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A prospective assessment of polypharmacy induced drug interactions with corticosteroids

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ABSTRACT

Drug interaction represents a major problem in day-to-day practice. The incidence of adverse reactions increases almost exponentially as the number of drugs co prescribed rises, and this is in part due to drug drug interactions. This study was aimed to study the incidence of polypharmacy induced drug interactions with corticosteroids and their severity. A prospective observational study was carried out in 211 In-patients from various departments of the hospital during 6 months period and subjected to statistical analysis. Out of 211 In-patients, 142(67.3%) were male and 69(32.7%) were female. A maximum of (44.9%) belonged to geriatric age group. Most of patients were prescribed with more than 6 drugs. The numbers of prescriptions having drug interactions with corticosteroids were 111, with majority (49.5%) of them were from general medicine ward. A total of 154 drug-drug interactions were found among these prescriptions including 124 moderate, 21 major and 9 contraindicated interactions. Most of the prescriptions (75) were having atleast 1 interaction and 28 prescriptions were having 2 interactions. Out of these interactions, 17, 75, and 62 were having excellent, good and fair scientific evidence. Regarding the onset of these drug-drug interactions, 74(48%) were with delayed onset, 43(27.9%) were unspecified and 37(24%) were with rapid onset. Dexamethasone with ciprofloxacin, tramadol, moxifloxacin, diclofenac, pantoprazole, theophylline were the most encountered combinations. A high prevalence of polypharmacy and drug interactions with corticosteroids was identified in our study. Since concurrent drugs can potentiate irreversible adverse effects of corticosteroids, a regular therapeutic intervention is necessary.

INTRODUCTION

Drug interaction represents a major problem in day-to-day practice. The incidence of adverse reactions increases almost exponentially as the number of drugs co prescribed rises, and this is in part due to drug drug interactions.[1]

Appropriate drug utilization is beneficial in global reduction of morbidity and mortality with its consequent medical, social and economic benefits.[2] Drugs are the most common medical interventions for betterment of patients but it had recognized long ago that they are fatal too. The saying rightly goes about the drugs that "Drugs are Double Edged Weapons". [2,3]

Critically ill, chronically ill and elderly patients are particularly at risk of drug interactions due to polypharmacy as well as impaired homeostatic mechanisms.[4] It is reported in several studies that elder patients (61-80 years) had more prevalence of polypharmacy and drug-drug interactions compared to the other age groups. The use of multiple medications increases the possibility of drug interactions and adverse reactions to drugs, poorer compliance, increased risk of hospitalization and medical errors caused by drugs. [5]

The definition of polypharmacy in the literature is not uniform. However, the word 'poly' is a Greek word and means many or much.[6] There are basically two approaches to the definition. The first refers only to the number of drugs taken simultaneously. According to this, polypharmacy means the concurrent use of 2 or more drugs. However, some authors distinguish between minor polypharmacy (the concurrent use of 3 to 5 drugs) and major polypharmacy (the concurrent use of 5 or

more drugs).[7,8] The other approach to the definition focuses on the clinical indication and the effect of the administered medication. According to this definition, irrational, clinically not indicated drug use is regarded as polypharmacy.[9,10]]

Corticosteroids are adrenal steroids, indicated for suppression of inflammation, suppression of immune response and replacement therapy. These life saving drugs play a major role in treatment of chronic diseases like asthma, COPD, arthritis and other diseases affecting skin, GIT and CNS. Use of these drugs must be carefully weighed in each patient since they produces number of complications. The goal of corticosteroids therapy is to use the safest and least number of drugs to get more efficacy in short period and to avoid ADRs & drug-drug interactions. Keeping present scenario in mind, this study was aimed to assess the incidence of polypharmacy induced drug interactions with corticosteroids with their severity and to identify whether it is associated with Polypharmacy.

MATERIALS & METHODS

A prospective observational study was conducted for 6 months period during November 2014 to April 2015 in the various departments of Navodaya Medical College Hospital and Research centre, Raichur, Karnataka, after obtaining the ethical clearance. A total of 211 patients were included in the study who were In-patients prescribed with corticosteroids from General Medicine, Orthopaedic, ICU & Emergency, Pediatrics and Pulmonary Medicine. Other departments were excluded from study criteria along with group of pregnancy and lactating women.

The data was collected from various sources such as patient's case reports, laboratory data, treatment charts and patient interview/patient care taker interview using specially designed data collection form. Data was analyzed using descriptive statistics namely total numbers, percentage, mean and standard deviation wherever applicable.

