes	(0%)	17(18.88%)
2	Steroid induced DM (SDM)	(0%)	27(30%)
3	Arterial HT	01(2.5%)	12(13.33%)
4	Cushingoid Features	07(17.5%)	36(40%)
5	Weight gain	10(25%)	74(82.22%)

Bone changes were seen in 17 (18.88%) out of 90 cases on Daily GC therapy in the present study. This included 12 patients with osteopenia (8 males and 4 females), 3 with osteoporosis (females) and 2 with AVN (a male and female of 28 years each).Out of 17, 8 were females who belonged to age group more than 40 years. Mean age of developing osteopenia in females was 45 years. Both patients with AVN were young (age 28 years). Bone changes in the current study vs. comparative study are shown in Table 3.

Table 3: Bone changes due to Daily glucocorticoid therapy: Present study vs. Comparative study

Bone changes	Present study (n=90)	Sharma P *et al*. (n=60) [11]
Osteopenia	12(13.33%)	04(6.7%)
Osteoporosis	3(3.3%)	02(3.3%)
AVN/ON	2(2.2%)	01(1.7%)
Total	17(18.88%)	07(11.7%)

Table 4: Metabolic ADR and SDM due to DGC therapy: Present study vs MAS study, SDM due to DGC Therapy: Present study vs P Arner study, HT due to DGC Therapy: Present study vs. PVK study, Lipid abnormalities due to DGC therapy. Present study vs Gunjotikar R V study, Ocular complications due to DGC therapy: Present study vs Matsunami C study, ADR of OMP in Alopecia areata: Present study vs Goyal NN study

ADR	Present study (n=90)	MAS study [12] (n=103)
SDM	27(30%)	(52.4%)
Arterial HT	12(13.33%)	(71.8%)
Weight gain	74(82.22%)	(79.6%)
SDM	Present study(n=90)	P Arner *et al*. (n=145) [13]
	27(30%)	36(25%)
HT	Present study (n=90)	PVK *et al*. (Moscow) (n=35) [14]
	12(13.3%)	07(20%)
Lipid abnormalities	Present study(n=90)	Gunjotikar R V study (n=27) [15]
	7(7.77%)	15(56%)
Ocular complications	Present study(n=90)	Matsunami C *et al*. (n=155) [16]
Cataract	12(13.33%)	54(34.83%)
Glaucoma	1(1.11%)	2(1.29%)
Ocular hypertension	0	2(1.29%)
ADR Of OMP in Alopecia areata	Present study(n=10)	Goyal NN *et al*. (n=14) [17]
Cushingoid facies	02(20%)	02(14.3%)
Weight gain	06(60%)	06(42.9%)
SDM	00	01(07.1%)

MAS [12] *et al*. reported weight gain-79.6%, SDM-52.4% and HT-71.8% in kidney and pancreas transplant recipients receiving long term steroid therapy compared to present study (Weight gain-82.22%, SDM-30% and HT-13.33%).

SDM was seen in 27(30%) patients out of 90 on Daily glucocorticoid therapy in present study vs. 36(25%) out of 145 in the comparative study. P Arner *et al*. [13] study was carried out in renal transplant recipients and incidence of steroid diabetes correlated with steroid dose, age, body weight and diabetes heredity. All cases in present study were belonging to mean age of 48.51 years age group.

Arterial hypertension developed in 12 (13.3%) out of 90 cases on Daily glucocorticoid therapy in present study, while it was 7 (20%) out of 35 cases in a prospective study by PVK *et al*. [14] which was done on patients of nephritic syndrome on long term steroids. All cases in present study with HT were belonging to the mean age of 47.91 years. 7 out of 12 were females and 5 out of 12 males. Out of these 12 patients 1 developed nephropathy, 5 cataracts, 4 osteopenia, 1 AVN.

7 (17.5%) out of 40 cases in OMP group and36 (40%) out of 90 cases in Daily glucocorticoid therapy group developed cushingoid features. 21 out of 43 (48.83%) cases were females. Moon facies was the most common finding among moon facies, truncal obesity and buffalo hump.

36 out of 90 patients in Daily glucocorticoid therapy group were of Pemphigus. LS *et al*. [18] study on 159 patients of pemphigus on long term steroid therapy showed SDM in 37(23.2%) and HT in 23(14.5%) compared to the present study (Bone changes-06(16.66%), SDM-17(47.22%) and HT-06(16.66%)). 7(7.77%) out of 90 patients on Daily glucocorticoid therapy developed lipid abnormalities in the present study, as compared to 15(56%) patients out of 27 in study by Gunjotikar *et al*. [15]. The indication in the later study was that of immunosuppresion for renal transplant patients. 11 out of 90 in the Daily glucocorticoid therapy group and 1 out of 40 in the OMP group patients out of 90 developed cataract in present study as compared to 54out of 155 in the Matsunami C [16] study. The major indication in this study was for Pemphigus patients, while it was immunosuppression after renal transplantation in the Matsunami study. 1(1.11%) patient out of 90 and 2(1.29%) patients out of 155 patients developed glaucoma in present study and Matsunami study respectively. When comparing ADR in OMP group (10 patients in present study) for alopecia areata with Goyal NN study [17] (14 patients) both

had 2 patients with cushingoid facies and 6 with weight gain. 1 patient had SDM in the comparative study.

Discussion

There were more females in the study as they suffer more from autoimmune disorders like vesiculobullous diseases. Both the dose and duration of steroid therapy was higher and longer in Daily glucocorticoid therapy group as compared to OMP group.

