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Drug-induced diseases (DIDs): An experience of a tertiary care teaching hospital from India

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***Background & objectives*: Drug-induced diseases (DIDs) are well known but least studied. Data on DIDs from India are not available. Hence, this retrospective cross-sectional study was undertaken using suspected adverse drug reaction (ADR) data collected form Pharmacovigilance Programme of India (PvPI) to evaluate profile of DIDs over two years, in a tertiary care teaching hospital from north India.**

***Methods*: The suspected ADRs in the form of DID were evaluated for drug and disease related variables and were classified in terms of causality.**

***Results*: DID rate was 38.80 per cent. Mean duration of developing DIDs was 26.05 ± 9.6 days; 25.16 per cent had more than one co-morbid condition. Geriatric population (53.99%) accounted for maximum DIDs followed by adult (37.79%) and paediatric (8.21%). Maximum events were probable (93.98%) followed by possible (6.04%). All DIDs required intervention. Gastritis (7.43%), diarrhoea (5.92%), anaemia (4.79%), hypotension (2.77%), hepatic dysfunction (2.69%), hypertension (1.51%), myalgia (1.05%), and renal dysfunction (1.01%) were some of the DIDs. Anti tubercular treatment (ATT), anti retroviral treatment (ART), ceftriaxone injection, steroids, non-steroidal anti-inflammatory drugs, antimicrobials and anticancer drugs were found as commonly offending drugs.**

***Interpretation & conclusions*: Our findings show that DIDs are a significant health problem in our country, which need more attention.**

Key words Adverse drug reaction - drug-induced disease - iatrogenic - pharmacovigilance

Adverse drug reaction (ADR) has been implicated as a leading cause of considerable morbidity and mortality worldwide. The prevalence rate of ADRs has been reported to range from 0.16 to 15.7 per cent[1]. Morbidity related to ADRs is also well known and causes a large number of hospital admissions[2]. Further, ADR related hospitalization in emergency and intensive care units (ICU) is very high among high risk population like elderly population with multiple co-morbidities[3]. Morbidity related to ADRs can be permanent sometimes to the extent of 20.4 per cent of admissions in ICU[4]. Besides, ADRs are known to pose huge economic burden on individual, society and nation at large[5].

Drug-induced diseases (DID) also called as iatrogenic diseases, are well known but least studied

entity. Some of the risk factors of DIDs are multiple chronic diseases, multiple physicians, hospitalization, medical or surgical procedures, long duration of medicine use, advancing age, female sex and a particular class of drugs[6-8]. Most of these DIDs are largely preventable[9], if strict vigilance and proper periodic clinical and diagnostic monitoring are undertaken. There are studies from the West regarding DIDs[9-22], however information from India is lacking. Hence, the current study was undertaken to analyze the profile of DIDs in a tertiary care teaching hospital at Jammu, India.

Material & Methods

A retrospective observational cross-sectional analysis was carried out for the data collected from November 2010 to November 2012 to evaluate the prevalence and profile of DIDs in Adverse Drug Reaction Monitoring (ADRM) Centre, working under Pharmacovigilance Programme of India (PvPI)[23] in a tertiary care teaching hospital from north India (Government Medical College, Jammu) using suspected drug reactions monitoring data collection form used under PvPI.

Institute Ethics Committee (IEC) permission was taken prior to commencement of the study.

The ADRs are defined and categorized as per the definition of Edwards and Aronson[24], as any response to a drug that is noxious, undesireable and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function. A drug-induced disease is defined as the unintended effect of a drug that results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or to require hospitalization and may persist even after the offending drug has been withdrawn[25].

Information about patient, suspected ADRs in the form of DID, suspected medication, reporter, date of reaction, date of recovery and presentation of problem was recorded. Under suspected medication, name of the drug, brand and generic name of manufacturer (if known), expiry date, dose used, route, frequency and therapy dates as well as reason for prescribing suspected drug were also assessed. The information about de-challenge and re-challenge, concomitant medical treatment record, the relevant biochemical abnormality and use of any diagnostic tool was recorded separately. Other relevant history including pre-existing medical conditions like allergy, pregnancy, smoking and alcohol used and any organ dysfunction was noted. The severity and seriousness of reaction, the outcome of reaction were recorded for every suspected ADR in the form of DID as recommended under PvPI. The suspected ADRs in the form of DIDs were classified in term of causality using WHO-UMC (Uppsala Monitoring Centre) scale[26]. Types of reaction were classified as Type A (augmented); Type-B (bizarre), Type C (continuous use); Type D (delayed); and Type E (end of use as per recommended standard operating procedure of PvPI[26].