Study protocol:

Patient who met the study criteria were included in the study. Demographics, lab data, diagnosis and treatment chart were noted. All the cases were reviewed prospectively and monitored extensively, the pattern of corticosteroids uses like their category, indication, and rationality of the prescription, concurrent drugs prescribed and/or number of drugs in prescriptions. Drug-drug interactions were identified and documented by using MICROMEDEX 2.0® software, drug.com and STOCKLEY's book. Potential drug-drug interactions were categorized into different levels as follows:[11]

Onset

- **Rapid**: The effect of interaction occurs within 24 hours of administration.
- **Delayed**: The effect occurs if the interacting combination is administered for more than 24 hours, i.e., days to week(s).
- **Unspecified**: The occurrence of effect of interaction is not specified.

Severity

- **Contraindicated**: The drug-combination is contraindicated for concurrent use.
- **Major**: There is risk of death and/or medical intervention is required to prevent or minimize serious negative outcomes.
- **Moderate**: The effect of interaction can deteriorate patient's condition and may require alteration of therapy.
- **Minor**: Little effects are produced that don't impair therapeutic outcome and there is no need of any major change in therapy.

Scientific evidence (Documentation)

- **Excellent**: The interaction has been clearly demonstrated in well-controlled studies.
- **Good**: Studies strongly suggest that the interaction exists except proof of well-controlled studies.
- **Fair**: Available evidences are poor, but the interaction is suspected on the basis of pharmacologic considerations; or, evidences are good for an interaction of pharmacologically similar drug.
- **Poor**: Theoretically the interaction may occur but reports are very limited, such as few case report.

RESULTS

Patient Demographics

As per patient demographic data obtained, out of 211 In-patients, 142(67.3%) were male and 69(32.7%) were female. A maximum of 48(22.7%) patients belonged to age group of 51-60 years followed by 47(21.8%) patients from the age group of more than 60 years. This data showed that commonly geriatrics male populations are more prone to diseases, for which corticosteroids are prescribed. (Table 1)

Incidence of Polypharmacy

In this study, we found that most of patients were having major polypharmacy 158(74.9%) followed by minor polypharmacy 53(25.1%). These results indicates high incidence of polypharmacy and this discrepancy in prevalence may be due to the patient's expectation and demand of quick relief, incorrect diagnosis and the influence of the lucrative promotional programs of the pharmaceutical companies. (Figure1)

Drug-Drug interaction Observed

Table 2 showed ward wise distribution and prescriptions containing corticosteroids interactions along with their severity. Out of 211 In-patients, 111 prescriptions were found to have drug-drug interactions with corticosteroids. Majority 94(44.5%) were from General Medicine ward followed by pediatric ward 37(17.5%). Out of these 111 prescriptions, a total of 154 interactions were found. Most of the prescriptions (75) were having atleast 1 interaction and 28 prescriptions were having 2 interactions.

This data confirms that patients admitted in General Medicine ward have higher exposure to polypharmacy including corticosteroids and drug-drug interaction. (Table 2)

Prevalence of Drug-Drug Interactions

One hundred fifty four (72.9%) patients had at least one potential to drug interaction if prescribed with corticosteroids regardless of type of severity, 124(80.5%) moderate, 21(13.6%) major and 9(5.8%) contraindicated interactions.

In around 68% of patients were identified with one interaction

Table 1. : Gender and Age Wise Distribution

Age group (years)	Male	Percentage (%)	Female	Percentage (%)	Total	Percentage (%)
0-10	23	10.9	12	5.7	35	16.5
11-20	6	2.8	6	2.8	12	5.6
21-30	8	3.7	5	2.3	13	6.1
31-40	15	7.1	9	4.3	24	11.3
41-50	23	10.9	9	4.3	32	15.1
51-60	31	14.6	17	8.0	48	22.7
>60	36	17.1	11	5.2	47	22.2
Total	142	67.3	69	32.7	211	100

Table 2. : Drug-Drug Interaction Observed with corticosteroids

Ward	No. of Patients, (%)	No. of prescriptions with Corticosteroids interaction, (%)	No. of moderate interaction	No. of major interaction	No. of contraindicated interaction
General med.	94 (44.5)	55 (49.5)	66	17	7
Pulmonary med.	31 (14.7)	13 (11.7)	14	0	0
Paediatrics	37 (17.5)	15 (13.5)	15	1	1
Orthopaedics	16 (7.6)	12 (10.8)	10	1	0
Emerg. & causality	21 (9.9)	8 (7.2)	9	2	1
ICU	12 (5.6)	8 (7.2)	10	0	0
Total	211 (100)	111 (52.6)	124	21	9