Osteoporosis is one of the most prevalent side effects that occur in patients on long term systemic glucocorticoid therapy. Osteoporosis occurs in 30-50% of all patients treated chronically with glucocorticoids without proper preventive measures [19, 20]. Bone changes were seen in 17 (18.88%) out of 90 cases on Daily GC therapy.

Radiographs can detect bone changes only when 30% of density has been lost. If recent techniques like quantitative CT and DEXA scan were employed, a greater number of cases could have been detected to have osteopenia and early therapeutic intervention could have been possible. Fractures occur in up to25% of patients receiving long term GCs but this rate increases in postmenopausal females [21, 22]. Out of17 cases that had developed Daily glucocorticoid therapy induced bone changes 8 were females who belonged to age group more than 40 years. Mean age of developing osteopenia in females was 45 years.

It is generally agreed that long- term, high dose steroid therapy carries a definite risk for steroid induced osteonecrosis (ON), but it is not clear whether short-term, high-dose; or long-term, low-dose steroid use also carries the same risk [13]. There is some evidence to show that daily administration of steroids is more strongly associated with ON compared to steroids administered as a bolus [14]. Two patients of either sex in the current study developed avascular necrosis of femur head, both being 28 years of age. The indications were Pemphigus vulgaris and MCTD.

Steroid induced HT is a known entity, however is controversial. The less no. of cases of steroid induced HT in present study could have been because of the reason that, in the comparative study the indication for long term steroids was nephritic syndrome. The most relevant study was performed 26 years ago, when Jackson and colleagues[15] studied the effects of corticosteroid therapy on BP in 129 asthmatic and 66 Rheumatoid Arthritis patients. They concluded that long – term (>1yr) 'low-dose' (<20 mg daily) GCs do not lead to BP increase, and that significant HT may be better explained by age and intial BP than by the use of GCs.

Glucocorticoids increase lipid levels because of increased lipid production in liver and due to lipolysis from adipose tissue. It causes redistribution of fat, carbohydrate and protein reserves. This along with increase in appetite leads to cushingoid habitus (moon facies, buffalo hump and central obesity). 21 out of 43 (48.83%) cases that developed cushingoid features were females. In a study by Fardet *et al*. it was reported that daily corticosteroid induced lipodystrophy was higher in women, in subjects younger than 50 years of age, in subjects with a high initial body mass index and in subjects with high energy intake.

Cushingoid features and weight gain (based on weights taken on initiation and after 6 months of therapy) was observed in both groups, while 1 patient in OMP group suffered from hypertension. Verma KK *et al*. [16] reported that except for weight gain in 2 out of 10 patients on oral mini pulse therapy and mild cushingoid features in 1 patient no other side effects were observed in any of the patients on oral mini pulse therapy [16]. In the present study 10 patients out of 40 had weight gain in OMP group.

Pemphigus group of disorders was the most common indication for Daily glucocorticoid therapy. 20 (55.55%) out of 36 patients of Pemphigus group were females. Mean age of developing pemphigus was 43.85 years in females and 44.43 years in males. It is a disease of 40-50years age group who are more prone to develop HT, DM and bone related ADRs of systemic oral GC therapy.

Hyperlipidemia is a common side effect of therapy, especially in patients with prior lipid abnormalities. Elevation of triglycerides is most common, but elevations of high-density lipoproteins or low-density lipoproteins occur in some patients. The mechanism of hypertriglyceridemia is likely related to relative insulin insufficiency [17].

The lipid abnormalities in the comparative study were significantly higher. The indication in the Gunjotikar R V study[5] was that of immunosuppresion for renal transplant patients. In addition to prednisolone, azathioprine and cyclosporine were given and the dose as well as duration was more in the later study. All patients with lipid abnormalities were females. In them, the social stress as well as the stress of disease itself may have aggravated the chances of hyperlipidemia because of GC therapy.

Long term use of topical and systemic steroids produces secondary open angle glaucoma similar to chronic simple glaucoma as well as cataract. Ocular complications in the Matsunami C [6] study were significantly higher than the present study. Here the major indication was for immunosuppression after renal transplantation.

OMP therapy using betamethasone/dexamethasone 5mg on weekdays was successfully used by Pasricha JS *et al*. [18] for arresting progressive vitiligo. They reported minor side effects like weight gain, mild headache, transitory general weakness for 2 days after the pulse and bad taste in the mouth.[18] Kanwar AJ *et al*. reported OMP using low dose dexamethasone 2.5mg on weekdays for progressive vitiligo and concluded that it was effective with minimal side effects [19]. On the contrary Goyal Nilesh N *et al*. [7] had reported that oral mini pulse steroid therapy in alpoecia areata does not confer any significant advantage over daily steroid therapy in terms of adverse effects.[7]Betamethasone on two consecutive days in a week as oral mini pulse therapy may be a safe, effective and a better therapeutic alternative for the treatment of lichen planus (Verma KK) [16].

Conclusion

in conditions like vitiligo, alopecia areata and lichen planus particularly in children, it is preferable to give oral mini pulse therapy. In pemphigus group of disorders while using daily GC therapy continuous monitoring and ADR prevention measures should be considered for patient's benefit. As and when feasible, steroid sparing agents (cyclophosphamide, azathioprine, methotrexate, cyclosporine, rituximab and Intravenous Immunoglobin therapy) and GC pulse therapy should be used, more so in high risk groups like elderly cases having pre-existing diabetes or hypertension.

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