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A Cross Sectional Study of Ethnic Differences in Occurrence and Severity of Adverse Drug Reactions (ADRs) Due to NSAIDs in Sikkim

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Abstract: *Non-steroidal anti-inflammatory drugs are the most widely used "over the counter" medication all over the world despite their complications in different major organs. Present studies envisaged for knowing the occurrence and severity of adverse drug reactions from NSAIDs in different ethnic communities of Sikkim. A cross sectional study was undertaken in the medicine outpatients department of a secondary and tertiary care hospital. The patients belonging to Nepalese, Bhutias, Lepchas ethnic communities and others community (settlers from other parts of India) were included to analyzed the data based on the age and gender, ethnicity and ADRs, drugs and ADRs. Severity assessment was done using Hartwing and Siegel scale and causality assessment by Naranjo scale. Total 109 cases of ADRs, predominating in female were detected. Nepalese were the most affected and Gastrointestinal tract (GIT) being the most affected organ in them. Diclofenac showed maximum number of ADRs in all the communities. Maximum number of cases occurred on single day use (40.36%) of drugs. All the cases were belonging to the "possible category" and the maximum being the mild (72.48%) in nature. It is advisable to consider the ethnic/racial differences equally with other factors, to improve the safety and efficacy of a drug.*

Keywords- *Adverse drug reactions, Bhutia, Ethnic, Lepchas, Nepalese.*

I. Introduction

There has been an exuberant increase in the use of drugs worldwide, but magnitude of morbidity and mortality of the population due to ADRs can also not be underestimated. According to USFDA, over 2 million patients suffer from serious ADRs globally, about 100,000 deaths and an incidence of about 350,000 ADRs occurs in private settings annually. In India, ADR accounts to the population ranging between 1.8-25.1%, with 8% resulting in hospitalization [1] and it is enlisted as seventh common cause of death [2].Therefore, detection and monitoring of ADRs is of vital importance for patient safety, as more than 50% of approved drugs are associated with some type of ADRs that are not detected prior to their approval for clinical use [3]**.** It is observed that there is individual variation in drug response which ultimately contributes to beneficial or harmful effect to an individual, such variation in turn depends on numerous factors, such as age, sex, disease state, co-morbid condition, concomitant medication, diet, environmental factors, race and ethnicity. Ethnicity is one factor that may account for the observed differences in both pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, resulting in variability in response to drug therapy [4] .Some of the genetic factors that are believed to affect response to drugs, such as cytochrome P450 (CYP) genotype are distributed differently in different ethnic groups. For example, two CYP2C9 alleles that result in poor metabolism have been found to occur in 11% and 8% of white individuals but only in 3% and 0.8% of black individuals. This has important implications for clinicians because CYP2C9 is responsible for the metabolism of warfarin and individuals with poor metabolism may therefore require lower doses [5].A tertiary care hospital based study from New Delhi reported less adverse effects to atenolol and propranolol compared to those observed in studies in the western populations [6,7]. The authors attributed this observation to possible racial differences. Similarly, ethnic differences in metabolism of paracetamol, a widely used analgesic, have suggested ethnic variability in adverse drug reactions [8]. Therefore, a well designed study to explore differences in occurrence of adverse drug reactions in ethnically and racially different populations can provide useful leads to pharmacogenomic investigation. An effective and sustainable pharmacovigilance system can provide the concrete information on the above findings. However**,** there is a wide

gap in good quality research and availability of data on adverse drug reactions based on ethnic/racial factors in India. Hence, there is a need of more and more pharmacovigilance to be undertaken in future that may focus on ethnic factors to ascertain the risk-benefit ratio of medicines and possible factors involved in the occurrence of ADRs. The data so generated would further aid to tailor the medication based on pharmacogenomic status of an individual patient.

Sikkim, a hilly state in north east India, is located in the foothills of the Himalayas and shares international borders with Nepal, Bhutan and Tibet. It is inhabited by indigenous population of *Lepchas*, *Bhutias* and *Nepalese* and has a population of 607,688 [9].Population of Sikkim is a unique mix of different ethnic origins including a sizeable population of settlers from other parts of India. Therefore, this setting provides an ideal opportunity to study possible differences in adverse drug reactions to analgesics among different ethnic subgroups and predict about genetic differences in drug effects. Moreover, so far not a single study of this type has been conducted in the state of Sikkim. Hence, the study was undertaken with the aim to detect any ethnic difference in occurrence and severity of ADRs due to NSAIDS in outpatients of medicine department in secondary and tertiary care hospitals of Sikkim.

