ORIGINAL ARTICLE

Comparative Adverse Drug Profile of Deflazacort Vs Conventional Corticosteroids in Spontaneous Reporting System of Pharmacovigilance

Vishal R. Tandon, Pritpal Singh*, Annil Mahajan*, Vijay Khajuria, Vivek Mahajan

Abstract

The current observational cross-sectional study was undertaken using suspected adverse drug data collection form available under (PvPI) to evaluate comparative ADR profile of DFZ Vs CCS for 3 years in spontaneous reporting system of ADRs in current PvPI. Total number of ADR reports during the study period was 3024, out of which ADRs reports due to CS were 112 accounting for a rate of 3.70%. The rate of total ADR events with CS was 4.11%. Geriatric, urban and female population predominated in contributing ADRs with both CCS and DFZ in the study. Self medication of CCS and DFZ contributed 10.95% and 7.69% of total ADRs. Oral route contributed maximal ADRs. Irrational drug prescription contributed substantially. Maximum ADRs due to CCS and DFZ were moderate, latent, non-serious, type A and were probable followed by possible in nature as per WHO UMC scale. Gastritis, new onset hypertension/ loss of hypertensive control, loss of diabetic control, obesity/overweight, dyslipedemia were common ADRs. Thus, ADRs due to CS is a substantial health problem. ADR profile did not vary although DFZ recorded less ADRs.

Key Words

Adverse Drug Reaction, Deflazacort, Corticosteroids, Pharmacovigilance

Introduction

Corticosteroids (CS) are the most frequently used class of highly potent anti-inflammatory and immunosuppressant agents in clinical practice for various clinical indications (1). However, their long-term use is associated with serious side effects, which restrict their clinical utility (2-3). Even low dose CS treatment has been suggested to be not free from risks (4). Moreover, cutaneous adverse effects have also been reported to occur even with prolonged treatment of topical CS (5).

Recently use of DFZ has increased in clinical practice. DFZ is a synthetic oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity (6, 7). There are studies existing in literature comparing the relative efficacy and safety of conventional CS to DFZ (8-11). These studies have shown DFZ to be as effective as prednisone or methylprednisolone (8-11). The overall incidence of adverse events in DFZ recipients has been recorded lower than that recorded in patients treated with prednisone or methylprednisolone (6). DFZ has been claimed to be associated with less serious metabolic sequelae and development of CS-induced osteoporosis (6, 7).

However, we failed to cite any observational study based on spontaneous reporting of ADR comparing profile of CCS and DFZ. Hence, the current study was undertaken to evaluate and compare ADR profile of DFZ Vs CCS in spontaneous reporting system of ADRs in current Pharmacovigilance Programme of India.

Material and Methods

An observational prospective cross-sectional analysis was done w.e.f Nov 2010 to Nov 2013 in Adverse Drug Monitoring Centre, working under (PvPI) in a tertiary care teaching hospital from India using suspected drug reactions monitoring data collection form after due

From the Department of Pharmacology and *Internal Medicine, Govt. Medical College, Jammu and India

Correspondence to : Dr Vishal R Tandon, Incharge ADRM centre, Department of Pharmacology, Govt. Medical College, Jammu- (J&K) - India.

approval and permission from Institution Ethics Committee vide Number Pharma/IEC/2014/3608/Research/Cat -12 C/7C/2012/2741 dated 1.11.2012. Verbal consent was obtained from all the participants. The ADRs were defined and categorized as per the definition of Edwards & Arsonson, 2000 (12). The severity and seriousness of reaction, the outcome of reaction and onset time was recorded for every suspected ADR (as per US-FDA) and recommended as per PvPI. The suspected ADRs were classified in term of causality using WHO-UMC scale.(13).

Inclusion: Any ADR from OPD or inward patients of any severity, duration, any type of reaction pertaining to any corticosteroids was followed up and included in current study.

Exclusion: Whereas, any case of poisoning, medication error, over dosage, over/ non- compliance, natural products/alternate medicines and unidentified drugs were excluded in the analysis.

