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**Original Research Article**

# Drug eruptions and hepatic involvement: a study

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## ABSTRACT

**Background:** Assessment by liver biopsy remains the gold standard in defining drug induced liver disease. Liver biopsy is an invasive procedure. Hence, a technique that is simpler is required to detect drug induced liver dysfunction. The profile of liver function tests (LFT) abnormalities, provides an initial guide to the clinical syndrome of drug induced hepatotoxicity. This study attempts to draw a possible correlation as well as to derive insight into the involvement of liver in drug eruptions through simple liver function tests.
**Methods:** 112 cases of patients with drug rash as out-patients and in-patients since 2015 to 2018 in Osmania General Hospital, and Dr. V. R. K Women's Medical College, Teaching Hospital and Research Centre were enclosed during this study. Total number of cutaneous drug rash cases enrolled: 83 Total number of drug rash cases with Liver Function Test abnormalities: 17.
**Results:** Out of 83 patients of drag rash 20% (17) had liver function test abnormalities while 80% (66) had normal hepatic function. Out of 17 drug rash cases with liver function test abnormalities 35% (6) were between 4-14 years of age group. Out of 17 drug rash cases with liver function test abnormalities 70.6% (12) were males and 29.4% (5) were females.
**Conclusions:** To conclude, a sound knowledge of morphological patterns of drug rashes with hepatic involvement, drugs implicated in causing drug rashes and hepatic dysfunction and an easy detection of impending danger by the simple biochemical tests (liver function tests) can evert a major crisis and thus help the clinicians to better manage their cases.

**Keywords:** Drug eruptions, Cutaneous reaction, Frequency of hepatic involvement

## INTRODUCTION

A drug is also outlined as a chemical substance or a mixture of drugs, administered for the investigation, interference or treatment of diseases or symptoms, real or imaginary. The United Nations agency has outlined a drug as a substance or product that's used or meant to be accustomed modify or explore physiological systems or pathological states of the recipient. An adverse drug reaction is also outlined as associate degree undesirable clinical manifestation ensuing from administration of a specific drug or as associate degree appreciably harmful or unpleasant reaction ensuing from associate degree intervention associated with the employment of a healthful product, that predicts hazard from future administration and warrants interference or specific

treatment or alteration of the indefinite quantity plan or withdrawal of the merchandise.[1]

Drug eruptions can mimic a wide range of dermatoses. The morphologies are myriad. Presentation range from simple maculopapular rash to life threatening complications like toxic epidermal necrolysis. Prompt identification and withdrawal of the violative agent might facilitate to limit the effects related to the drug. The choice to discontinue a probably important drug typically presents a perplexity. A drug elicited tissue reaction ought to be thought of in any patient is taking medications and United Nations agency suddenly develops a bilaterally symmetric eruption. Medication reactions embody antimicrobial agents, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs), cytokines, chemotherapeutical agents and hallucinogenic agents.

In India Homeopathy, Ayurvedic, Unani and Herbal medicines and a vast array or organic and inorganic substances that are ingested for various diseases as age old remedy or prescribed by quacks also contribute too many drug eruptions.

Drug eruptions may be predictable or unpredictable, immunologically or non-immunologically mediated. A hypersensitivity reaction as an etiology of a drug eruption may often affect the liver. Each drug has its own peculiar organs of affliction. Most of the drugs are metabolized in the liver. This warrants the liver as a prime organ of drug assault.

### *Aims and objectives*

- To detect the incidence of liver function test abnormalities in patients with drug eruptions.
- To study the frequency of hepatic involvement in various types of drug eruptions.
- To correlate the severity of drug eruptions to functional derangement of liver based on liver function tests.
- To compare the percentage of hepatic involvement in severe group and non-severe group of drug rashes.

## METHODS

### *Selection of patients*

During our tenure 112 cases of patients with drug rash attended the department of Dermatology, Venereology and Leprosy attended as out-patients and in-patients to the department of Dermatology, Venereology and Leprosy and those who were referred from other departments of Osmania General Hospital, and Dr. V. R. K Women's Medical College, Teaching Hospital & Research Centre since 2015 to 2018 were included in this study. 9 Patients who were HIV positive, 5 patients with severe systemic disease and 14 patients who were alcoholics, and one patient who was Hbs Ag positive were excluded in this study. Total patients included were 83.

### *Method of study*

All patients suspected of having cutaneous drug reactions seen in out-patient and admitted in the ward during this period were evaluated. In every case a detailed history, (age, sex, duration of eruptions, drugs responsible, history of addictions especially alcoholism) thorough physical and systemic examination including icterus and hepatomegaly was carried out.[2] To establish the etiological 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. Both haematological and biochemical investigations (Hb, total RBC count, total WBC count, differential leukocyte count, complete urine examination, serum electrolytes, blood sugar, renal function tests) were carried out. Liver function tests viz. serum bilirubin total, serum alanine aminotransferase (SGPT), serum alkaline phosphatase and Vandenberg reaction were performed before and after symptomatic treatment and resolution of drug rash. Viral causes of hepatitis were excluded patients who had liver function test abnormalities. Only those patients who were non-alcoholics, those without serious systemic illness and whose LFT tests became normal after symptomatic treatment of drug rash were included in the study.

If more than one drug was thought to be responsible, the most likely offending agent was noted and the mean impression was confirmed by subsidence of the rash on withdrawing the drug one after the other. The rashes were attributed to a drug following the guidelines of Boston collaborative drug reactions surveillance program.[3]

The severity of the reaction was graded according to the University of Virginia Health System Adverse Drug Reaction Reporting Program criteria as follows.[4]

- *Mild:* A reaction that does not require treatment or prolongation of hospitalization.
- *Moderate:* A reaction that requires treatment and /or prolongs hospitalization by at least one day.
- *Severe:* A reaction that is potentially life-threatening or contributes to the death of the patient, is permanently disabling, requires intensive medical care (including extended hospitalization, or results in a congenital anomaly, cancer, or un-intentional overdose.

Mild and moderate reactions were included under non-severe group. All the information regarding history examination, laboratory findings and treatment was carefully recorded in a specially designed proforma.

## RESULTS

Total 53 male and 30 female patients were enrolled in this study. 12 (70.6%) out of 17 patients of drug rash with liver function test (LFT) abnormalities were males and 5 (29.4%) out of 17 were females while 41 (62%) out of 66 patients of drug rash with normal hepatic function were males and 25 (38%) out of 66 were females.

**Table 1: Sex distribution.**

| Sex | Drug rash cases with LFT abnormalities | Drug rash cases without LFT abnormalities |
|---|---|---|
| **M** | 12 | 41 |
| **F** | 5 | 25 |
| **M : F ratio** | 2 : 1 | 2.1 : 1.2 |

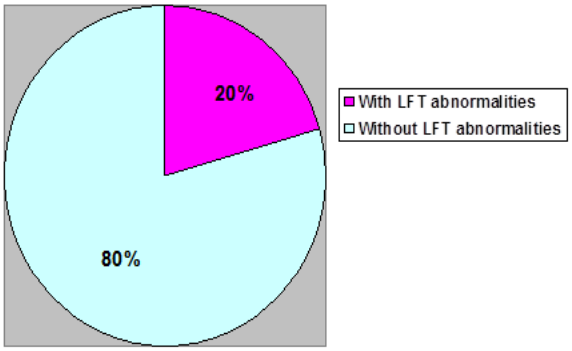


**Figure 1: Frequency of liver function test abnormalities in cases of drug rash.**

Total 17 out of 83 cases of cutaneous adverse reactions had LFT abnormalities i.e 20% of drug eruption cases had LFT abnormalities, whereas 66 out of 83 drug rash cases had normal hepatic function.

**Table 2: Age distribution of drug rash cases with LFT abnormalities.**

| Age in years | With LFT abnormalities | Without LFT abnormalities |
|---|---|---|
| **4–14** | 6 | 9 |
| **15–25** | 5 | 26 |
| **26–35** | 1 | 13 |
| **36–45** | 5 | 10 |
| **46–55** | - | 4 |
| **56–65** | - | 2 |
| **66–75** | - | 2 |

In the present series, the majority of patients of drug rash with LFT abnormalities (35%) i.e. 6 out of 17 were between 4-14 years of age while the majority of drug rash patients with normal hepatic function (39%) i.e. 26 out of 66 were between 15 - 25 years of age.

**Table 3: Clinical patterns with LFT abnormalities.**

| Sl. No. | | Frequency of cases with LFT abnormalities | Frequency of cases without LFT abnormalities |
|---|---|---|---|
| **1** | Acneiform eruptions | 0 | 1 |
| **2** | Angioedema | 0 | 2 |
| **3** | DRESS | 12 | 1 |
| **4** | EMF | 0 | 7 |
| **5** | Erythroderma | 3 | 3 |
| **6** | Exanthematous rash | 1 | 16 |
| **7** | FDE | 0 | 9 |
| **8** | Lichenoid eruption | 0 | 2 |
| **9** | Phototoxic rash | 0 | 1 |
| **10** | Purpura | 0 | 1 |
| **11** | SJS | 1 | 4 |
| **12** | TEN | 0 | 1 |
| **13** | Urticaria | 0 | 16 |
| **14** | Vasculitis | 0 | 2 |

Majority of patients of cutaneous drug reactions with liver function test abnormalities (70.6%) i.e. 12 out of 17 were of DRESS syndrome (drug rash with eosinophilia and systemic symptoms) while majority of drug rash patients with normal hepatic function (24%) i.e. 16 out of 66 were of exanthematous rash and an equal no. of them (24%) i.e. 16 out of 66 were of urticaria.

**Table 4: Commonly incriminated drugs in cutaneous adverse reactions with LFT abnormalities.**

| | Frequency of cases with LFT abnormalities | Frequency of cases without LFT abnormalities |
|---|---|---|
| **Ampicillin** | 0 | 1 |
| **Antipsychotic** | 1 | 0 |
| **Isoniazid** | 2 | 5 |
| **Carbamazepine** | 0 | 1 |
| **Ciprofloxacin** | 0 | 1 |
| **Indeginous** | 4 | 9 |
| **NSAIDS** | 0 | 21 |
| **Ofloxacin** | 0 | 2 |
| **Others** | 0 | 10 |
| **Phenytoin** | 9 | 5 |
| **Septran** | 0 | 5 |
| **Sodium valproate** | 1 | 0 |
| **Unknown allopathic** | 0 | 7 |

Majority of drug rash cases with LFT abnormalities (53%) i.e 9 out of 17 were due to Phenytoin; the next common group implicated were Indigenous medicines affecting (23.5%) i.e 4 out of 17 whereas Majority of drug rash cases with normal hepatic function (32%) i.e 21 out of 66 were due to NSAIDS.

- Cases with past history of adverse drug reaction: 14
- Total number of drug rash cases with normal Liver Function Tests: 66
- Total number of drug rash cases with LFT abnormalities: 17
- Total number of drug rash cases with icterus: 6
- Total number of drug rash cases with hepatomegaly: 10

For the purpose of analysis the patients were divided into two groups based on severity i.e. severe and non-severe. Both mild and moderate cutaneous adverse reaction cases were included in non- severe group.

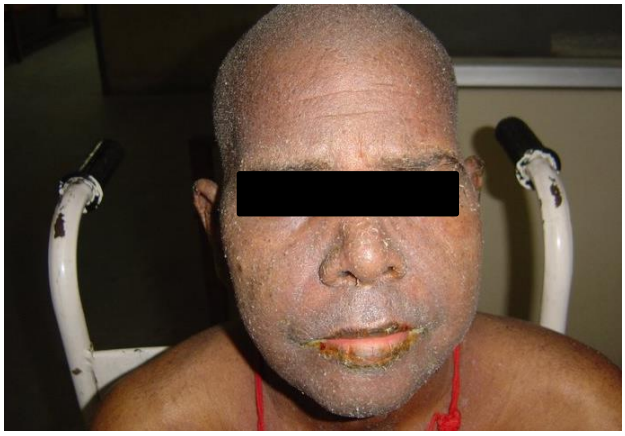

**Figure 2: Case of dress syndrome.**

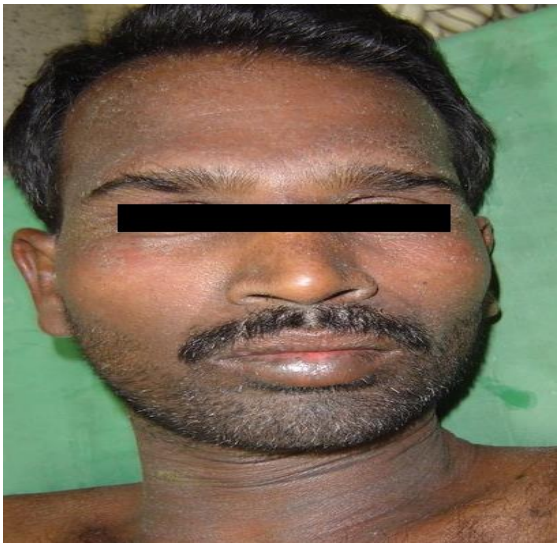

**Figure 3: Drug induced hypersensitivity syndrome patients due to T.Eptoin.**

**Table 5: Correlation of the severity of drug eruptions with various clinical parameters in relation to hepatic involvement.**

| Parameters studied | Non-severe cutaneous adverse drug reactions | Severe cutaneous adverse drug reactions |
|---|---|---|
| **Mean age (in years)** | 27.9 | 25.6 |
| **Sex (M:F ratio)** | 1.63:1 | 2.1:1 |
| **LFT abnormalities (%)** | 1.75 | 64 |
| **Icterus (%)** | 0 | 31.58 |
| **Hepatomegaly (%)** | 0 | 40 |

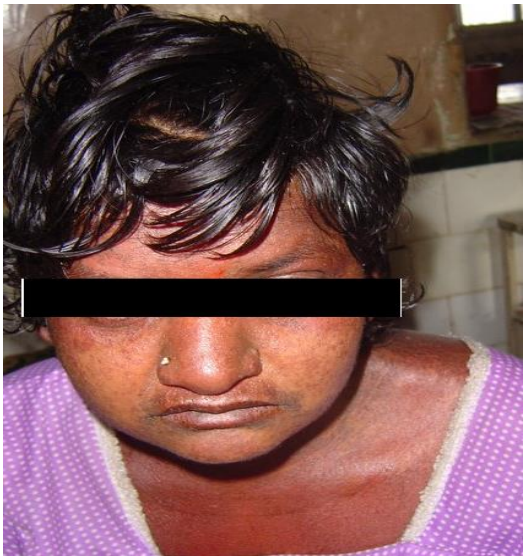

**Figure 4: Case of drug induced erythroderma with icterus.**

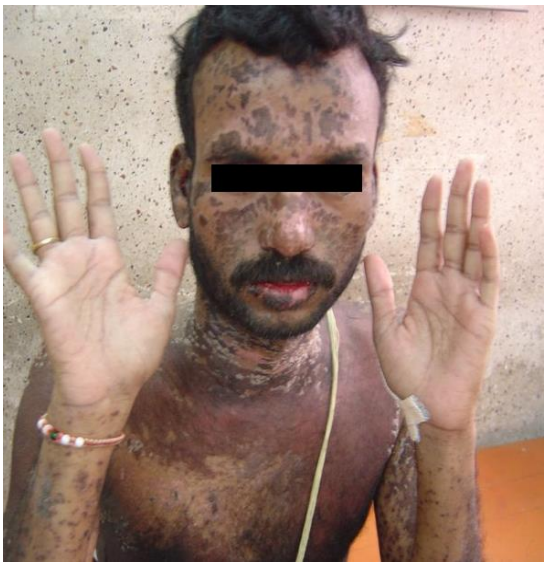

**Figure 5: Case of Stevens- Johnson Syndrome/erythema multiforme due to sulfonamides.**

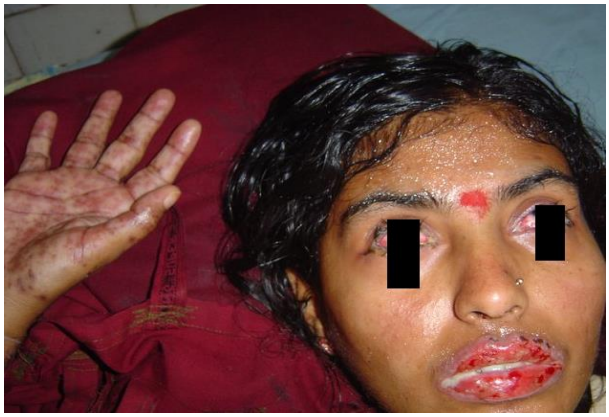

**Figure 6: Involvement of plams, conjunctiva and lips is seen in these cases of SJS syndrome / EMF.**

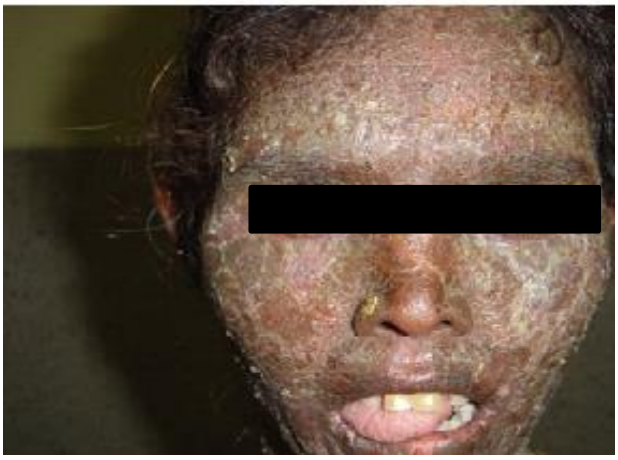

**Figure 7: A case of exfoliative dermatitis due to indigenous medicine.**

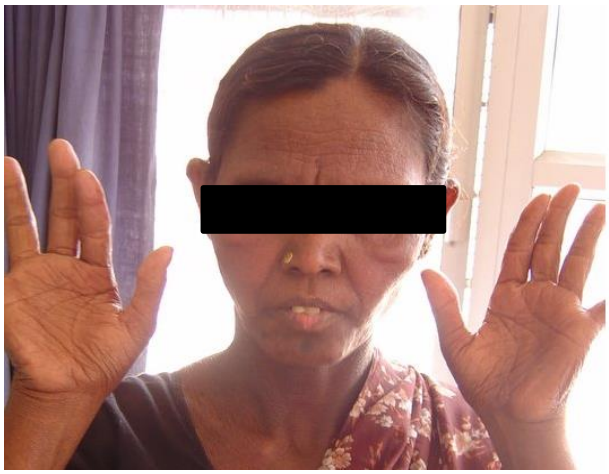

**Figure 8: A case of exfoliative dermatitis due to indigenous medicine after treatment.**

## DISCUSSION

In this study conducted at department of dermatology, Osmania General Hospital 83 cases were enrolled. 17 cases i.e. 20% had liver function test abnormalities while 66 cases of drug rash i.e. 80% had normal hepatic function. In the present series, a majority of patients of drug rash with LFT abnormalities (35%) i.e. 6 out of 17 were between 4-14 years of age, while the majority of drug rashes patients with normal hepatic function (39%) i.e. 26 out of 66 were between 15-25 years of age. Adverse drug reactions amongst paediatric patients are influenced by several factors like prolonged hospital stay, various classes of drugs and polypharmacy.[5]

Majority (70.6%) of patients of drug rash with LFT abnormalities were males i.e. 12 out of 17 and only 5 out of 17 were females i.e. 29.4%. In this study adverse cutaneous reactions with hepatic involvement varied in their patterns of morphology; the most common being DRESS (drug rash eosinophilia systemic symptoms) syndrome. 70.6% i.e. 12 out of 17 while those cases of drug rash with normal hepatic function mostly presented with exanthematous rash and urticaria (24%) i.e. 16 out of 66 each. In DRESS syndrome cases 12 out of 13 i.e. 92% had Liver Function Test abnormalities and 1 out of 13 i.e. 8% had normal hepatic function. Hepatic involvement in DRESS syndrome may range from a transient rise in Transaminases to hepatic necrosis with fulminant failure. Incidence of hepatic involvement in DRESS syndrome was 51% according to the study by Roujeau et al.[6] In erythroderma patients 3 out of 6 had LFT abnormalities i.e. 50%. In Stevens-johnson syndrome out of 5 cases only 1 had LFT abnormalities (elevated Aspartate Transaminase 520 u/dl) i.e. 20%. 50% of patients have a slight increase in transaminases and 10% overt hepatitis in Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) patients as stated by Breathnach while out of 24 Stevens-Johnson Syndrome patients 1 had overt hepatitis i.e 4.2% in a study by Sharma et al.[7,8]

In this study most commonly implicated drug causing both cutaneous adverse reaction and LFT abnormalities is Phenytoin– 53% i.e. 9 out of 17 cases; the next most common group implicated was indigenous medicines - 24% i.e. 4 out of 17 cases, while majority of drug rashes with normal hepatic function (32%) i.e. 21 out of 66 were due to NSAIDs (non-steroidal anti-inflammatory drugs). Phenytoin was the cause of drug rash in 14 cases and in 9 cases caused hepatic dysfunction also.

Correlation of the severity of drug eruptions to various clinical parameters was done in this study. Mean age in non-severe group of cutaneous adverse reactions was 27.9 years and in severe group was 25.6 years. While David et al observed the mean age to be 36.62 years in non-severe group 38.07 years in severe group.[9] In this study male to female ratio in non-severe group of drug rash was 1.63:1 and in severe group was 2.1:1 in contrast to David et al who observed 0.9:1 in non-severe group and 0.8:1 in severe group.[9]

In this study liver function test abnormalities were seen in 1.75% of patients of non-severe cutaneous adverse

reactions and 64% of patients in severe group. David et al observed 11.11% liver function test abnormalities in non-severe group of drug rash cases and 88.9% in severe group of drug rash cases.[9] Abnormal liver function test has been described as an independent indicator of the severity of a drug induced cutaneous eruption. Icterus was present in 31.58% of severe group and was not observed in non-severe group of drug rash cases. Hepatomegaly was present in 40% of cases in severe group of drug rashes and was not observed in non-severe group of drug rash cases.

A retrospective study was performed by Mehrholz et al on a group of 261 patients with drug reactions hospitalized in the department of dermatology from 2004 until 2017.[10] There were ten cases of DRESS among 261 hypersensitivity drug reactions observed in the Department. The drug which most frequently caused DRESS in the studied group was carbamazepine – six patients (60%). Lamotrigine was the cause of DRESS in two cases, oxycarbamazepine in one patient and dexketoprofen in one patient. The skin lesions were present in 100% patients. Mainly it was erythematous confluent rash accompanied by face edema. Eosinophilia was noticed in 80% of patients and the presence of atypical lymphocytes – in 40%. The main infiltrate organ was liver. DRESS diagnosis should be taken into consideration especially in patients treated with antiepileptic drugs. Early diagnosis and drug discontinuation can contribute to preventing serious complications of DRESS.

In a study by Sharma et al, a complete of forty four patients were enclosed wherever as males outnumbered the females, and most patients were within the cohort of 21–40 years.[11] SJS was the foremost common SCARD found followed by DRESS. Medicinal drug category of drug was found to be most ordinarily concerned. Immediate withdrawal of the perpetrator drug and administration of general steroids reverted the SCARD in most patients. Severe cutaneous adverse drug reactions may be related to serious morbidity likewise as mortality. Their information and prompt recognition area unit essential for clinicians as early recognition, and immediate withdrawal of the perpetrator drug/drugs with adequate management may be lifesaving. A study by Patel et al of 8337 retrieved references, eighteen prospective studies were selected for analysis.[12] The pooled incidence was 9..22/1000 total among outpatient and inpatient cases. Unremarkably ascertained reactions were maculopapular rash (32.39%), mounted drug eruptions (FDEs) (20.13%), hypersensitivity reaction (17.49%) and SJS/TEN (6.84%). The main causative drug teams were antimicrobials (45.46%), NSAIDs (20.87%) and anti-epileptic medicine (14.57%). Unremarkably involved medicine was antibacterial (13.32%), β-lactams (8.96%) and carbamazepine (6.65%). High frequency of CADRs is ascertained with anti-epileptic medicine in DPC studies solely. Carbamazepine, hydantoin and fluoroquinolones had higher severe to nonsevere body covering reaction quantitative relation than different medicine. Antimicrobials were the most causative medicine for maculopapular rash, FDEs and SJS/TEN, and NSAIDs for the hypersensitivity reaction. The mortality for overall CADRs, SJS/TEN, and exfoliative eczema were 1.71%, 16.39%, and 3.57%, severally. "Definitely preventable", "probably preventable" and "not preventable" classes CADRs were fifteen. 64%, 63.14%, and 34.64%, severally. Antimicrobials, NSAIDs and anticonvulsant area unit common r agents of CADRs in Asian country anticonvulsant agents show high rates of severe body covering reactions.

## CONCLUSION

Liver function test abnormalities were present in 1.75% of non-severe group. Icterus and hepatomegaly were absent in non-severe group. Icterus was observed in 31.58% of severe group of drug rashes. Hepatomegaly was present in 40% of severe group of drug rash cases.

Liver function abnormalities are present in 20% of drug rash cases and 64% of severe group of drug rash cases. So liver can also be an organ of drug assault in cutaneous adverse drug reactions. Abnormal liver function tests are an independent indicator of the severity of drug induced cutaneous eruptions. The LFT abnormalities provide an initial guide to the clinical syndrome of hepatotoxicity in cutaneous adverse reactions.

To conclude, a sound knowledge of morphological patterns of drug rashes with hepatic involvement, drugs implicated in causing drug rashes and hepatic dysfunction and an easy detection of impending danger by the simple biochemical tests (liver function tests) can evert a major crisis and thus help the clinicians to better manage their cases.

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