II. Methodology

The cross sectional observational study was conducted to record ADRs due to NSAIDs. The study was conducted from December 2012 to June 2014 among out patients, reporting in medicine department of two tertiary care hospital, CRH, Gangtok; STNM Hospital, Gangtok and two secondary hospitals located at Singtam and Namchi. The study populations belonging to *Nepalese, Bhutias, Lepchas* ethnic communities and others community (settlers from other parts of India) were included. Patients with the history of kidney disease, peptic ulcer disease, cardiovascular disease, skin disease, pregnancy, lactation and patients on antibiotics, corticosteroids, anticoagulants, anti-epileptics were excluded from the study. Provocation test and re-challenge were not performed due to the ethical issues. The data for suspected adverse drug reactions related to NSAIDs was collected from personal interviews with patients enquiring about specific ADRs related to NSAIDs and also by contacting doctor working at the study centre and the missed out data were collected from patient case records available in the hospital medical record department during that period and demographic information were recorded in case record forms and all other relevant information regarding drug therapy, history, examination details, investigations performed were recorded in suspected ADRs forms circulated by CDSCO ministry of health and family welfare, government of India, for reporting of suspected adverse drug reactions by health professionals. When any particular information with respect to drug reaction was required, the treating consultant's opinions were considered. At the end of each working day, data were transferred to secure excel data files and paper forms were kept securely in charge of the study investigators. Completed ADR reporting forms were finally transferred to the Pharmacovigilance Programme of India (PvPI). Data regarding age and sex of the patients, ethnicity and adverse drug reaction, ethnicity and drug involved, drugs and organ system involved, severity of adverse drug reaction, time of occurrence of adverse drug reaction, were analyzed using SPSS 20.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, USA). The Chi-square (X^2), test was applied to detect the association between the above parameters and $p \leq 0.05$ were considered as significant. Hartwing and Siegel scale were used for severity assessment. Causality assessment was carried out as per the Naranjo scale. The study was conducted upon approval by the Institutional Research Protocol Evaluation Committee as well as Institutional Ethics Committee (IEC). There was no written informed consent procedure; however, verbal consent was taken while interviewing the patients. At the same time he or she was informally briefed about the study and confidentiality was ensured. This was an exploratory study and no baseline information on incidence of adverse drug reactions was available in this population. Therefore, statistical modeling and estimation of sample size was not performed. However, it was found that active surveillance from approved ADR Monitoring Centre (Department of Pharmacology), Sikkim Manipal Institute of Medical Sciences, Gangtok, had collected on an average 10 ADRs in a month during July – August, 2012. Therefore, over a period of 16 months we expected to record 150 ADRs. But during this study period we succeeded to collect only 109 ADRs, due to NSAIDs.

III. Results

A total of 109 suspected adverse drug reactions to analgesics (NSAIDs) were recorded during the study. The prevalence of adverse drugs reaction was significantly ($p<0.05$) higher in case of female than the male across all the age range except in the age range of 41-50yrs. Amongst the recorded ADRs,(n=67;61.46%) were females and males were (n=42;38.53%) as shown in **Fig.1.** Percent difference in the occurrence amongst the gender was found maximum in the age range of 31-40yrs (Males-2.75 %, Females-9.17%) and least in the age group of 41-50yrs (Males-6.42%, Females- 6.42%). Total occurrence was lowest (11.92%) in the age range of 31-40yrs and elderly (> 70 years) were the most affected age group ($p<0.05$) with 23.85% as shown in **Fig.1**.