Statistical Analysis

Analysis was carried out with the help of computer software SPSS Version 15 for windows.The data was expressed in n (%).Chi-square test with Yates Correction was applied to prove their statistical significance. P value < 0.05 was considered significant.

Results

In a 3 year study, total number of ADR reports due to corticosteroids was 112 accounting a rate of 3.70%. The rate of total ADR events was 4.11% due to CS. CCS accounted 2.41% in comparison to 1.28% of ADRs resulting because of DFZ. Whereas, 2.69% was ADR event rate of CCS in comparison to 1.42% contributed by DFZ. Geriatric, urban and female population predominated in contributing ADRs both with CCS and DFZ. Self medication of CCS and DFZ contributed 10.95% and 7.69% of total ADRs. Patients from OPD contributed maximum for ADRs due to CS. Oral route contributed maximal for ADRs due to both CS and DFZ. Irrational drug prescription contributed substantially for

Table-1. Comparative Profile of ADRs Due to CCS and DFZ

	Conventional Corticosteroids	Deflazacort	
Total Adverse Reports & Events Due to Corticosteroids	73(2.41%) & 85(2.69%)	39(1.28%) & 45(1.42%)	
Age wise classification- Adult, Geriatric & Pediatric	13(17.80%), 60(82.19%), 0(0%)	8(20.51%),30 (76.92%),1(2.56%)	NS
Sex Distribution- Male vs Female Ratio	33(45.20%) vs 40(54.79%)	15(38.46%) Vs 24(61.53%)	Chi-square=0.47,df=1, P=0.49 NS
Urban vs Rural	40(54.79%) Vs 33(45.20%)	9(23.07%) vs 30(76.92%)	Chi-square=10.13,df=1, P=0.0012
OPD Vs Inward	61(83.56%) Vs 12(16.43%)	29(74.35%) vs 10(25.64%)	Chi-square=1.36,df=1, P=0.242
Self Medication Vs Prescribed Medication	8(10.95%) Vs 65(89.04%)	3(7.69%) Vs 36(92.02%)	Chi-square=0.05,df=1, P=0.825
Route of Drug Administration- Oral/I.V/IM/IA/MDI	63(86.30%)/2(2.73%)/5(6.84%),1(1.36%),2(2.73%)	39(100%)/0%/0%/0%/0%	NS
Irrational Vs Rational	13(17.08%) Vs 60(82.19%)	3(7.69%) Vs 36(92.02%)	Chi-square=2.12,df=1, P=0.144
Severity of ADRS – Mild/ Moderate/ Severe/ Fatal	10(13.69%)/43(58.90%)/20(27.39%)/0(0%)	9(23.07%)/20(51.28%)/10(25.64%)/0(0%)	Chi-square=1.61,df=2, P=0.447
Mode of onset – Acute/Sub acute/ Latent	8(10.95%)/6(8.21%)/59(80.82%)	4(10.26%)/6 (15.38%)/29 (74.35%)	Chi-square=1.36,df=2, P=0.505
Nature of ADR- Serious Vs Non serious	20(27.39%) Vs 53(72.60%)	10(25.64%) Vs 29(74.35%)	Chi-square=0.404,df=1, P=0.841
Type of reactions - A,B,C,D,E	71(97.26%),0(0%),26(35.61%)%),0(0%), 2(2.73%)	38(97.43%), 0(0%),10(26.64%)%),0(0%), 1(2.56%)	NS
Overlap with in A &C			
Causality as per WHO - UMC scale – Certain/Probable/Possible/Unlikely/Unclassified/Unassessible	0(0%)/62(84.93%)/11(15.06%)/0(0%)/0(0%)/0(0%)	0(0%)/30(76.92%)/9(23.07%)/0(0%)/ 0(0%)/0(0%)	Chi-square=1.11,df=1, P=0.291
Outcome of the ADRs - Recovered/Recovering/Continuing/Unknown	0(0%)/53(72.60%)/20(27.39%)/0(0%)	0(0%)/20(51.28%)/19(48.71%)/0(0%)	Chi-square=5.09,df=1, P=0.024

