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From the Editor's Desk . . . . ✍

Dear Friends and Colleagues,

Our small attempt to create awareness in pharmacovigilance, through this bulletin, is about to complete 7 years now with this issue.

We highly appreciate your views and comments which has helped us to bring about improvement in the presentation of these issues.

This issue contains 2 review articles which are more so related and relevant especially to the geriatric population, along with the others. These articles give an overview of the common drugs, conditions and few measures for preventing adverse reactions in vulnerable populations.

Other features in this issue include analysis of the ADRs from our institute for your quick review, an interesting case, current news related to drug regulatory news and puzzles.

I hope the readers find all the sections of this bulletin interesting and informative.

We would like to thank all the authors who have contributed to this bulletin over the span of 7 years and to elaborate upon the adverse drug reactions including the prevention and treatment. We would also like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance. Finally, we would like to thank to all the members of Department of Pharmacology for their efforts in bringing out the current issue of this bulletin.

Thank you,

Dr. Sudhir Pawar

PREVENTING ADVERSE DRUG REACTIONS IN GERIATRIC POPULATION

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Introduction

The United Nation (UN) has defined geriatric population as those who are above the cut off age of 60 years.[1] There is a rapid growth in geriatric population worldwide. By 2050 the elderly population is expected to reach 1.4 billion and will buy 50% of prescription drugs. Various studies have also shown that consumption of medication increases with age and that many elderly use at least three prescribed drugs concurrently.[2,3] As a result, elderly people are at higher risk of adverse drug reactions (ADRs) and drug-drug interactions. These people have special problems regarding their health, social support and economic security.

There are many physiological changes that occur in geriatric people, which affect pharmacokinetics and pharmacodynamics of drugs.[4] Hence it is essential to monitor drug effects, especially the ADRs and drug interactions in these patients. It has been found that 35% of ambulatory older patients experience an ADR of which 29% require health care services. Thus 40% health service expenditure is spent on geriatric people.[5] Physicians should be aware of the normal age related physiological and pharmacological changes taking place in geriatric people. This will help to prevent irrational drug prescribing, minimize ADRs and maximize benefits of medications to elderly patients.

Pharmacokinetic changes in elderly[5]

Drug absorption decreases in elderly due to various changes in gastrointestinal(GI) tract such as decreased blood flow, reduced absorptive surface area and reduced gastric secretions. Absorption of basic drugs like propranolol is enhanced due to decreased gastric acidity.

Lean body mass decreases and there is increase in total body fat/water ratio. As a result there is wider distribution of lipid soluble drugs requiring higher dose eg:- diazepam. Volume of distribution of water soluble drugs is decreased requiring low dose eg:- aminoglycosides, digoxin. The elderly patients with congestive heart failure require lesser loading and maintenance doses of digoxin.

There is decrease in plasma albumin levels which results in increase in percentage of unbound drug. This is especially important for drugs like phenytoin with high albumin binding. In a patient with normal renal function, 92% of phenytoin is bound to plasma protein and 8% is in free form. This free form increases to 16% in renal impairment, thus producing ADRs. However α-1-acid glycoprotein which binds to basic drugs increases with aging and binding of basic drugs like antidepressants, antipsychotics increases resulting in decreased free drug level and reduced action. Hence, theoretically speaking, the

dose of acidic drugs like phenytoin need to be decreased to prevent ADRs and dose of basic drugs need to be increased to prevent therapeutic failure.

Drug metabolism also decreases with age as there is reduced blood flow to the liver and decreased production of liver enzymes. This can result in prolonged half life of drugs requiring reduction in dose of drugs eg:- amlodipine, diltiazem. Renal function decreases with age, which results in increased duration of action of drugs. Hence dose of the drugs which are primarily excreted through kidneys should be reduced eg:- digoxin, penicillins etc.

Pharmacodynamic changes in elderly[5]

The end organ response to a drug is increased in elderly resulting in toxicity at normal therapeutic doses. The enhanced sensitivity is seen with commonly used drugs like non-steroidal anti-inflammatory drugs, opioids, benzodiazepines, antipsychotics and anti-parkinsonian drugs. Postural hypotension is frequent in elderly people and may be exacerbated by many drugs. The pathogenesis is multifactorial and includes decreased baroreceptor response, altered sympathetic activity and impaired vasomotor response in both arterioles and veins. Phenothiazines, tricyclic antidepressants, levodopa and antihypertensive drugs are frequent causes of postural hypotension in elderly people. Hence, care should be taken to reduce the dose while prescribing these drugs in elderly.