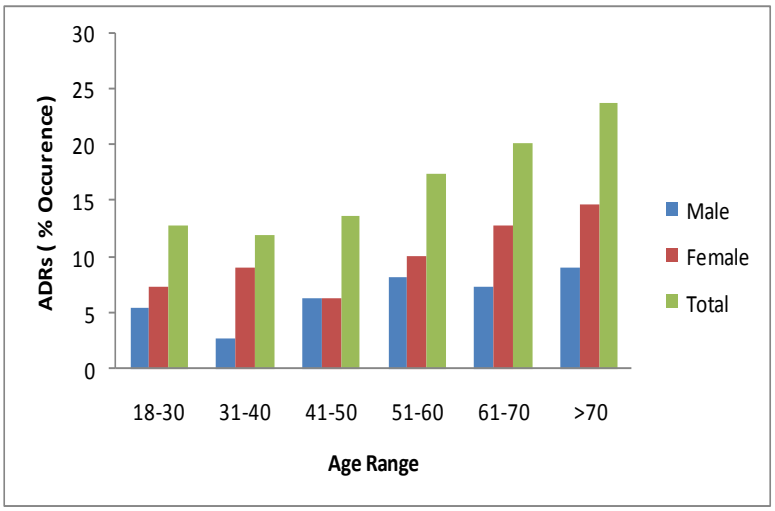

Figure 1: Prevalence of ADRs due to NSAIDs in different gender and age group

The gender and ethnic communities showed differences in occurrence of ADRs on different system (gastro intestine tract (GIT), skin, central nervous system (CNS) and others systems) during the study. Some of the important findings are presented here. The gastrointestinal adverse effects accounts for (51.37%), dermatological (38.53%), CNS (8.25%) and (two other ADRs) i.e., one case of myalgia and one case of Steven Johnson's syndrome were noted in the study period. The ADR on GI systems were found to be more prevalent in females (71.42%) than the males (54.76%) as shown in **Table1.** ADRs on Skin were higher in male whereas, effects on CNS and other systems were higher in female populations as shown in **Table1.**

Table 1: System Wise Suspected ADRs based on Gender and Ethnic Communities

	Suspected ADRs				
	GI	Dermatological	CNS	Others systems	Total
Gender					
Male	16	23	3	0	42
Female	40	19	6	2	67
Total	56	42	9	2	109
Ethnic Communities					
Bhutia	3	7	1	0	11
Lepcha	0	1	1	0	2
Nepali	49	25	4	2	80
Others	4	9	3	0	16
Total	56	42	9	2	109

Amongst the ethnic communities, Nepalese (n=80;73.39%) were most commonly affected and *Lepchas* (n=2;1.83%) were the least (P=0.031, df=9) with NSAIDs as shown in **Table 1.** All the ADRs in different system were found to be more prevalent in *Nepalese* females (n=53; 66.25%) than the male *Nepalese* (n=27;33.75%) (not shown on the table)**.** Among the *Bhutia*s (n=11;10.09%) and others communities(n=16;14.67%) dermatological adverse effects were observed more in numbers in comparison to GIT and CNS effects as shown in **Table 1**. The occurrence of dermatological manifestation in *Bhutia* community were predominant in male (n=5; 45.45 %,) than female (n=2;18.18%) genders which is in contrast to results obtained from *Nepalese* and others communities (settlers from other parts of India) (not shown on the table). While accounting for the drugs, diclofenac alone (46.8%) or in combination (8.25%) was found causing maximum numbers of ADRs followed by aceclofenac and paracetamol combination then ibuprofen, paracetamol and aceclofenac alone in all the communities ($p<0.05$).

Diclofenac in particular has been involved in causing all types of ADRs in all the communities but maximum prevalence was observed in *Nepalese* females (n=25; 49%) followed by *Nepalese* male (n=12; 23.52%). Among the *Bhutia*s community, diclofenac followed by aceclofenac showed maximum number of ADRs and diclofenac

alone has shown (n=6; 11.76%) of dermatological adverse effects. In others community also (n=7; 43.75%) out of (n=16; 14.67%) ADRs were only due to diclofenac followed by aceclofenac and paracetamol combination (n=3; 18.75%). The routes of administration of drug also found to have significant bearing on ADRs. Maximum number of ADRs were found in drugs administered by oral route *i.e.* (n=86; 78.90%) in contradictory to parenteral route (n=23; 21.10%) as shown in **Table 2** where (*p=0.000*).