Table 3. : Number of Interactions with Corticosteroids per Prescription

Number of drug-drug Interaction	No. of Prescription	Percentages (%)
1	75	67.6
2	28	25.3
3	5	4.5
4	3	2.7

Table 4. : Level/Severity of Identified Interaction

Severity of drug-drug interaction Severity	No. of severity	Percentages (%)
Contraindicated	9	5.8
Major	21	13.6
Moderate	124	80.5
Documentation		
Excellent	17	11.0
Good	75	48.7
Fair	62	40.3
Onset		
Rapid	37	24.0
Delayed	74	48.0
Unspecified	43	27.1

Table 5. : Commonly Involved Drug Classes in Drug

Classes of Drug	Examples of drug
Corticosteroids	Dexamethasone, Prednisolone, Hydrocortisone, Deflazacort, Budesonide
Antihypertensive	Amlodipine, Telmisartan, Ramipril, Fosinopril, Hydrochlorothiazide
Antibiotics	Ciprofloxacin, Moxifloxacin, Levofloxacin
Antimalarial	Artemether
Acid Suppressants	Pantoprazole
Analgesics	Diclofenac, Mefenamic Acid, Tramadol
Others	INH, MTX, Alprazolam, Rifampicin

followed by 25.3% of two, 5.1% of three and 1.9% of four interactions. This discrepancy in prevalence may be result of high utilization of drugs having more interacting potentials in our setup. This confirms that higher prevalence of drug-drug interactions associated with high exposure of polypharmacy. (Table 3)

Level/Severity of Drug-Drug Interactions

The identified drug interactions with corticosteroids were categorized into different levels according to severity, scientific evidence and onset. Among the 154 drug-drug interaction identified, most were of moderate 124(80.5%) followed by major 21(13.6%) and contraindicated severity 9(5.8%). Based on

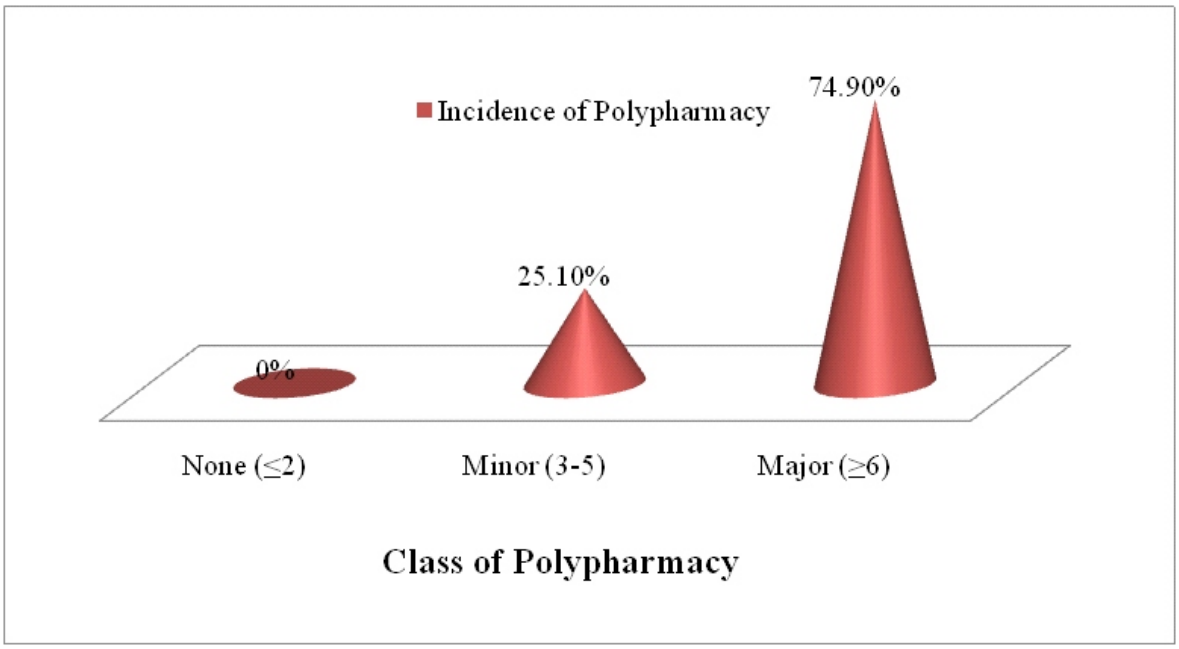

Figure 1: Incidence of Polypharmacy

scientific evidence, 75(48.7%) were good documented, 62(40.3%) were fair and 17(11%) were excellent. On assessing the onset of the potential drug-drug interaction, 74(48%) were with delayed onset, 43(27.9%) were unspecified and 37(24%) rapid onset.

