INTRODUCTION:

An adverse drug reaction as defined by WHO is a “response to a medicinal product which is noxious, unintended and occurs at dosage normally used in men for the prophylaxis, diagnosis or treatment of disease or for the restoration, correction or modification of physiological function [1]. According to center for health policy research, more than 50% of the approved drugs in the United States were associated with some type of adverse effects not detected prior to the approval [2]. At least one ADR has been reported to occur in 10 to 20% of hospitalized patient [3]. Recent epidemiological studies estimated that ADRs are fourth to sixth leading cause of death, [4] though some researcher implicated as they are 7th common cause of death [5].

Although many of the ADRs are relatively mild and disappear when drug is stopped or dose is reduced, others are more serious and last longer [6, 7]. The commonest organ system involved in occurrence of suspected ADRs was skin and mucous membrane as reported by several studies [8-12]. A cutaneous adverse reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruption, regardless of the etiology. Drug reactions can be classified into immunologic and non-immunologic etiologies. The majority (75-80%) of
adverse drug reactions are predictable, non-
immunologic and the remaining 20-25% are
unpredictable that may or may not be immune-mediated
[13]. Immune-mediated reactions account for 5-10% of
all drug reactions and constitute drug allergies falling
into this category [14, 15].

Cutaneous adverse drug reactions (ADR) can
be caused by a wide variety of agents. They are
responsible for approximately 3% of all disabling
injuries during hospitalization and complications of
drug therapy are the most common type of adverse
event in hospitalized patients. Many of the commonly
used drugs have reaction rates above one percent [16].
There is a wide spectrum of cutaneous ADR ranging
from a transient maculopapular rash to fatal toxic
epidermal necrolysis (TEN) [17]. The pattern of
cutaneous ADR and the drugs responsible for them is
changing every year. The reported percentage of
cutaneous ADR that are potentially serious are varies
greatly but is probably about 2 percent. Hence, we had
tried to assess the clinical pattern, spectrum, frequency
and severity of suspected cutaneous ADRs and their co-
relation with specific drug group in ICU and ward
admitted patients in Department of Medicine of Sanjay
Gandhi Memorial Hospital, Rewa (M.P.).

MATERIAL & METHODS:
This study was carried out in the Department
of Pharmacology, after getting approval from
institutional ethical committee. The data of suspected
ADRs were recorded in a specially designed proforma
(CDSCO ADR reporting form) from October 2014 to
September 2015; in ICU and ward admitted patients at
the department of Medicine of SGM Hospital, Rewa
(M.P.). Total 130 patients were enrolled in study that
was presented with suspected ADRs. For each patient
with suspected ADR, a detailed history including drug
history, personal history, family history, present and
past medical history and history of previous drug
allergy were documented after taking written informed
consent. The any untoward event was labeled as adverse
drug reaction after discussion with the treating
physician. To establish the etiologic agent for a
particular type of reaction, attention was paid to the
drug history, temporal correlation with the drug,
duration of the rash, approximate incubation period,
morphology of the eruption, associated mucosal or
systemic involvement, improvement of lesions on
withdrawal of drug and recurrence of lesion on
rechallenge. In case of more than one drug was thought
to be responsible, the most likely offending agent was
noted and the impression was confirmed by subsidence
of the rash on withdrawing the drug. Clinical
evaluations were done to assess the clinical pattern,
frequency and severity of suspected cutaneous ADRs
and involvement of therapeutic drug classes. The data
were analyzed by using Microsoft Office Excel sheet
2007 and expressed in form of number and percentage.

RESULTS:
In this study total 130 patients were enrolled,
of these maximum (25%) patients were belonged to the
18-25 years of age group, in which 55% were males and
45% were females. Among males maximum 26% were
belonged to 18-25 years and 41-60 years of age group.
In females maximum 35% were belonged to 26-40
years of age. The mean (± SD) age of these patients was
34.84 ± 20.99 years. (Figure-1)