Table 1. Comparison of drug doses for adults vs. elderly[5]

Drug	**Average daily dose (mg)**	
	Adult	**Elderly**
Alprazolam	0.5-6	0.25-3
Diazepam	5-30	2-15
Lorazepam	1-6	0.5-3
Chlordiazepoxide	25-100	5-50

Drug-Drug Interactions[6]

The risk of drug-drug interactions increases with age and number of drugs used. These interactions can affect pharmacokinetics or pharmacodynamics. In pharmacokinetic interactions, one drug affects absorption, distribution, metabolism or excretion of another drug. Pharmacodynamic interactions occur when one drug changes the response to other drug. Some common drug-drug interactions in elderly patients are described in Table 2.

Table 2. Common drug-drug interactions in elderly patients[6]

Drug 1	Drug 2	Potential Outcome
Angiotensin converting enzyme inhibitors	Non-steroidal anti-inflammatory drugs	Hyperkalemia, decline in renal function
Digoxin	Furosemide	Hypokalemia and increased risk of digitalis intoxication
Nitroglycerine	Sildenafil	Severe hypotension
Verapamil	Atenolol	Bradycardia and hypotension
Warfarin	Acetylsalicylic acid	Increased risk of bleeding
Spironolactone	Potassium chloride	Hyperkalemia

In order to reduce the risk of adverse drug effects in geriatric patients, we require close monitoring of functional status, early identification of symptoms, and recognition of the impact a medication can have on multiple organ systems.

Some of the following measures can be taken into account to reduce ADRs.

a. Non-pharmacological measures

Before starting treatment, non-pharmacological measures should be tried.[7] These measures include alteration in life style, regular walking, reduced salt intake, cessation of smoking and alcohol consumption. Early stage of diabetes should be managed with measures like proper diet, exercise, weight reduction etc.

b. Choosing the appropriate drug[7]

If the patient needs pharmacological treatment, most efficacious drug with less ADRs should be selected. Co-morbidities like renal failure, hepatic failure, cardiac failure, diabetes mellitus and hypertension should also be taken into consideration eg:- Beta-blockers should not be used in hypertensive patients with asthma.

A diuretic is a good first step in treating hypertension in the elderly, and a thiazide or thiazide-like diuretic is usually the most suitable to use. However, some extra care is appropriate because of their sensitivity to diuretics. Inappropriately high doses may provoke hypotension, electrolyte disturbances or uremia. Hypokalemia is less likely to occur when a diuretic is combined with a potassium conserving diuretic (spironolactone, amiloride). Diuretics may be contraindicated in subjects with gout, hyperuricemia, diabetes, or renal impairment. Alternatively, a calcium channel blocker, an ACE inhibitor or angiotensin II receptor blocker can be used at the first step.[8]

c. Dose adjustment

Standard dose of a drug should be adjusted in elderly people considering their decreased hepatic and renal function. Table 3 shows the examples of drugs requiring dose adjustment in elderly people.

Table 3. Drugs requiring dose adjustment in elderly[6]

Drugs requiring dose adjustment	Reason for dose adjustment	Dose adjustment
Digoxin	Clearance is decreased and its half life is prolonged.	Loading and maintenance doses need to be reduced.
Penicillins, cephalosporins, aminoglycosides	Half life is prolonged due to decrease in renal function.	Dose reduction
Lithium	Renal toxicity	Dose reduction and therapeutic drug monitoring
Sedatives- diazepam, chlordiazepoxide, barbiturate	Prolongation of half life due to age related decline in hepatic and renal function	Dose reduction

d. Formulation[7]

Prescribing drugs in the form of syrups, suspensions and effervescent tablets can improve adherence in elderly as they find it easy to swallow. Following measures should be taken to improve compliance in elderly people :

- Reduce dose frequency and use long acting dosage forms.
- Use combination medications.
- Introduce reminder strategies such as pill organizers, calendars, phone reminders etc.
- Involve family members
- Educate the patient about disease process and treatment.

e. Maintaining record and periodic review

Maintaining a drug record will help to check adherence, possible drug interactions, ADRs and the economic burden of the patient. Patients receiving long term therapy should be reviewed carefully to assess the need for the drug. Depending on the disease condition, the drug can be either stopped or changed.