The current study showed that, delayed onset was contributed of around 48% of all the identified drug-drug interactions. This takes relatively longer time to occur their harmful effect and it could be due to frequently administered corticosteroids and higher accumulation effect or larger extent of plasma binding. (Table 4)

Common Interaction Drugs

Table 5 showed common interacting drugs with corticosteroids. Dexamethasone with ciprofloxacin, moxifloxacin, diclofenac, pantoprazole, theophylline and hydrocortisone with diclofenac, phenytoin, theophylline, amlodipine, telmisartan, were the most encountered combinations.

DISCUSSION

Geriatric population suffers from multiple disorders, including chronic conditions. This may be the major reason for prescribing more number of drugs per prescription. The effect of polypharmacy in elderly patients may lead to confusion with drugs name, doses and dosage schedule. Hence, strict monitoring and counselling is required. It has been shown that age is negatively correlated with health literacy. In the current study it was found that around 45% patients belonged to geriatric age group. It was found similar when compared with study done by *John NH et al.,* 2012 [1] and *Ashok Kumar Malpani et al.,* 2015 [10]. It has been estimated the 16% of adults aged 65-69 have a poor understanding of health information, and this figure leaps to 58% for those 85 and older stated by *American Medical Association,* 1999 [12].

In our study, we found most of patients were having major polypharmacy 158(74.9%) which was higher when compared with study done by *Ashok kumar Malpani et al.,* 2015 [10] and *Kumara Swamy RC et al., 2014 [2]*. As the amount of illness increases, the amount of prescription medication use often increases as well. As this happens, it becomes ever more challenging to achieve an ideal balance between the risks and benefits of medications. This can lead to an increased risk of adverse drug events. It has been reported that the probability of an adverse drug event is 13% in patients taking 2 drugs, and increases to 82% in those taking more than seven concluded by study of *Goldberg et al.,* 1996 [13]. In patients taking 10 medications or more, this probability nears 100% concluded by study of *Nolan and O'Malley,* 1988 [14].

Majority of observed drug-drug interactions 94(44.5%) were from General Medicine ward in this study which was similar with study done by *Kumara Swamy RC et al., 2014 [2].* One hundred fifty four (72.9%) patients had at least one potential to drug interaction if prescribed with corticosteroids regardless of type of severity. This was lower when compared with study done by *Shobha Churi et al.,* 2011 [15].

Our finding on prevalence of potential drug-drug interactions of major and moderate severity (42.8%) was lower compared to other study done by *Haftay BM et al.,* 2015 [11]. This discrepancy may be due to the reason that their study was done in psychiatric patients which were prescribed with multiple therapy. The current study showed that delayed onset was contributed 74(48%) of all the identified potential drug-drug interactions. This finding was similar to study done by *Haftay BM et al.,* 2015 [11]. However, data for rapid onset 37(24%) was much higher. This may be due to greater plasma binding, shorter half lives and higher frequency of corticosteroid administration. The study currently was conducted for a short period (6 months) which can be extended. The criterion for this study was limited to drug interactions with corticosteroids only which can be elaborate to general study and also study was conducted in six different wards which can be extended to other departments like ENT, OBG, surgery etc.

Assessment of drug-drug interactions and suggestion for modification of drug therapy of patients are the emerging scope of clinical pharmacist. Such study can play a key role in helping the healthcare system to understand, interpret and improve the prescribing, administration and use of medications. Repeated monitoring of drug usage combined with regular feedback to the prescribers is essential. Measures to facilitate and encourage rational prescribing among the students and prescribers should be undertaken. Rational drug use studies can be conducted to promote safe and cost effective use of corticosteroids.

CONCLUSION

A high prevalence of polypharmacy and drug interactions with corticosteroids was identified in our study. Most of interactions were found to be harmful and may cause tendon rupture, gastroenterology related problems, negative effects on blood pressure and most of were delayed onset in nature. Since the irreversible adverse effects of corticosteroids can be potentiated by use of other concurrent drugs, a regular therapeutic intervention is necessary.

Polypharmacy found in the prescriptions can be accepted, as they are clinically appropriate and/or meet the need of the patient condition, but monitoring is required for the occurrence of drug related problems. Hence, the Clinical Pharmacist act as a potential role in health care system in assisting physician in altering the number of medications taken, the number of doses taken, improving the patient medication adherence, preventing the adverse drug reactions, drug-drug interactions, improve the health related quality of life and decreasing the health care cost of the patient.

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