Table 2: Distribution of Systemic ADRs based on Drugs and Routes of Administration

Drugs	GIT		Skin		CNS		Others		Total
	Oral	Inj.	Oral	Inj.	Oral	Inj.	Oral	Inj.	
Paracetamol	6	0	2	1	0	0	0	1	10(9.2)
Ibuprofen	6	0	2	0	1	0	0	0	9(8.3)
Diclofenac	24	0	8	15	3	1	0	0	51(46.8)
Aceclofenac	3	0	1	3	0	2	0	0	9(8.3)
Aceclofenac+ Paracetamol	8	0	3	0	0	0	1	0	12(11.0)
Ibuprofen+ Paracetamol	3	0	0	0	0	0	0	0	3(2.8)
Diclofenac+ Paracetamol	2	0	2	0	0	0	0	0	4(3.7)
Nimesulide	0	0	1	0	0	0	0	0	1(0.9)
Lornoxicam+ Paracetamol	1	0	0	0	0	0	0	0	1(0.9)
Metaxalone+ Paracetamol	0	0	1	0	0	0	0	0	1(0.9)
Diancerin+ Aceclofenac	1	0	0	0	0	0	0	0	1(0.9)
Diclofenac+ Serratiopeptidase	2	0	3	0	0	0	0	0	5(4.6)
Aceclofenac+ Serratiopeptidase	0	0	0	0	2	0	0	0	2(1.8)
Total	56	0	23	19	6	3	1	1	**109(100)**

Note: *value in parentheses is percentage*

All the gastrointestinal adverse effects were seen in drugs administered by oral route only, no parenterally administered drugs showed GI adverse effect whereas the dermatological and CNS symptoms were observed in both the routes. Parenteral diclofenac is shown to have maximum number of dermatological manifestation. The findings assert that the reaction was expressed even with single day use of drugs. Majority of patients (n=44; 40.36%) reporting with ADRs had single day use of drugs, (n= 31; 28.44%) acquired the reaction in 2nd day,(n=11;10.00%) in 3rd day and rest (n=16;14.6%) in 4 to 7 days.

While assessing the severity of reaction using Hartwing and Siegel scale, the majority of ADRs (n=79;72.48%) were mild followed by moderate (n=29;26.60%). Only one patient showed severe ADR. The causality assessment revealed that all the cases belonged to the "possible category" according to the Naranjo's Algorithm.

IV. Discussions

The present study confirmed that the female were the most affected gender similar to other study reports [10, 11].The sex difference in occurrence of ADRs could involve hormonal changes in women at puberty, during menstrual cycle, at menopause as well as the genomic constitutional difference may affect the various enzymes involved in drug metabolism [12]. In relation to the age, elderly were found to be the main affected age group. Numerous other reports also showed similar findings where they coined the causative factor as polypharmacy due to comorbid illness, resultant drug interactions and altered pharmacokinetics and pharmacodynamic factors leading to accumulation of drugs in the body and thus increased the risk of ADRs[13].It has been suggested that "type A" ADRs are more common in the elderly and the unpredictable "type B" ('bizarre' or idiosyncratic reactions) are less common[14] which is also eminent in this study**.** The ADRs pertaining to oral route of administration were more pronounced than parenteral route which corroborates Bhala et. al. [15] and in the same study gastrointestinal tract and skin were the organ which were mainly affected due to NSAIDs which is similar in this study. The loss of gastro-protective function due to non-selective cyclooxygenase enzyme inhibitors

attributes to the gastrointestinal adverse effects whereas the dermatological adverse effects due to NSAIDs is reported only in 0.5 – 1.9% of the general population[16]. In this study 38.53% of adverse drug effects were dermatological related which is quite significant and must be taken into account. All the GI adverse effects were related to oral route whereas dermatological and CNS related ADRs were the manifestation of both the routes. In relation to ethnic communities and adverse effects, the *Nepalese* were significantly affected due to NSAIDs which could be due to the unique genetic makeup leading to difference in pharmacokinetic and pharmacodynamic drug responses making them more vulnerable to adverse drug effects than in other ethnic communities.