Among the affected organ system, skin and
mucous membrane were most commonly (52.29%)
involved in development of ADRs followed by central
nervous system (9.19%), gastrointestinal system
(8.62%), respiratory system (4.59%), hepatobiliary
system (1.72%) and others (17.24%) which includes –
tinnitus, visual disturbances, fever, rigor, weight gain
and dryness of mouth. (Figure-2) Among the suspected
cutaneous ADRs reported in this study; maximum
51.64% was skin rashes, followed by 29.67% pruritus,
5.49% oral ulcers, 3.29% Stevens-Johnson syndrome
(SJS), 2.19% bullous eruption, 2.19% swelling lips,
2.19% toxic epidermal necrolysis (TEN), 1.09% oral
candidiasis, 1.09% red man syndrome and 1.09% hair
changes. (Table-1) Among the total suspected ADRs;
most of these were associated with use of antimicrobials
(68%) followed by NSAIDs (10.0%), haematinics
(10.0%), antihypertensive (3.12%), antianimal,
anti-epileptics, oral hypoglycemics, corticosteroids (1.8%)
and ionotrops were associated with 1.25% of ADRs.
(Table-2) Among the cutaneous ADRs only; maximum
(82.42%) were related with use of antimicrobials
followed by 14.28% with NSAIDS, 2.19% steroids and
1.09% were seen with anticonvulsant drugs.(Table-
2)/(Figure-3) Amongst AMAs maximum 20.97% of
cutaneous ADRs were associated with the use of
fluoroquinolones followed by 18.68% cephalosporin,
10.98% penicillin, 5.49% sulphonamide, 4.39%
antimalarial, 4.39% antiamoebic, minimum with 1.09%
antifungal and 15.38% with other drugs which includes
doxycycline, tetracycline, meropenem, vancomycin,
nevirapine and albendazole.(Table-3)

OBSERVATIONS:

**Fig 1: Age wise distribution of cases.**

**Fig 2: Percentage distribution of suspected ADRs according to the affected organ system.**

**Table 1: Frequency distribution of suspected cutaneous ADRs during study period**

<table>
<thead>
<tr>
<th>Suspected ADRs</th>
<th>Frequency of suspected cutaneous ADRs</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Number</td>
<td>Percentage</td>
<td>Female</td>
</tr>
<tr>
<td>Skin rashes</td>
<td></td>
<td>31</td>
<td>49.20%</td>
<td>16</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>20</td>
<td>31.74%</td>
<td>07</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td></td>
<td>04</td>
<td>6.34%</td>
<td>01</td>
</tr>
<tr>
<td>SJS*</td>
<td></td>
<td>02</td>
<td>3.17%</td>
<td>01</td>
</tr>
<tr>
<td>Bullous eruption</td>
<td></td>
<td>02</td>
<td>3.17%</td>
<td>00</td>
</tr>
<tr>
<td>Swelling lips</td>
<td></td>
<td>01</td>
<td>1.58%</td>
<td>01</td>
</tr>
<tr>
<td>TEN**</td>
<td></td>
<td>01</td>
<td>1.58%</td>
<td>01</td>
</tr>
<tr>
<td>Red man syndrome</td>
<td></td>
<td>01</td>
<td>1.58%</td>
<td>00</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td></td>
<td>01</td>
<td>1.58%</td>
<td>00</td>
</tr>
<tr>
<td>Hair changes</td>
<td></td>
<td>00</td>
<td>00%</td>
<td>01</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>63</td>
<td>69.23%</td>
<td>28</td>
</tr>
</tbody>
</table>

*SJS = Stevens-Johnson syndrome  ** TEN= toxic epidermal necrolysis

Table 2: Comparison of distribution of total and cutaneous suspected ADRs according to drug classes.

<table>
<thead>
<tr>
<th>Class of drugs causing suspected ADRs</th>
<th>Total and Cutaneous ADRs reported during study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All total ADRs</td>
</tr>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Anti-microbials</td>
<td>109</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>16</td>
</tr>
<tr>
<td>Hematinics</td>
<td>16</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>5</td>
</tr>
<tr>
<td>Antianginal</td>
<td>3</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>3</td>
</tr>
<tr>
<td>Hypoglycemic drugs</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3</td>
</tr>
<tr>
<td>Inotrops (Digitalis)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
</tr>
</tbody>
</table>

Fig 3: Frequency of total suspected cutaneous ADRs (in numbers) produced by different class of drugs.

Table 3: Distribution of suspected Cutaneous ADRs according to drug classes.

<table>
<thead>
<tr>
<th>SN</th>
<th>Drug Groups / Classes</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antimicrobials (75) 82.42%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>20</td>
<td>20.97%</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
<td>17</td>
<td>18.68%</td>
</tr>
<tr>
<td></td>
<td>Penicillins</td>
<td>10</td>
<td>10.98%</td>
</tr>
<tr>
<td></td>
<td>Sulphonamide</td>
<td>05</td>
<td>5.49%</td>
</tr>
<tr>
<td></td>
<td>Antimalarial drugs</td>
<td>04</td>
<td>4.39%</td>
</tr>
<tr>
<td></td>
<td>Antifungal drugs</td>
<td>01</td>
<td>1.09%</td>
</tr>
<tr>
<td></td>
<td>Antiamoebic drugs</td>
<td>04</td>
<td>4.39%</td>
</tr>
<tr>
<td></td>
<td>**Others</td>
<td>14</td>
<td>15.38%</td>
</tr>
<tr>
<td></td>
<td>NSAIDS (13) 14.28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nimesulide/Paracetamol/Buprofen/Aceclofenac/ Combination.</td>
<td>13</td>
<td>14.28%</td>
</tr>
<tr>
<td></td>
<td>Steroids (02) 2.19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beclomethasone</td>
<td>02</td>
<td>2.19%</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant drugs (01) 1.09%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>01</td>
<td>1.09%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>91</td>
<td>100</td>
</tr>
</tbody>
</table>