Inclusion & exclusion criteria: Any ADR in the form of DID reported from OPD or inpatient of any severity, duration, and any type of reaction was included pertaining to drugs and vaccines. Any case of poisoning, medication error, over dosage, over/non-compliance, natural products/alternate medicines and unidentified drugs were excluded from the analysis.

Statistical analysis: Analysis was carried out with the help of computer software SPSS Version 15 for windows (SPSS, Inc., Chicago, USA). Chi-square test was applied for statistical comparison.

Results

The total number of ADR events reported during the two years study period was 2381 and of these 926 (38.89%) were the drug induced disease rate (Table I). Total number of ADRs was 2242. Mean duration of appearance of DIDs was 26.05±9.6 days. Overall, 10.79, 15.11, 73.98 and 0.10 per cent DIDs were mild, moderate, severe and fatal, respectively; 15.11, 10.79 and 74.08 per cent, respectively were sub acute, acute and latent in nature. Further, 80.99 per cent DIDs were serious and 19.00 per cent non serious in nature. Maximum events were probable (93.95%), followed by possible (6.04%). Overall, 94.60 per cent of DIDs recovered and 5.37 per cent continued in similar mode at the time of report collection (Table I).

Gastritis (7.43%), diarrhoea (5.92%), anaemia (4.79%), hypotension (2.77%), hepatic dysfunction (2.69%), were some of the common DIDs in the current study. The list of other DID and the common suspected drugs are depicted in Table II a, b.

Discussion

In the current study the DID rate was 38.9 per cent suggesting DIDs to be a significant health problem. The present results were comparable with those of Atiqi *et al*[9] depicting incidences of DIDs between 3.4 and 33.9 per cent. However, the current study largely

Table I. Profile of drug-induced diseases (DIDs)

Study parameters	Variables
Total number of ADRs & events reported	2242 & 2381
Total number of drug-induced diseases (DID) & detection rate	924 (38.80%)
Clinical symptoms (A) vs drug-induced disease (B) vs biochemical investigation(C) vs diagnostic tools(D) vs (E) unclassified DID - detection rate A vs B* A vs C* A vs D*	1082 (45.44%) vs 924(38.80%) vs 347(14.57%) vs 26 (1.09%) vs 2(0.08%)
Mean duration of appearance of DID in days (Mean±SD)	26.05±9.6
Single disease vs >1 co-morbid conditions *(%)	74.94 vs 25.16
Route of drug administration- Oral/iv/im/sc (%)*	83.15 /12.95/2.15/1.72
Age-wise classification-adult, geriatric & paediatric (%)	37.79 vs 53.99 vs 8.21
Sex distribution- male vs female ratio	1: 1.69
OPD vs In ward (%)*	80.99 vs 19.00
Urban vs rural (%)*	64.79 vs 35.20
Severity – mild/moderate/severe/fatal (%)*	10.79 /15.11/73.97/0.10
Mode of onset DID – sub acute/acute/latent(%)*	15.11/10.79/74.08
Nature of DID- serious vs non serious (%)*	80.99 vs 19.00
Type of reactions - A,B,C,D,E & unclassified (%)*	99.35/0/0.64/0/0/0
Causality as per WHO - UMC scale – certain/probable/possible/unlikely/unclassified/unassessible (%)*	0/93.95/6.04/0/0
Outcome of the DIDs - recovered/recovering/continuing (%)*	0/94.60/5.37
Management of DIDs - intervention required vs non intervention required (%)*	100 vs 0

DIDs labelled as per definition of disease. Clinical, biochemical and diagnostic detection rates depicted in the Table are the one which could not be classified as DIDs.
*$P<0.001$

depended on spontaneous nature of ADR reporting. The prevalence rate of 10.3 per cent of DIDs as reported in a French study[10] is far low in comparison to our study. This may be because their study focused on DIDs mainly reported from medicine department, unlike our study which was largely a cross-sectional study.

The females predominated in the current study with male: female ratio of 1: 1.69 and these results were in accordance with a study by Zopf *et al*[6]. Geriatric population (53.99%) accounted for maximum DIDs, similar to a study by Permpongkosol[7] where elderly patients were shown to encounter more DIDs as a result of multiple chronic diseases, multiple physicians, hospitalization, and medical or surgical procedures. Mean duration of developing DID in the current study was 26.05 days, 25.16 per cent had more than one co-morbid condition and 99.35 per cent of the total events were type A reaction. This clearly indicated that most of the DIDs could have been prevented if strict vigilance, proper periodic clinical and diagnostic monitoring were undertaken. Similar results have been reported by Ahern *et al*[8].