Table 2. Comparative List of ADRs Due to CCS and DFZ

	Conventional Corticosteroids N=85	Deflazacort N=45	Total 130	Chi-square with Yates Correction
Moon Face and Red Plethoric Cheek	3(3.52%)	2(4.4%)	5(3.84%)	Chi-square=0.05,df=1, P=0.824
Cushing Syndrome	2(2.35%)	2(4.4%)	4(3.07%)	Chi-square=0.02,df=1, P=0.9
Muscle wasting	1(1.17%)	1(2.22%)	2(1.53%)	Chi-square=1.51,df=1, P=1.291
New Onset Hypertension/ Uncontrolled HT	10(11.76%)	7(15.55%)	17(13.07%)	Chi-square=0.37,df=1, P=0.541
Dyslipedemia	5(5.88%)	3(6.66%)	8(6.15%)	Chi-square=0.04,df=1, P=0.83
Peptic Ulcer	2(2.35%)	1(2.22%)	3(2.30%)	Chi-square=0.32,df=1, P=0.57
Gastritis	16(18.82%)	10(22.22%)	26(20%)	Chi-square=0.21,df=1, P=0.064
Acne	3(3.52%)	1(2.22%)	4(3.07%)	Chi-square=0.02,df=1, P=0.90
Straie	2(2.35%)	1(2.22%)	3(2.30%)	Chi-square=0.32,df=1, P=0.057
Bruising	1(1.17%)	1(2.22%)	2(1.53%)	NS, P> 0.05
Depression	1(1.17%)	0(0%)	1(0.76%)	NS, P> 0.05
Psychosis	1(1.17%)	0(0%)	1(0.76%)	NS, P> 0.05
Obesity	6(7.05%)	4(8.88%)	10(7.69%)	Chi-square=0.00,df=1, P=0.97
Electrolyte imbalance	5(5.88%)	1(2.22%)	6(4.61%)	Chi-square=0.25,df=1, P=0.61
Cognitive Dysfunction	2(2.35%)	0(0%)	2(1.53%)	NS, P> 0.05
Osteoporosis	2(2.35%)	1(2.22%)	3(2.30%)	Chi-square=0.32,df=1, P=0.057
Loss of Diabetes Controlled/Recent DM	9(10.58%)	4(8.88%)	13(10%)	Chi-square=0.00,df=1, P=1.0000
Oral Candid Infection	2(2.35%)	1(2.22%)	3(2.30%)	Chi-square=0.32,df=1, P=0.057
CAP	2(2.35%)	1(2.22%)	3(2.30%)	Chi-square=0.32,df=1, P=0.057
Latent TB	1(1.17%)	0(0%)	1(0.76%)	NS, P> 0.05
TB Consolidation	3(3.52%)	2(4.4%)	5(3.84%)	Chi-square=0.05,df=1, P=0.824
Opportunistic /Secondary Infection	3(3.52%)	1(2.22%)	4(3.07%)	Chi-square=0.02,df=1, P=0.90
Septic Arthritis	1(1.17%)	0(0%)	1(0.76%)	NS, P> 0.05
Withdrawal Syndrome	2(2.35%)	1(2.22%)	3(2.30%)	Chi-square=0.32,df=1, P=0.57

total ADRs due to CS and DFZ accounting for 17.08% and 7.69% respectively. Maximum ADRs due to CCS and DFZ were moderate followed by severe and mild in nature. There was no fatal ADR recorded in both type of steroids. As far as time of their onset, the maximum of the ADRs were latent in nature. Maximum reactions were non-serious in nature but required intervention in 100% of the cases for both type of CS. Maximum ADR cases were of type A in nature. As per causality assessment maximum reactions were probable followed by possible in nature both by WHO UMC. (*Table-1*)

Gastritis (20%), new onset hypertension/ loss of hypertensive control (13.07%), loss of diabetic control and new onset diabetes (10%), obesity/overweight (7.69%), dyslipedemia (6.15%), electrolyte imbalance (4.61%), moon like face and red plethoric cheeks, TB

consolidation (3.84%) each, cushing syndrome, secondary infection each, acne (3.07%), peptic ulcer, withdrawal syndrome, community acquired pneumonia, osteoporosis, striae, oral candidiasis (2.30%) each, muscle wasting, cognitive dysfunction (1.53%), psychosis, depression, septic arthritis, latent TB (0.76%) each were the common ADRs as the results of corticosteroids in the current study. (*Table-2*) Gastritis, new onset hypertension/ loss of hypertensive control, loss of diabetic control and new onset diabetes, obesity/overweight, dyslipedemia were most common ADRs among both CCS & DFZ. None of the ADR vary significantly from each other P>0.05. (*Table-2*)

Discussion

The results of current study are in agreement to the known profile of these agents by recording substantial ADR reports rate due to CS to the magnitude of 3.70% and events 4.11%. CCS however, accounted more 2.41% in comparison to 1.28% of total ADRs due to DFZ.

These results are in agreement to the study of Markham A and Bryson HM, 1995. (6) They reported overall incidence of adverse events in DFZ recipients (16.5%) to be lower than that recorded in patients treated with prednisone (20.5%) or methylprednisolone (32.7%) and similar to that in betamethasone recipients (15.3%).

There are studies existing in literature which have shown DFZ to be as effective as prednisone or methylprednisolone. (8-11) Even short (4 to 6 weeks) and longer term (13 to 52 weeks) use of DFZ have been shown to be as effective as prednisone or methylprednisolone.(6) The overall incidence of adverse events in DFZ recipients has been recorded lower than that recorded in patients treated with prednisone or methylprednisolone. (6)

DFL may be associated with less development of CS-induced osteoporosis. (6, 8) Cacoub P *et al* (8), recorded less bone loss than prednisone in older patients taking long term DFZ who were at risk of osteoporosis.

However, the results of the current study are unlike these studies. (8, 14-17) ADRs among CS (2.35%) & DFZ (2.22%) did not vary significantly (P>0.05) from each other in regards to producing osteoporosis.

Scudeletti M *et al* and Saez Barcelona JA *et al* have indicated that DFZ is less diabetogenic than prednisone in healthy subjects. (18,19, 5)

However, the results of the current study are contrary to these studies as new onset hypertension/ loss of hypertensive control, loss of diabetic control and new onset diabetes, obesity/overweight, dyslipedemia as ADRs due to CS & DFL did not vary significantly from each other (P>0.05).

The study of Gonzalez-Perez O *et al* (20) advocated that DFZ has, in fact, greater immunosuppressive activity than was thought previously. Therefore, it is possible that DFZ may increases the risk of acquiring opportunistic infection compared to other synthetic GC. The result of the current study endorse their hypothesis as CAP, super infections, TB consolidation and latent TB cases as ADR did not vary significantly (P>0.05) from each other among DFZ and CCS. Gastritis was the most common ADR noticed both with CCS and DFZ in the current study in accordance to the observations of Nayak S, 2008. (10)

Geriatric, urban and female population predominated in contributing ADR in comparable manner both by CCS and DFZ in the current study. Irrational drug prescription and self medication of corticosteroids contributed substantially to total account of ADRs both by CCS and DFZ. The result of the current study suggests such risk factors need to be recognized and kept in mind while prescribing CS to enhance their safety. The clinical utility of these agents and safety profile of CS can be enhanced if used with rationality, judiciously and by adopting recommended principles. Withdrawal phenomenon like CCS was also recorded by DFZ in the current study, thereby suggesting similar need of gradual withdrawing of therapy even with DFZ like CCS. The maximum number ADR events were type-A in nature with both CCS and DFZ, which all could have been preventable largely if these principals/guidelines were followed. As far as time of their onset is concerned maximum of the ADRs were latent in nature thereby providing window of opportunity to ameliorate these ADRs to larger extent.

There are some limitations in the current study. It does not reflect the true prevalence/incidence of ADRs due to CS because of spontaneous nature of reporting used in current analysis. There is no attempt made to study statistical correlation of various risk factors likely to affect the outcome.

Conclusion

ADRs due to CS is a substantial health problem. ADR profile did not vary among DFZ and CCS although DFZ contributed less to the total account of ADRs.

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