The maximum GI involvement was shown by females where as skin involvement was shown that by male genders. A study done on Non-steroidal anti-inflammatory drug hypersensitivity in preschool children showed strong association of NSAID hypersensitivity with atopy and clinical atopic disease in children has relative male predominance as opposed to female predominance in adults[17].This is differing in this study where male patients are found to be predominantly affected. The pattern of the gender predominance may differ in different geographical regions because of genetic and ethnic factors, disease prevalence, differing pattern of drug prescription and consumption. Among the *Nepalese* women, maximum number showed GI adverse effect followed by dermatological whereas in *Bhutias* and other community, showed maximum of dermatological adverse effect where male gender were predominating. This finding could not be compared with any other similar type of study as no study in relation to the incidence of adverse drug effects in different ethnic communities of Sikkim's population could be found. A study conducted in Nepal on adverse effect of anti-tubercular drugs found significant difference in ethnic group '*Gurung*' where author concluded that they are at greater risk for ADRs to anti-TB drugs [18]. In this study also 20 percent of the total patient population were the '*Gurung*' under *Nepalese* community; therefore, we can conclude that these specific groups of population may be more susceptible to the ADRs of NSAIDs too. Diclofenac followed by aceclofenac alone or in combination were found to be the most common drug involved in all type of ADRs, similar findings were observed in other studies [15, 19, and 20] where diclofenac were found to show maximum number of ADRs. In this study parenteral diclofenac was found to be most commonly involved in dermatological ADRs. In a study done in a tertiary care hospital in Dehradun, Uttarakhand, it was found that common ADRs were FDE and most frequent drug associated with such were NSAIDs[21] which is similar to the study report from Omani population and in the same study, injection diclofenac was associated with maximum cases of Toxic Epidermal Necrolysis (TEN) where the author has reported that there may be pharmacogenetic predisposition among Omani population to react against NSAIDs and in particular with injection diclofenac[22] .Similar to the above findings there may be association of pharmacogenomic and NSAIDs among the population of Sikkim, specially with injection Diclofenac, as such study has not been conducted so far in this population therefore findings cannot be compared with similar studies. In a study, Diclofenac were found to be the leading cause for cutaneous ADRs, involving erythematous drug reactions, FDE, urticaria and SJS, probably reflecting widespread use of this drug [23]. The most common CNS ADRs observed in this study was drowsiness which is similar to the result observed by Bhalla et. al. where they found drowsiness followed by other reactions as the commonly encountered CNS ADRs due to NSAIDs[15].Majority of ADRs observed were mild followed by moderate in nature in all the community and a single case of Steven Johnson's syndrome was reported due to injection Paracetamol in *Nepalese* male. A study conducted by Mujahid et. al. also showed similar report with maximum cases to be mild followed by moderate and severe in nature [19]. In two other study by Bhalla et. al. and Sivasankari et. al. showed similar results except that their studies did not have any case of severe ADRs due to NSAIDs[15,20]**.** In this study the causality assessment according to the Naranjo's Algorithm revealed that all the cases belonged to the "possible" category whereas Sivasankari et. al. reported (63.64%) possible and (36.36%)probable reactions[20].While another study by Gor et. al. revealed, six cases of "possible", eleven cases of "probable" and one case of "definite" category[24]. In this study all ADRs have occurred in first 10 days use of the NSAIDs which is similar to the study reports from Gor et. al., where significant number of ADRs were seen in initial 10days of medication which emphasizes the need of observing the patients closely in the initial period of treatment[24].

There are scanty literature showing the studies on ethnicity/racial and adverse drug reactions particularly on NSAIDs, but there are some reported evidences to assert the racial/ethnic differences in occurrence of ADRs due to NSAIDs as well as other drugs. African American were found to have at lesser risk than the white when associated with over-the-counter (OTC) NSAIDs and Rx NSAIDs[25], threefold higher risk of angioedema due to ACEI in blacks is reported as compare to non-black patients[5]. Despite of enough evidence for racial /ethnicity and occurrences of ADRs, the degree of susceptibility to ADRs is still obscure, as is it really due to to ethnicity or a result of genetic or environmental/cultural factors [26].Pharmacogenomic is the most recent science which will provide a new perspective in dealing with the ADRs and their relation with ethnicity and the genetic mechanism involved in the occurrence of ADRs. This innovative science would fill up the gap between genetic relationship and occurrence of adverse drug reactions in near future.

V. Conclusion

This study concludes that *Nepalese* are the most affected ethnic communities due to NSAIDs and diclofenac in particular is associated with maximum adverse drug reactions related to gastrointestinal system, therefore, to maximize patient's safety as well as to improve patient's compliance, the treating clinician should use this drug with caution particularly in this community. The understanding of the different effects of various factors that lead to variation in drug response from individual to individual will enable the healthcare professionals to choose the most appropriate medication for a particular patient which undoubtedly brings rationality in drug therapy. Since this type of study is a pioneer of its type in Sikkim Himalayan state, the data obtained from this study would provide a good platform to carry out such studies in large population in future.

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