As far as common DIDs caused by most common suspected drugs and class were concerned, varied results were noticed on comparison with various studies. Atiqi *et al*[9] recorded cardiac disease, hypertension and gastrointestinal conditions as most common DIDs resulting due to anticoagulant treatment and use of non-steroidal anti-inflammatory drugs (NSAIDs). Gastrointestinal bleeding due to NSAID, acetylsalicylic acid and warfarin were the most common DIDs reported by Brvar *et al*[11]. Unlike our study, phlebitis at the injection site has been reported as most frequently occurring iatrogenic event in another study[12].

Thiessard *et al*[27] recorded skin and subcutaneous tissue disorders (29%), followed by nervous system

Table II a. Commonly suspected drug causing drug-induced diseases (DID)

System	Drug induced diseases	No. of events (DID)	%	Commonly suspected drugs (n=number of events)
GIT	Gastritis	177	7.43	ATT (23), acetylsalicylic acid (20), diclofenac (12) & others
	Diarrhoea	141	5.92	Inj. ceftriaxone (16), FDC (aceclofenac+chlorzoxazone+ acetaminophen) (11), azithromycin (11), amoxycillin & others
	Pancreatitis	1	0.04	ATT
	Paralytic ileus	1	0.04	Loperamide
	Upper GI bleed	19	0.8	Diclofenac (10), ibuprofen (4) & others
CVS	Hypertension	36	1.51	Prednisolone (17), deflzacort (4), etophylline+theophylline (4) & others
	Shock	2	0.08	Inj. iron sucrose, bupivacaine
	AF with embolic stroke and hemiplegia	1	0.04	Digoxin+Acenocumarol+Amlodipine
	Heart block	1	0.04	Carbamazepine
	Arrhythmia	3	0.13	Digoxin
	Hypotension	66	2.77	Inj. furosemide (11), FDC-amlodipine + telmesartan + hydrochlorthiazide (3), amlodipine 10mg (3), FDC-telmesartan + metaprolol (3) Inj etophylline+theophylline (11), Inj ceftriaxone (9) & other
	Hyponatremia and electrolyte imbalance leading to IHD	1	0.04	Carbamazepine
	Bradycardia	9	0.38	Metaprolol (7), diltiazem(1), digoxin(1)
CNS	Anxiety	34	1.43	Aceclofenac+thiocolchicoside (8), etophylline+theophylline (5), Thyroid hormone (9) , F DC(aceclofenac+chlorzoxazone+acetaminophen) (3) & others
	Peripheral neuropathy	15	0.63	ART (10), ATT(5)
	Psychosis	5	0.21	ATT (1), methylprednisolone (2), Levodopa + carbidopa (2)
	Cognitive dysfunction	2	0.08	Phenobarbitone, prednisolone
	Depression following obesity	1	0.04	Flunerazine
	Extrapyramidal symptoms	14	0.59	Metocloperamide (4), escitalopram (3)
	Seizures	12	0.50	DPT (9)
	Abnormal behaviour/self harm behaviour	4	0.17	Levodopa + carbidopa (3), pregabalin (1)
	Hallucinations	2	0.08	Levodopa +carbidopa
HBS	Hepatic dysfunction	64	2.69	ATT (33), ART (5) & others
	Hepatic encephalopathy	1	0.04	ATT
Skin	Acne	9	0.38	Steroids (9)
	TEN	1	0.04	Amoxycillin
	Measles	1	0.04	MMR vaccine
	Lipodystrophy	6	0.25	ART (4), insulin (1), bleomycine(1)
	Bullous pemphigoid	3	0.13	Co-trimoxazole
	Dermatitis	1	0.04	Phenobarbitone

GIT, Gastrointestinal tract; CVS, cardiovascular system; CNS, central nervous system; HBS, hepato-billary system; GI, gastrointestinal; AF, atrial fibrillations; IHD, ischaemic heart disease; TEN, toxic epidermal necrolysis; ATT, anti-tubercular treatment; FDC, fixed drug combination; ART, anti-retroviral treatment; MMR, measles, mumps and rubella; DPT, diphtheria pertussis tetanus

Table II b. Commonly suspected drug causing drug-induced diseases (DID)

System	Drug induced disease	No. of events (DIDs)	%	Commonly suspected drugs (n=number of events)
Renal system	Cystitis	1	0.04	Cyclophosphamide
	Renal dysfunction	24	1.01	ATT (12), Inj ceftriaxone (2)
Blood	Anaemia	114	4.79	ART (29), tirofiban (12), methotrexate (11) & others
	Thrombocytopenia	19	0.80	Enoxaparin (5), tirofiban (4), paclitaxel (2), trimethoprim/sulfamethoxazole (4) Inj vancomycin (2), quinine (2)
	Bone marrow suppression	2	0.08	Anticancer drugs (2)
	Haemolysis	1	0.04	Acetylsalicylic acid
Musculoskeletal	Osteoporosis	4	0.17	Steroids (4)
	Myalgia	25	1.05	Paclitaxel (10), Atorvastatin (10), ART(3), ATT(2)
	Septic arthritis	2	0.04	Methylprednisolone
	Athralgia	5	0.21	Paclitaxel (4)
Metabolic	Hypothyroidism	3	0.13	Carbimazole (3)
	Hyperuricemia leading to acute attack of gout	4	0.17	Prednisolone, torsemide, pyrazinamide, etophylline+theophylline
	Cushing syndrome	2	0.08	Prednisolone (2)
	Obesity	1	0.04	Risperidone
	Dyslipidemia	16	0.67	Olanzapine (5), Steroids (5), ART(6)
	Hyperthyroidism	2	0.08	Thyroid hormone (2)
	Diabetes	8	0.34	Deflazacort (3), methyl prednisolone(3), prednisalone(2)
Eye	Ocular toxicity	6	0.25	Hydroxychloroquine (6)
	Optic neuritis	3	0.13	ATT (3)
	Loss of vision	1	0.04	ART
Gynaecological	Amenorrhoea	6	0.25	5-fluorouracil in combination (3)
	Menstrual dysfunction	2	0.08	Deflazacort (2)
	Menorrhagia	1	0.04	Misoprostol
Immunological	Vasculitis	4	0.17	Levofloxacin (1), co-trimoxazole (1)
	IgA nephropathy	2	0.04	Tacrolimus + mycophenolate
Chest	Exacerbation of COPD	1	0.04	Nimesulide + paracetamol
	TB chest Consolidation	5	0.21	Deflazacort(1), Prednisolone (1), Hydroxychloroquine+ methotrexate+sulfasalazine (1), Methotrexate+sulfasalazine+leflunamide (1)
ENT	Allergic rhinitis	1	0.04	Ibuprofen
Others	Multi-organ failure	3	0.13	Inj. Iron sucrose, diclofenac, bupivacaine
	DRESS syndrome	1	0.04	Carbamazepine
	Oligospermia	2	0.08	Acyclovir (2)
	Secondary infections	19	0.8	Steroids (9), ceftriaxone (4)& others

DRESS, drug reaction (or rash) with eosinophilia and systemic symptoms

(19%), gastrointestinal (12%), blood and lymphatic system (12%) and vascular disorders (12%) as most common DIDs in their study. Peripheral neuropathy, anaemia, hepatitis and gastritis were the most prevalent DIDs with use of highly active anti-retroviral therapy (HAART) treatment in the study of Anwikar *et al*[28]. Rather *et al*[29] reported anaemia, hepatic toxicity, itching, skin rash, elevated triglycerides and peripheral neuropathy to be the most common DIDs in their study due to ART. Common cardiovascular adverse drug events reported were drug-induced arrhythmias, blood pressure abnormalities and heart failure[22]. The specific drug-induced events included bradycardia, tachycardia, corrected QT interval prolongation, hypertension, hypotension and heart failure exacerbation. In the present study hypotension, hypertension, bradycardia, arrythimias and irregular pulse were recorded as common cardiovascular DIDs.

Drug-induced immune haemolytic anaemia has been commonly reported in few studies[17,18] with cefotetan, ceftriaxone, and piperacillin. However, ART, tirofiban and methotrexate were most commonly offending agents to cause anaemia in our study.

Enoxaparin, tirofiban, paclitaxel, trimethoprim/ sulphamethoxazole, injection vancomycin and quinine were responsible for thrombocytopenia, as also reported by Arnold *et al*[19]. They recorded quinine, quinidine, trimethoprim/sulphamethoxazole and vancomycin as the most common culprit for drug induced thrombocytopenia.

Anti-tuberculosis treatment (ATT) induced hepatic and renal dysfunction were common DIDs in our study which were in accordance to Tariq *et al*[20]. However, our results were in variance to the results of another study[21] where antidepressants were shown to be associated with causing hepatotoxicity. Paroxetine, fluoxetine, fluvoxamine, citalopram, mirtazapine and venlafaxine were associated with reversible liver injury. This was because their field of research was exclusive with anti-depressants unlike ours which was a cross-sectional study.

The major limitation of the current study is that it does not represent the true prevalence of the problem due to voluntary/spontaneous nature of reporting. Risk factor correlation was not done in the current study. The present data were generated by spontaneous reporting system as proposed by PvPI. Thus, there might be many other confounding factors which could have affected the final outcome of the study. There exist a lot of variations in the trends of DIDs reported worldwide. Such studies carried out across the country in future shall go long way to provide clinicians and policy regulators valuable information about DIDs which can be largely prevented in the interest of patient safety.

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