**Others includes doxycycline, tetracycline, meropenem, vancomycin, nevirapine and albendazole
DISCUSSION:

In every day of clinical practice, almost all physicians come across many instances of suspected adverse cutaneous drug reactions (ACDR) in different forms. Although such cutaneous reactions are common, but their comprehensive information regarding their incidence, severity and ultimate health effects are often not available. It is also a fact that in the present world, almost every day a new drug enters in market; therefore, a chance of a new drug reaction manifesting somewhere in some form in any corner of world is unknown or unreported.

In the present study, the mean age of subjects was 34.84±20.99 years for males and 29.98±19.58 years for females; the mean age difference between the gender was not statistically significant (p>0.05), the eldest being 85 years and the youngest subject being 1 year of age. According to affected organ system of suspected ADRs, the skin and mucous membrane is the commonest organ that involved in 52.29% of total suspected ADR, which is similar with previous studies in which dermatological manifestations were most common ADR [8-12]. This was followed by involvement of Central nervous system (9.19%), gastrointestinal system (8.62%), respiratory system (6.32%), cardiovascular system (4.59%) and hepatobiliary system (1.72%) and remaining 17.24% ADR as others.

Of total cutaneous ADRs; 69.23% were occur in males and 30.76% occurs in females, which is similar to Gupta et al.; [18] and Chavola et al.; [19] studies. However the incidence of cutaneous adverse reactions such as skin rashes, Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are more in females in our study this was similar to Sarajit Nayak et al.; [13] study in which cutaneous drug reactions have higher incidence in women than in men. In present study, cutaneous ADRs were most commonly (52.29%) reported ADR; this incidence is more variable to Gruchalla et al.; [20] study according to which cutaneous reactions comprise approximately 2-3% of all adverse drug reactions.

Amongst the cutaneous ADRs, skin rashes was most commonly (51.64%) reported cutaneous ADR which is similar to Chatterjee et al.; [21] study. Various other studies show that the exanthematous eruptions are the most common type of drug eruption [22-24]. Exanthematous drug eruptions, also known as maculopapular drug eruptions. It was 51.64% in our study which was dissimilar to Thappa et al.; [25] study in which fixed drug eruptions (31.1%) were observed most commonly and maculopapular rash (12.2%) are second most common. However another study [26] was reported that the incidence of skin eruptions is approximately 45% of all the cutaneous adverse drug reactions. Most of these rashes are mild, self-limited and usually resolve after the causative drug has been discontinued. Severe and potentially life-threatening reactions (e.g. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) occur 3.29% and 2.19% respectively) were also reported in this study.

In present study among the total suspected ADRs; most of these were associated with use of antimicrobials (68.12%) which is similar to various previous studies Wester et al.; [27] Gor et al.; [28], Vora et al.; [29] Leape et al.; [30] probably this may due to that, the AMAs are most commonly prescribed drug in our hospital followed by NSAIDs and haematinsics. Among cutaneous ADRs only; maximum 82.42% cases were related with the use of antimicrobials followed by 14.28% with NSAIDS, this was similar to V K Sharma et al.; [31] study in which the drugs most commonly responsible for cutaneous ADRs were antimicrobials (42.6%), anticonvulsants (22.2%) and NSAIDs (18%). Amongst AMAs, maximum cutaneous ADRs were associated with fluoroquinolones (20.97%) followed by cephalosporin (18.68%), penicillin (10.98%) and sulphonamide (5.49%), this was differ to the study conducted by Fiszenson-Albala et al.; [32] in which penicillin is most common AMAs associated with cutaneous ADRs.

CONCLUSION:

In every day of clinical practice, almost all physicians come across many instances of suspected adverse cutaneous drug reactions (ACDR) in different forms. Cutaneous adverse drug reactions (ADRs) can be caused by a wide variety of agents. They are responsible for approximately 3% of all disabling injuries during hospitalization. In this study, males have higher incidence of suspected cutaneous ADRs, which have a ranged from common mild reactions like skin rashes, pruritus to severe reactions like SJS and TEN. The most common cutaneous ADRs were exanthematous skin rashes and pruritus. The commonest drug groups associated with suspected ADRs were antimicrobials and NSAIDs. Amongst AMAs fluoroquinolones is a major cause of cutaneous ADRs.

REFERENCE: