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Original Research Article

INCIDENCE OF ADVERSE DRUG REACTIONS AT GGH, KURNOOL, UNDER PVPI, ADR MONITORING CENTRE, DEPARTMENT OF PHARMACOLOGY, KURNOOL. A PROSPECTIVE STUDY

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Abstract

Background: Adverse drug reactions are the fourth leading cause of death[1]. ADRs risk increases with age (>60), gender (female), number of prescribers (>2), prescription of multiple drugs (>5), duration of treatment(>1month), and multiple diagnoses2. ADRs cause prolongation of hospital stay. Inaddition ADRs may trigger prescription cascades when new medications are prescribed for conditions that are a consequence of another medication, which is often an unrecognized ADR. **Materials and Methods:** This is a prospective study among all case reports(ICSR) collected and uploaded under PvPI in the AMC at Kurnool Medical College. The study was conducted for a period of one year from June 2016 to May 2017, after getting consent from the IEC. **Result:** A total of 475 ADR forms were reported during the one year period of study (June 2016 – May 2017). Incidence of ADRs is of 0.6%. Mortality was 0.2%. Higher percentage of ADRs are noted with antimicrobials 43.2% with antiretrovirals 22.6% among them. Immune system is associated with most of the ADRs (29.89%). According to WHO- UMC scale of causality assessment majority of ADRs were possible 50.9%. Polypharmacy is associated with 60% of cases. One rare ADR is detected with imatinib induced hyperthyroidism. According to HARTWIG scale of severity majority of ADRs are moderate in severity (52.4%). **Conclusion:** Finally, Indian contribution of ADRs to global data base is 3%, where as in KMC KNL, it is only 0.6%. There is a need to identify the ADRs and improve their reporting by doctors, nurses, pharmacists, patients.

INTRODUCTION

Adverse Drug Reaction (ADR).[1,5]
It is defined as a response to a medicinal product that is noxious or potentially harmful and un intended, which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of a disease (WHO report 498,1972[5]).
ADRs are the fourth leading cause of death.[2] ADRs may be responsible for the death of 15 out of 1000 patients admitted.[4] Approximately 35% of hospitalized patients experience an ADR during their stay.[4] They represent 5% to 10% of the hospital costs.[4] Incidence of fatal ADRs is 0.23% to 0.4% in INDIA.[4]
ADRs risk increases with age (> 60), gender (females), number of prescribers (>2), prescription of multiple drugs (>5), duration of treatment (>1 month) & multiple diagnoses.[6] Other factors are gender, race, pregnancy, breast feeding, kidney problems, liver function, drug dose and frequency and many other factors. Some of these factors can be changed like smoking or alcohol intake whereas others cannot be changed like age, presence of other diseases or genetic factors.[7]
ADRs affect patient's quality of life and are also responsible for patient's loss of confidence in their doctors, increasing cost of patient care, precluding use of drug in most patients; they may mimic disease resulting in unnecessary investigations as well as treatment delay.[4]
Prior to drug release, a drug is studied in just 4,000 cases. Therefore, adverse reactions having frequency of less than 0.5 to 1% are missed[2]. Children, pregnant

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women, and elderly are not included in clinical trials for ethical reasons. Therefore, the safety of the drug in these cases remains unknown until its release.

MATERIALS AND METHODS

The present study was carried out at Adverse Drug Reaction Monitoring Centre (AMC), in the department of Pharmacology under Pharmacovigilance Programme of India, Kurnool Medical College, Kurnool.

Nature of study
This is a prospective study among all case reports collected and uploaded under PvPI in the AMC at Kurnool Medical College.
The study was conducted for a period of one year from June 2016 to May 2017, after getting consent from the IEC (Institutional Ethics Committee).

Inclusion Criteria
All the suspected ADRs that may be due to the medications, both prescribed and over the counter, taken by patients either as in patients or out patients that were ultimately noted and reported.

Exclusion Criteria
Use of alternative medicines like Ayurveda, Homeopathy, Unani etc.
Drug addicts; all mentally retarded people.
Patients taking more than ten prescription drugs.
Over dosage and excess consumption.
Unconscious patients and patients unable to respond to verbal questions were also excluded from study.

Study Protocol
All the patients with adverse drug reactions are assessed by using WHO-UMC CAUSALITY assessment scale and HARTWIG scale of severity assessment.

Statistical Analysis: Collected data was entered in Microsoft office excel 2012 and analysis was done by Statistical Package For Social Sciences (SPSS) Version 22.
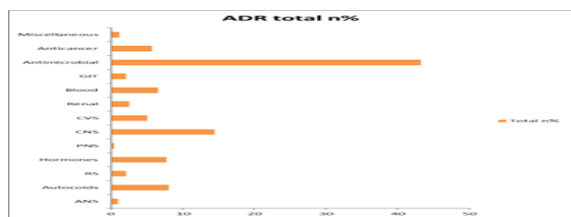
RESULTS

Figure 1: Percentage of incidence of ADRs based on drug class

The results of the incidence of ADRs at GGH Kurnool, at AMC, department of Pharmacology Kurnool Medical College Kurnool are analysed after a study period of one year i,e from June 2016 to May 2017.
Patient characteristics: All the ICSR (filled forms) are taken and studied. A total of 475 ADR forms are reported during the one-year period of study.
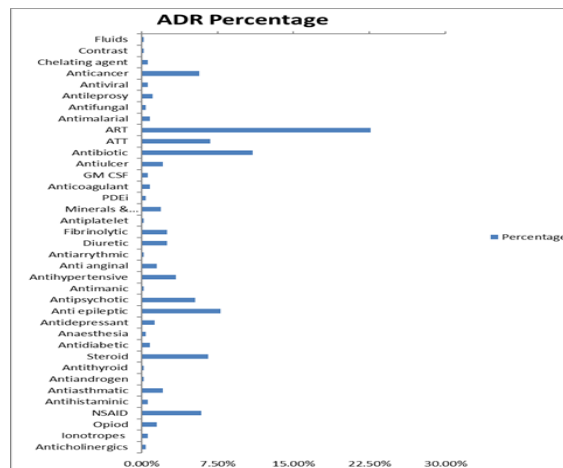

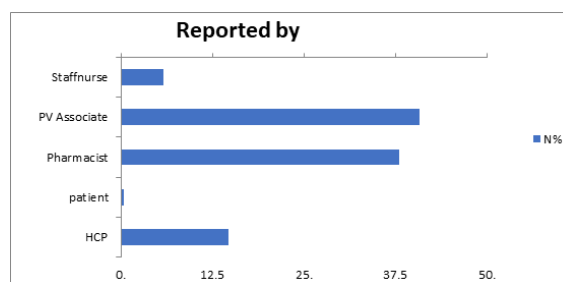**Figure no 2: Individual drug class resulted in ADRs in the study**

Figure no 3: ADR reporting awareness among different groups of people in the study
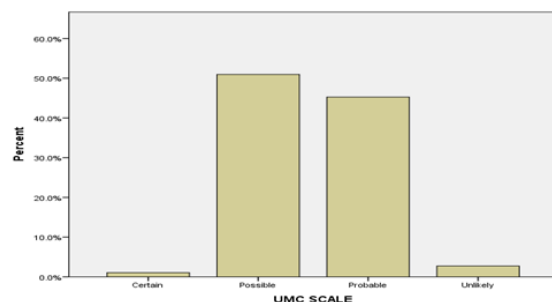
Figure no 4: Causality assessment of ADR according to WHO-UMC scale

Table 1: WHO-UMC causality assessment scale[18]

Causality term	Assessment Criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs

	• Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Table 2: Hartwig's Severity Assessment Scale,[17]

Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment was required. No increase in length of stay(LOS).
Level 3	The ADR required that treatment with the suspected drug be withheld, discontinued, or otherwise changed. and/or An Antidote or other treatment was required. No increase in length of stay (LOS).
Level4	Any level 3 ADR which increases length of hospital stay atleast by 1 day. or The ADR was the reason for admission.
Level 5	Any level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction causes permanent harm to the patient.
Level7	The adverse reaction either directly or indirectly leads to death of patient.

Mild = levels 1 and 2, Moderate=levels 3 and 4, Severe=5,6, and 7levels.

Table 3: Mean age of Patients in the Study

Descriptive Statistics			
	N	Mean	Std. Deviation
Age(yrs)	475	43.45	16.909

Table 4: Age and Gender Distribution of Patients in the Study

		Gender			
		Male (263)55.4%		Female (212)44.6%	
		Count	N %	Count	N %
AGE category	0-18 Yrs	16	6.1%	21	9.9%
	19-40 yrs	78	29.7%	105	49.5%
	41-60 Yrs	118	44.9%	68	32.1%
	61-80 Yrs	49	18.6%	18	8.5%
	>81 Yrs	2	0.8%	0	0.0%

Table 5: Percentage of incidence of ADRs based on drug & system(blurred)

ADR SYSTEM INVOLVED	Drug based on system												
	ANS	Autocoids	RS	Hormones	PNS	CNS	CVS	Renal	Blood	GIT	Antimicrobial	Anti cancer	Miscellaneous
	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
GIT	20.0%	30.8%	0.0%	16.7%	0.0%	29.0%	4.2%	50.0%	19.4%	60.0%	27.8%	37.0%	40.0%
Blood	0.0%	5.1%	0.0%	2.8%	0.0%	1.4%	0.0%	0.0%	3.2%	0.0%	3.9%	7.4%	0.0%
CNS	20.0%	7.7%	10.0%	16.7%	0.0%	17.4%	37.5%	0.0%	3.2%	10.0%	17.1%	14.8%	20.0%
PNS	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.3%	3.2%	0.0%	0.5%	3.7%	0.0%
CVS	40.0%	0.0%	60.0%	16.7%	0.0%	0.0%	29.2%	8.3%	22.6%	20.0%	1.5%	0.0%	0.0%
Renal	0.0%	5.1%	0.0%	0.0%	0.0%	1.4%	0.0%	8.3%	9.7%	0.0%	0.5%	0.0%	0.0%
Eye	0.0%	0.0%	0.0%	11.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.9%	0.0%	0.0%
ENT	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	3.7%	0.0%
Skin	0.0%	0.0%	0.0%	5.6%	0.0%	1.4%	0.0%	0.0%	0.0%	0.0%	1.5%	7.4%	20.0%
Immune	0.0%	43.6%	20.0%	5.6%	100.0%	33.3%	8.3%	8.3%	32.3%	10.0%	37.1%	18.5%	20.0%
Musculoskeletal	0.0%	2.6%	0.0%	0.0%	0.0%	7.2%	4.2%	0.0%	0.0%	0.0%	2.4%	3.7%	0.0%
RS	20.0%	0.0%	0.0%	5.6%	0.0%	1.4%	8.3%	0.0%	6.5%	0.0%	1.0%	0.0%	0.0%
Endocrine	0.0%	2.6%	10.0%	19.4%	0.0%	5.8%	8.3%	16.7%	0.0%	0.0%	2.4%	3.7%	0.0%
Genetic	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Genital	0.0%	2.6%	0.0%	0.0%	0.0%	1.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table 6: Evidence of lab reports related to the ADRs

	Count	Number	Percentage %
LAB reports	No	412	86.7%
	Yes	63	13.3%
	Total	475	100%

Table 7: Type of Adverse drug Reaction according to Rawlins and Thompson criteria

	Count	Number	Percentage %
Type of ADR	A	330	69.9%
	B	130	27.4%
	C	15	2.5%
	Rare case	1	0.2%

Table 8: Dechallenge of drug due to ADR by patients

Dechallenge		Count	N %
	No	255	53.7%
	Yes	220	46.3%

Table 9: Rechallenge of drug by the patients due to ADR

Rechallenge		Count	N %
	No	470	98.9%
	Yes	5	1.1%

Table 10: Association of drug interaction and polypharmacy with ADR

		Count	N %
DI	No	475	100.0%
	Yes	0	0.0%
PP	No	190	40.0%
	Yes	285	60.0%

Table 11: ADR reporting percentage or reporting awareness among different groups of people

Reported by		Number	Percentage %
	HCP	70	14.74%
	Patient	2	0.42%
	Pharmacist	181	38.11%
	PV associate	194	40.84%
	Staffnurse	28	5.89%

Table 12: Association of genetic factors and past drug history and signal detection in the study

		Number	Percentage %
Genetic factors relation	No	475	100.0%
	Yes	0	0.0%
Past drug H/o	No	469	98.8%
	Yes	6	1.2%
Explained /Not Explained AS PER LITERATURE	No	1	0.2%
	Yes	474	99.8.0%

Table 13: Causality assessment of ADRs according to WHO-UMC scale in the study

UMC SCALE	N	%
Certain	5	1.1%
Possible(242)	242	50.9%
Probable(215)	215	45.3%
Unlikely(13)	13	2.7%

Table 14: Severity assessment of ADRs according to Hartwig scale

HARTWIG SCALE	Number	Percentage %
Mild	104	21.9%
Moderate	249	52.4%
Severe	122	25.7%

Table 15: Patients response to treatment with involved ADR

Response to ADR Rx	Number	Percentage %
No	11	2.3%
Yes	144	30.3%
Delayed	305	64.2%
Unknown	14	2.9%
Fatal	1	0.2%

Table 16: Cutaneous symptoms of drug hyprsensitivity reaction[9]

Type of cutaneous reaction	Associated immune mediated mechanism
1) Exanthematous or morbilliform eruption originating on trunk	1)Classic "drug rash" most common
2) Urticaria	2)IgE antibody mediated or direct mast cell stimulation
3)Purpura	3)Vasculitis or drug induced thrombocytopenia
4) Maculopapular lesions with distribution on the fingers,toes,or soles.	4) Serum sickness
5) Blistering lesions with mucous membrane involvement.	5) SJS or TEN
6) Eczematous rash in sun exposed areas.	6) Photoallergic reaction
7) Solitary circumscribed erythematous raised lesion.	7) Fixed drug eruption
8) Papulovesicular lesion	8) Contact dermatitis

Table 17: Diagnostic testing and therapy for drug hypersensitivity.[9]

Immune reaction	Laboratory test	Therapeutic consideration
Type 1(IgE mediated)	Skin testing Radio allegro sorbent test Serum tryptase	Discontinue drug. Consider epinephrine, antihistamines, systemic steroids, bronchodilators. In patient monitoring if severe.
Type 2 (cytotoxic)	Direct or indirect coombs test	Discontinue drug. Consider systemic corticosteroids Transfusion in severe cases.
Type 3 (immune complex)	ESR C reactive protein Immune complexes or complement studies Anti nuclear Ab Anti histone Ab Tissue biopsy for immune fluorescence studies	Discontinue drug. Consider NSAIDS antihistaminics or systemic steroids. Corticosteroids or plasmapheresis if severe.
Type 4 (delayed cell mediated)	Patch testing Lymphocyte proliferation assay	Discontinue drug. Consider topical corticosteroids, antihistaminics or systemic corticosteroids if severe.

Table 18: Severe ADRs in the present study are:

ADR	CAUSATIVE DRUG	PERCENTAGE
1)Anuria	Diclofenac	0.4%
2)encephalopathy	Phenytoin	0.2%
3)hypokalemia	Dexamethasone furosemide	0.63%
4)cardiorespiratory failure	ceftriaxone	0.2%
5)ventricular tachycardia	amiodarone	0.2%
6)increased creatinine	Amoxicillin-clavulonicacid Miokinase	0.4%
7)seizures	ZLN, cisplatin, ciprofloxacin	0.63%
8)cerebral hemorrhage	Nitroglycerin	0.2%
9)deafness	ATT	0.2%
10)optic neuritis	HRZE	0.4%
11)acute hepatitis	ATT	0.8%
12)anaphylaxis	Vitamin K, paclitaxel	0.63%
13)SOB	Midazolam, atenolol, atropine, metformin	1.2%
14)anemia	Vitamin A, streptomycin	1.47%
15)thrombocytopenia	ART	0.42%
16)hypoglycemia	Cisplatin, sodium valproate Metformin, glimiperide	0.42%
17)SJS	Antiepileptics, streptomycin, amikacin, Diclofenac, celecoxib, TLE, propranolol	3.37%
18)TEN	Ciprofloxacin, ofloxacin	0.42%
19)jaundice	ATT	0.63%
20)asthma	Diclofenac	0.42%
21)drug hypersensitivity	Heparin, carbamazepine	0.63%
22)elevated liver enzymes	ATT, ART, sodium valproate	0.6%
23)dress syndrome	Phenytoin, dapsone	1.05%
24)orchitis	Deutasteride	0.2%
25)PCOD	Quetiapine	0.2%
26)raised T3,T4,TSH	Imatinib	0.2%
27)blurred vision	Dexamethasone, HRZE, artesunate	1.2%
28))altered visual acuity	Ethambutol	0.42%
29)acute pancreatitis	Tigecycline	0.2%
30)leucopenia	Cisplatin	0.2%
31)thrombocytopenia	Cisplatin, sodium valproate	0.42%
32)irregular heart beat	Salbutamol, digoxin	0.42%

Table 19: drug rechallenge protocol [13]

Isoniazid	50mg	300mg
Rifampin	75mg	300mg
Pyrazinamide	250mg	1.0gm
Ethionamide	125mg	375mg
Cycloserine	125mg	250mg
Ethambutol	100mg	500mg
PAS	1.0gm	5.0gm
Streptomycin	125mg	500mg

DISCUSSION

NCC (National Coordination Centre) has played significant role in creating awareness among health care professionals about reporting of ADRs which were more than 1,49,000 ADRs till December 2015.[8] Currently the contribution of INDIA to the WHO global ICSRs (Individual Case Safety Reports) database is 3%.[8] In Kurnool Medical College, the incidence of ADRs is of 0.6% during the period June 2016–May 2017. While the No of OP (Out Patient) 2000/day and IP (In Patient) 200/day. A total of 475 cases are reported at AMC (adverse drug reaction monitoring centre) in the department of Pharmacology at KMC, KNL for the period of June2016 - May2017. In the present study, majority of patients affected by ADRs were from adult population (19-60yrs) which is 74%. Least age affected with ADR is 9 months whereas highest age affected with ADR is 93 yrs.

In the present study,

(Men have been reported to have more ADRs (55.4%). Majority of cases are moderate (52.4%) in severity according to Hartwig scale.)

(Skin rash (13.47%) is the commonly reported ADR in this study followed by vomiting 6.74%. The most common organ system involved with ADRs is immune system, which is (29.89%) followed by GIT (26.74%).)

ADRs due to immune system include acute hepatitis, acute urticaria, anaphylaxis, asthma, bullous eruption, cardiorespiratory failure, cellulitis, dermatitis, DRESS syndrome, drug hypersensitivity, dyspnoea, erythema multiforme, exfoliative dermatitis, fixed drug eruption, fever, itching, maculopapular rash, pruritus, puffiness of face, rash, Steven Johnson Syndrome (16 cases), Toxic Epidermal Necrolysis (2 cases) & urticaria.

(General Criteria for Drug Hypersensitivity Reactions:[9]

1. The patient's symptomatology is consistent with an immunologic drug reaction.
2. The patient was administered a drug known to cause such symptoms.
3. The temporal sequence of drug administration and appearance of symptoms is consistent with a drug reaction
4. Other causes of the symptomatology are effectively excluded.

Laboratory data are supportive of an immunologic mechanism to explain the drug reaction. It may not present or available in all cases.)

Hapten hypothesis: Drug metabolism typically occurs in 2 different steps, phase 1 and phase 2 reactions. Most often the reactive metabolite formed by phase1 metabolism is promptly detoxified and eliminated. However, reactive drug metabolites may act as haptens that bind covalently with cellular macromolecules such as serum proteins or cell surface membranes. Such binding results in the formation of large multivalent immunogens that may intiate an immune response. e.g: antibiotics.[10,11]

Ig E mediated allergy.[12]

The best understood example for haptenation and induction of an Ig E-mediated drug allergy are beta-lactam antibiotics. They do contain a reactive beta lactam ring structure and do not have to be metabolized before haptenation can occur. In penicillin, the beta-lactam ring is unstable, and thus opens and acetylates lysine residues form the penicilloyl determinant called the 'major'penicillin determinant. Numerous other conjugates are also found, which as a whole have been termed the 'minor' determinant mixture. Specific Ig E antibodies to penicillin and other beta-lactam antibiotics appear to recognize a multitude of antigenic determinants.

Some beta-lactam-allergic individuals exhibit specific Ig E antibodies to structures of the beta-lactam ring and may show cross-reactivity to other beta-lactam antibiotics, but others are highly selective in their recognition pattern and have Ig E antibodies specific to side chains and thus react. Examples include reactions to immunoglobulins, insulins, chemotherapeutic agents and streptomycin.

Involvement of T-Lymphocytes:[12]

Drug allergy can be mediated by drug-specific antibodies, drug-specific T-lymphocytes, or may share features of different types of immunological reactions. The finding that drugs might induce drug-specific activation of T-lymphocytes, particularly in exanthematous skin reactions, has been demonstrated already in 1970s and has been extended recently only to a single or few beta-lactam antibiotics. There is evidence that drug haptens can be processed and presented to T-cells. CD8+T-cells were demonstrated to be the predominant T-cell subset in beta-lactam and in sulfamethoxazole induced vesiculo bullous exanthems.

The epidermal T cell clones from these patients were antigen specific and MHC class restricted. T cell clones derived from the peripheral blood of patients with beta-lactam induced maculopapular exanthems were demonstrated to be CD3+, CD4+, CD8+ and HLA-DR+ subset. The cytokine gene expression and protein production has been compared in peripheral

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blood mononuclear cells (PBMCs) in patients with immediate and non-immediate drug-induced reactions. Drug hypersensitivity reactions (type B) are classified according to the clinical symptoms and/or to the kinetics of the reaction.

Acute (0–1 h after drug Application),

Subacute (1–24 h),

or Accelerated (> 24 h)[12]

reactions can be distinguished. However, recently it has become more common to divide into immediate vs late or delayed type reactions.

Immediate drug hypersensitivity reactions are generally characterized by anaphylactoid symptoms, and the severity of the reaction.

Non-immediate reactions more often affect the skin, manifesting as exanthematous skin reactions (exanthematous drug eruptions, EDE).[12] Toxic epidermal necrolysis (Lyell's syndrome) is the maximal life threatening variant of a cutaneous drug reaction.

In some cases, anaphylactoid features may occur several hours to days after application of a drug. Radiocontrast media, for example, do cause anaphylactoid immediate type reactions, but in some patients delayed reactions after 6–12 h like angioedema, dyspnoea, EDE, cardiovascular reactions, gastrointestinal complaints, headache and flu-like symptoms may occur.

In patients with immediate reactions, the TH2 cytokine IL-4 was expressed and produced early in the PBMCs12, whereas in patients with non-immediate reactions no expression of IL-4 was present, but over expression of theTH1 cytokines IL-2, IFN-Á (interferon) and TNF was demonstrated.

In other maculopapular drug reactions, predominance of CD4+ T-cells has been described in the dermal infiltrate. In some patients with immediate reactions to beta-lactam antibiotics, high levels of IFN-α, but little IL-4 were found, indicating that in this interesting area, still more research is needed.[12] In drug allergy, immunological reactions may require a sensitization period of several days, whereas idiosyncratic and pseudo-allergic reactions may occur at the first course of therapy.[9]

For Adverse Drug Reactions (type A), the drug may be tolerated at a lower dose and dose modifications often help in drug-drug interactions.

For patients with drug hypersensitivity reactions (type B), more caution is advised and allergy diagnosis, to find the culprit drug as well as possible alternatives should be performed.

(In the present study, SJS (3.37%) is caused by 16 drugs, which include AEDs like phenytoin, carbamazepine, phenobarbitone, antimicrobials like streptomycin, amoxicillin, amikacin, TLE (ART), NSAIDs like diclofenac, celecoxib. Urticaria 5.68%, erythema multiformae 0.21%, maculopapular rashes 13.68%, itching 5.05%.TEN (0.4%) is caused by 2 drugs mainly quinolones group ofloxacin and ciprofloxacin)

Gell and Coombs Classification of Drug Hypersensitivity Reactions

IMMUNE REACTION	MECHANISM	CLINICAL MANIFESTATIONS	TIMING OF REACTIONS
Type I (IgE-mediated)	Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators	Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis	Minutes to hours after drug exposure
Type II (cytotoxic)	Specific IgG or IgM antibodies directed at drug-hapten coated cells	Hemolytic anemia, neutropenia, thrombocytopenia	Variable
Type III (immune complex)	Tissue deposition of drug-antibody complexes with complement activation and inflammation	Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis	1 to 3 weeks after drug exposure
Type IV (delayed, cell-mediated)	MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release	Allergic contact dermatitis, maculopapular drug rash*	2 to 7 days after cutaneous drug exposure

Figure 5: Hypersensitivity reactions may be scored from grade I to grade IV[9]

Allergy Diagnosis:[12]
Non-Specific Tests: Laboratory tests can be applied to assess organ involvement (e.g. creatinine, liver function tests, complete blood count).

A biochemical marker of mast cell involvement in ADR is the neutral serine protease tryptase.[12] This enzyme exists in an α and β form; whereas levels of ·α tryptase are believed to be a reflection of the total body burden of mast cells, the β form is released in immunologically mediated as well as in non-immunologically mediated anaphylactoid reactions.

It is recommended to obtain serum for tryptase determination 1–2 h after the onset of an anaphylactoid reaction, but increased levels also have been found several hours later, e.g. in a case of a fatal anaphylactoid reaction.

Allergic specific tests:[12] In vitro diagnostic tests are sufficiently validated in the case of penicillins where specific IgE antibodies can be detected to confirm sensitization.

Skin Tests:[12] A positive skin test or detection of specific Ig E antibodies are an indication for a specific immunological reaction (sensitization) of an individual to a specific drug. However, a negative test reaction does not exclude a hypersensitivity reaction as inappropriate immunogens may have been used or an idiosyncratic reaction may be present.)

In vitro lymphocyte tests (LTT or cytokine secretion):[12]
May in selected cases prove helpful in exanthematous drug eruptions especially after co incubation with mouse liver microsomes in order to facilitate metabolite production.

Skin prick tests and intradermal tests:[12] for the detection of Ig E-mediated immediate reactions are widely used for beta-lactam antibiotics, but are also often indicative for a drug hypersensitivity reaction in other drugs, including immunoglobulins, insulins, streptomycins. With increasing evidence of specific T-lymphocytes being important in drug hypersensitivity reactions, patch tests and intradermal tests with delayed readings should be applied for late or delayed reactions.

(Provocation Tests:[12] In cases where the culprit drug cannot be identified by these measures, provocation tests have to be considered. The

controlled challenge with increasing doses of a drug should only be performed by an experienced allergist under in patient or emergency conditions.

In cases of very severe life threatening reactions where no reliable therapeutic modality exists (e.g. toxic epidermal necrolysis, cytotoxic reactions), provocation tests are not indicated.[12]

In certain cases with increased cross-reactivity to possible alternative drugs, as it is the case with analgesics or insulins, provocation tests may also be indicated.[12]

If no reaction to a drug does occur to a provocation test, the drug may be continued, if medically indicated. If objective anaphylactoid symptoms or the previous symptoms are reproduced upon provocation test, the hypersensitivity is proven and generally the drug should be discarded. The patient should carry documentation of this hypersensitivity (e.g.medic alert bracelet, 'allergy passport') at all time.).
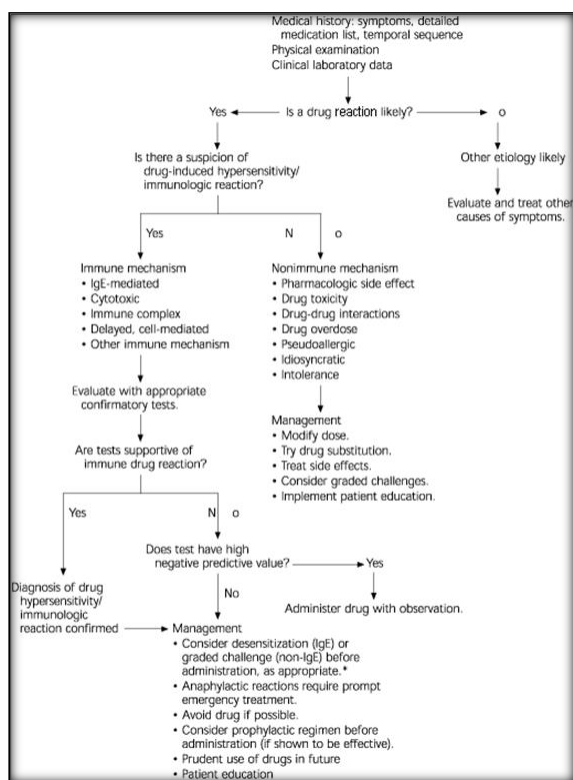
Figure 6[9]: Evaluation and Management of Drug Reaction. Source: MARC.RIEDL, ADRIAN.M, Adverse drug Reactions types and treatment options. Am Fam Physician.2003 Nov 1;68(9):1781-1791

(In the present study, Group of drugs causing most of the ADRs are anti microbials, 205 cases (43.2%) which probably reflects their widespread use and ART was reported to cause 107 cases (22.6%) due to intolerance. Effective reporting also may contribute by ART centre.

Most of ADRs in the present study are type A reactions (70%) followed by type B 27.4%, type C 2.5%. One rare case was detected, that was imatinib induced hyperthyroidism.

In this study 60% of ADRs are associated with polypharmacy but no drug –drug interaction.

Past history of drug allergy is seen with 6 cases (1.3%), but no genetic relation is associated with ADRs Most of the ADRs are of moderate severity (52.4%) according to Hartwig scale of severity, Severe cases were 25.7%.

Causality assessment by UMC scale revealed that
• 50.9% cases are in the" possible" category
• 45.3% cases are in the "probable" category
• 1.1% cases are in the "certain" category
• 2.7%. cases are in the "unlikely" category

In the present study Preventable ADRs were of 30.3% (responded to treatment) fatal (0.2%) and those that didn't respond to treatment 2.3% & majority of ADRs are associated with delayed response to treatment 64.2%.

Drug induced hepatotoxicity is found to be 2% caused by ATT (hepatitis, jaundice, elevated LFT), ART (elevated liver enzymes), sodium valproate (elevated liver enzymes).

Drug induced nephrotoxicity is found to be 1% & is caused by diclofenac (anuria), amoxicillin-clavulonic acid, miokinase (raised creatitinine levels), tenecteplase (urethral bleeding).

15 out of 475 cases of Blood dyscrasias are reported in this study accounting for 3.16%, in the form of anemia, leucopenia, thrombocytopenia, bleeding and purpura.)

(ADRs for ATT (6.8%) recorded in the present study include skin rashes acute hepatitis, itching, hepatitis, anemia, jaundice, altered visual acuity, bullous eruption, deafness, skin rash, SJS, dyspnoea & elevated liver enzymes)

Measures to be taken for ATT ADRs:[13]

Causative agents for liver toxicity INH+rifampin>INH alone >>pyrazinamide alone> rifampin alone >ethionamide.

Asymptomatic patients with an increase in LFTs is <3-5x normal: continue the current regimen and monitor for symptoms of liver dysfunction.

If LFTs >3-5 x normal: hold INH until levels return to baseline.

If the transaminases increase with rechallenge of INH, discontinue INH, substitute another drug (e.g. ethambutol) and adjust treatment duration as required.

If the patient is receiving a twodrug regimen, substitute at least one other drug until the INH is restarted.

If the serum bilirubin increases, therapy usually does not require modification as rifampicin competes with bilirubin for elimination resulting in increased serum bilirubin initially; usually return to normal with continued therapy.

For symptomatic patients hold all drugs and obtain LFTs if LFTs are elevated, hold drugs until symptoms resolve and the transaminases decreases to <2x normal[13].

Ethambutol and pyrazinamide should be started if drug therapy cannot be held secondary to patient clinical condition.

Use streptomycin if pyrazinamide is suspected to be the cause of hepatotoxicity.[13]

Rechallenge the patient after resolution of signs and symptoms by adding drugs to the regimen every 4 days.

a) rifampicin for 3 days, if patient remains asymptomatic then add.
b) INH for 3 days, if patient remains asymptomatic then add
c) pyrazinamide for 3 days.

If signs and symptoms recur with rechallenge, discontinue the responsible drug and the regimen and duration of therapy as required.

For visual problems (ethambutol>>INH) go for ophthalmic checkup (visual acuity, color vision) and discontinue drug.

Ototoxicity; cochlear damage (hearing loss occurs first) is produced by the aminoglycosides in this order 1)kanamycin followed by 2) amikacin followed by 3)streptomycin and vestibular toxicity (problem with balance) most commonly was seen with streptomycin followed by kanamycin followed by amikacin. If these are present, discontinue the drug.

For hypersensitivity reactions: 1) discontinue all drugs 2) rule out viral infection 3) if viral infection is present restart all TB medications. 4) if viral infection is ruled out drug rechallenge guidelines are to be followed.

First discontinue all drugs until the reaction resolves. Identify the causative drug by rechallenging each drug every 4 days according to the table.

Begin rechallenge with INH 50mg on day1; if the reaction is severe, begin with 1/10 th the day 1 dose 5mg for INH.

If reaction does not occur after day 1 dose, increase the INH to 300mg on day 2. If a reaction does not occur after the day 2 dose continue INH 300mg once a day continue to add drugs in the order and doses specified in the table. RNTCP formally entered into collaboration with the PvPI on October 11, 2013.

(In the present study) ADRs for ART (22.6%) were reported TLA (Tenofovir Lamuvudine Abacavir), TLE (Tenofovir Lamuvudine Efavirenz), SLN (Stavudine Lamuvudine Nevirapine), ZLN (Zidovudine Lamuvudine Nevirapine), Nevirapine drugs include hypertryglycerelemia, breathlessness, rashes, itching, diarrhea, increased liver enzymes, weight loss, SJS (2cases), anemia, nightmares insomnia, skin rashes, exfoliative dermatitis, gastritis, vision problems, vomitings, dyspepsia, hyperglycemia, weight loss, peripheral neuropathy, depression, sedation, headache, insomnia, muscle stiffness, myalgias.)

Measures to be taken for the ADRs of ART drugs:
The magnesium content of didanosine may account for the GI adverse effects such as diarrhoea which occurs in 15-20% of patients.[14,15]

• Diarrhoea can be ameliorated with antidiarrheals like loperamide. Usually diarrhea is self -limiting.

Other drugs causing diarrhoea are Nevirapine, Protease Inhibitors.

• If there is anemia or neutropenia due to zidovudine (CD4 cell count <200cells/mm3, HB, 6gm/dl) consider blood transfusion, then substitute with tenofovir or abacavir or stavudine.

• If there is drug hypersensitivity reaction like SJS due to Nevirapine then substitute with another therapeutic class (integrase inhibitors/boosted PIs).[14]

• For hepatitis particularly with nevirapine & PIs, ALT>5 fold discontinue ART and replace with efavirenz or other class of drugs. If there is dyslipidemia due to ART drugs like PIs, efavirenz then substitute with another therapeutic class like integrase inhibitors.

• For SJS or TEN cases, antihistamines are given for mild cases, for moderate rash without skin or mucosal involvement consider single NNRTI substitution i,e from Nevirapine to Efavirenz, in severe cases discontinue treatment resume ART with 3 NRTI or 2NRTI+PI regimens.

• For GI intolerance as it is self -limiting, there is no need to discontinue the ART.[15]

• For ADRs (hepatomegaly, decreased bone mineral density, chronic kidney disease) due to Tenofovir; substitute with Zidovudine or Abacavir or Stavudine.

• Do not intiate tenofovir at GFR <50ml/min, uncontrolled hypertension, untreated diabetes or in the presence of renal failure.

• For CNS toxicity (efavirenz) such as dizziness, insomnia, depression, anxiety, mental confusion, convulsions, shift to low dose efavirenz 400mg/day or substitute with nevirapine or integrase inhibitor.

• If lower dose is not effective in reducing symptoms, substitute with another therapeutic class like integrase inhibitors or boosted PIs.

• Usually neuropsychiatric symptoms need no discontinuation of Rx. They are self -limiting.

• For dyslipidemias and insulin resistance, mainly due to PIs and Efavirenz - consider replacing the suspected PI by drugs with less risk of metabolic toxicity.

• For Lamivudine ADRs like peripheral neuropathy (Stavudine) substituted with Tenofovir or Zidovudine or Abacavir is used. Most of the ICSRs are reported to the AMC by pharmacovigilance associate about 40.84%, pharmacists - 38.11%. others by doctors including house surgeons and residents 14.74% followed by staff nurse 5.89% & patients (through toll free number) 0.42%.

CONCLUSION

(In the present study, the total number of ADRs reported were 475 for the period of June 2016 - May2017. Incidence of ADRs is of 0.6%. Mortality was 0.2%. Higher percentage of ADRs are noted with

antimicrobials 43.2% with antiretrovirals 22.6% among them. Immune system is associated with most of the ADRs (29.89%). According to WHO- UMC scale of causality assessment majority of ADRs were possible 50.9%. Males(55.4%) are affected due to ADRs more than females. Type A (69.9%) reactions are commonly associated with ADRs. Polypharmacy is associated with 60% of cases. Past H/O drug allergy history is positive for 1.2%cases. One rare ADR is detected with imatinib induced hyperthyroidism. According to HARTWIG scale of severity majority of ADRs are moderate in severity (52.4%). Preventable ADRs are 30.3%.)

Finally, Indian contribution of ADRs to global data base is 3%, where as in KMC KNL, it is only 0.6%. There is a need to identify the ADRs and improve their reporting by doctors, nurses, pharmacists, patients.

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