The old maxim "start low and go slow" plays an important role while prescribing drugs to geriatric

patients.[9] The tendency to treat every symptom with a drug should be avoided to prevent adverse drug reaction in geriatric patients. Various non-pharmacological measures should be used as far as possible before initiating pharmacotherapy. The number of drugs per patient should be reduced in order to prevent drug-drug interactions and adverse drug reactions. Polypharmacy should be avoided in geriatric patients.

Regular medical follow-ups of these patients should be done in order to check for compliance, ADRs, efficacy, etc.[9] Compliance should be checked by various methods like pill counts, patient questionnaires, assessment of patient's clinical response, measurement of level of drug/metabolite in drug or urine etc.

Table 4. Various tools to assess medication adherence [10]

Pill count	• Compares the number of doses remaining in the patient's supply with the number of doses that should be present.
Patient Estimates of Adherence	• Direct questioning of patients to assess adherence can be an effective method.
Scaled - Questionnaires	• Brief Medication Questionnaire (BMQ) was developed to assess patients at risk for medication non-adherence, and includes the regimen screen, belief screen, recall screen, and access screen.
	• Morisky et al. developed an 8-item-scaled questionnaire to assess adherence with antihypertensive treatment.

Clinical Tools

BEERS CRITERIA[11,12]

The Beers criteria are the guidelines for the clinicians to help improve the safety of prescribing drugs for geriatric patients. They emphasize deprescribing medications that are unnecessary, which helps to reduce polypharmacy, drug-drug interactions, and ADRs. They are comprised of two comprehensive lists of medications to be avoided in older adults, one list independent of diagnosis and the other considering the diagnosis. A third list contains medications to be used with caution. These criteria are used in geriatrics clinical care to monitor and improve quality of care.

STOPP AND START CRITERIA[13]

Potentially inappropriate medications, defined by the validated STOPP (screening tool of older persons potentially inappropriate prescriptions) criteria, are significantly associated with avoidable adverse drug events that cause or contribute to urgent hospitalization in geriatric people.[13] The STOPP criteria comprise of 65 clinically significant criteria for potentially inappropriate prescribing in geriatric people.

The STOPP criteria represent the more common avoidable instances of inappropriate prescribing in geriatric people in day-to-day clinical practice.[13]

The STOPP criteria are designed to be used in tandem with the START (screening tool to alert doctors to right treatment) criteria. The START criteria represents the more common instances of inappropriate omission of potentially beneficial medications. The START criteria consist of 22 evidence-based prescribing indicators for commonly encountered diseases in older persons.

Table 5. Using Clinical Tools to Detect Potentially Inappropriate Medications [14]

Case example[14]

An 85-year-old white woman with metabolic syndrome and heart failure comes to the clinician. She also has a history of seizures, anxiety, depression, and alcoholism, weighing 110 lb (50 kg) and has a serum creatinine level of 1.0 mg per dL.

Current medications for case example	Clinical tools		Comments
	Beers criteria	STOPP criteria	
Alprazolam, 1mg orally three times daily	Avoid benzodiazepines (any type) for treatment of insomnia, agitation, and delirium All benzodiazepines increase the risk of falls, fracture, cognitive impairment, delirium, and motor vehicle crashes in older adults	Potentially inappropriate to use long-acting benzodiazepines (e.g., chlordiazepoxide, flurazepam, clorazepate) and benzodiazepines with long-acting metabolites (e.g., diazepam) for longer than one month because of the risk of prolonged sedation, confusion, impaired balance, and falls Also potentially inappropriate to use benzodiazepines in patients who fall, because the sedative may cause reduced sensorium and impair balance	Because of significantly increased risk of falls in older adults, benzodiaze-pines should be weaned and dis-continued

Geriatric patients also use number of herbal drugs and dietary supplements. A significant consequence resulting from multiple use of drugs, herbal products and nutritional supplements together is the potential for drug-drug (DDI) and drug herb interactions among the various products.[15,16] Further research needs to be done on identifying potential drug-herbal and drug-drug interactions. There are number of free and low-cost software systems (eg:- Micromedex, medscape, lexi-interact etc.) which identify potential drug-drug interactions.

Conclusion

Drug therapy in older patients varies from that of adults due to altered physiological functions, altered pharmacokinetics and pharmacodynamics, co-morbidities, age related disability, loneliness and stress. A number of precautions should be taken while prescribing drugs in geriatric patients. The success of a drug therapy in geriatrics depends upon considering these factors in addition to correct diagnosis, treatment, patient education and dose adherence. It is also advised to regularly use a standardized method to review patient medications (eg:- Beers criteria, STOPP and START criteria) for better and safer patient outcome.

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POLYPHARMACY AND ADVERSE DRUG REACTIONS

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Introduction

Increased availability of many new drugs in the armament of health care system is one of the causes for increased lifespan of individuals. But in many individuals increased life span is frequently accompanied by multimorbid states like hypertension, diabetes, arthritis, renal and central nervous system related disorders especially in geriatric population.[1] This is followed by prescription and subsequent consumption of multiple drugs by patients. A prospective study conducted by Veehof et al found 42% incidence of polypharmacy during his follow up of 1,544 elders for three years.[2] In addition to it, sometimes in same individual various drugs for different comorbidities are being prescribed by respective specialists and also patients many a time take complimentary medications like pain killers or vitamins and herbal products without making physician aware of it. All these circumstances resulted in increased medication errors and polypharmacy as reported by several authors.[3] Such use of multiple drugs often end up in effective drug therapy, loss of resources, increased morbidity and mortality, cost of the treatment, adverse drug reactions (ADRs) and drug interactions.

What is polypharmacy?

Term 'polypharmacy' is often used in literature but its precise definition is still lacking and varies from author to author. Polypharmacy is defined as use of five or more medications.[4] Few authors defined it as 'where medication did not match diagnosis'.[3] As per the WHO, polypharmacy refers to the use of multiple medications by a patient or more drugs are prescribed than clinically warranted.[5] Sometimes polypharmacy can be justifiable in cases where all prescribed medications are clinically indicated but are too many to take, which is commonly called as 'pill burden'. But many times polypharmacy has failed to achieve targeted goals of therapy and has resulted in unfavourable consequences.

Epidemiology of polypharmacy:

One of the surveys from US indicated that 25% of the overall population takes 5 or more medications per week. When considered population >65 years of age, about 50%, with 44% of men and 57% of women taking 5 or more medications per week and 12% of both sexes taking 10 or more medications per week.[6] Similarly a Brazilian study in elderly found polypharmacy in 33.3% with antihypertensive agents (53.3% of total medications) as the most commonly used drugs.[7] Indian study by Romana et al, found mean use of drugs in elderly population was around 8 with 38% of patients receiving 9 or more drugs.[8]

Types of polypharmacy: It is classified into two main types[9]

1. Therapeutic polypharmacy:

Here multiple drug regimens are prescribed based on associated comorbidities and all the regimens are carefully monitored, e.g. combination therapy of isoniazid, rifampin, ethambutol and pyrazinamide used in the treatment of tuberculosis. Multiple drug therapy is needed to achieve intended therapeutic goal with additional agents occasionally (e.g. pyridoxine with anti-TB drugs) to prevent side effects of prescribed drugs.

2. Contra-therapeutic Polypharmacy:

Here individual experiences unanticipated/unintentional adverse effects while patient is on unmonitored drug regimens. e.g. if the patient receives valproate and carbamazepine (CBZ) at the same time, valproate blocks metabolism of CBZ (i.e. hydrolysis of CBZ) which may cause neurotoxicity later due to higher concentration attained.

Classes of Polypharmacy [9]:

1. Same-class polypharmacy:

When multiple drugs belonging to same drug class are used. E.g. two selective serotonin reuptake inhibitors, such as fluoxetine plus paroxetine.

2. Multi-class Polypharmacy:

Use of multiple drugs from different classes for the same clinical condition. E.g. the use of lithium along with an atypical antipsychotic such as fluoxetine plus olanzapine.

3. Adjunctive Polypharmacy:

Use of one drug to treat the side effects or secondary symptoms of another drug from different classes. E.g. use of trazodone along with bupropion for insomnia.

4. Augmentation:

Use of drug at a lower than normal dose along with another medication from a different drug class at its full therapeutic dose, for the same clinical condition. E.g. the addition of low dose of haloperidol in a patient with a partial response to risperidone.

5. Total Polypharmacy:

Total number of drugs used in a single patient i.e. total drug load. Consideration of total polypharmacy should include prescription medications, over-the-counter medications, alternative medical therapies and herbal products.

Causes of Polypharmacy[10]:

- Elderly patients associated with multiple co-morbidities that warrant multiple medications.
- Patients themselves taking over-the-counter (OTC) and other medications and herbal preparations without being aware of their efficacy and adverse reactions.
- Patients frequently visit several physicians and often fail to reveal previous prescriptions and continue to take all medications prescribed by each physician.
- Many a time patients themselves demand for medications like vitamins and minerals and analgesics etc. without their actual need.
- Sometimes side effects of one drug can be misinterpreted as symptom of a disease and more drugs might get added into the list of previous drugs for the relief of that symptom. Few examples are mentioned in table below.

Side effect	Common drugs causing side effect	Common drugs treating side effect
Constipation	-Tricyclic antidepressants - Verapamil or diltiazem - Opioid analgesics - Calcium supplementation	- Psyllium - Docusate/senna - Lactulose
Insomnia	- Prednisone, pseudoephedrine - Stimulants, antidepressants - Theophylline	-First-generation antihistamines - Benzodiazepines - Zolpidem, zaleplon
Cognitive impairment	- Antihistamines - Opioid analgesics - Benzodiazepines	- Donepezil - Rivastigmine - Galantamine - Memantine
Diarrhea	- Metformin - Antidepressants - Antibiotics	- Loperamide - Diphenoxylate

Consequences of polypharmacy:

Near about every drug is associated with some side effects or ADR and the chances of it increases with increase in number of each new additional drug. The chances of occurrence usually increase

when 5 or more drugs are consumed simultaneously. Older patients living with more chronic diseases requiring multiple drug therapies are often at the risk of ADRs, drug-drug and drug-disease interactions.[11]

Consequences of polypharmacy can be summarised as[12]:

Advantages	Disadvantages
Prophylactic drugs counter side effects of other drugs prescribed	Increase risk of drug-drug, drug-disease interactions
Increase adherence due to lower side effects	Increase incidence of adverse drug reactions resulting in hospitalisation and rarely death
Increased disease control due to multiple targets resulting in increased life span of patient	Higher risk of poor compliance
Reduction in symptoms	Higher medication error risk
It is advisable in conditions like TB, AIDS or H. pylori infection	Higher mental and economical stress on the patients and his family

Polypharmacy and adverse drug reactions (ADRs):

Major ensuing harm associated with polypharmacy is increased risk of adverse drug reactions that increases with addition of each prescribed drug. A population based study conducted by Bourgeois et al in an outpatient setting observed that those taking 5 or more drugs have an increased risk of adverse drug events by 88% compared to those taking fewer drugs.[13]

Risk Factors: All these factors directly or indirectly responsible for adverse drug reactions due to polypharmacy

1. Paediatric population: physiological immaturity of drug metabolising enzyme systems and excreting organs is mainly held responsible for these insults.
2. Geriatric population: many physiological factors play vital role viz. decreased renal elimination, decreased hepatic function, decreased total body water and lean body mass.

3. Aging : With increasing age there is reduction in liver size by 25-35% with reduced hepatic blood flow by more than 40%. It subsequently results into decreased first pass metabolism and clearance of the drug.[14] This leads to increase in drug concentration (bioavailability) at normal doses which may be responsible for adverse reactions (e.g. propranolol) for which dose reduction warranted. All these changes result in alterations of pharmacokinetics of the drugs including altered volume of distribution and half-life and the likelihood of causing ADR.

4. Other factors contributing to it are pathophysiological changes due to disease itself, other associated comorbidities and different physicians prescribe different drugs to same patient.[3]

The polypharmacy associated ADRs are also extended to health care cost. A study by Hovstadiuset al, reported 6.2% increase in the prescription drug expenditure among those taking 5 or more medications while it was increased by 7.3% in those taking 10 or more medications.[15] Several authors have shown that increase in the occurrence of ADRs associated with increased consumption of medications resulting in the increased incidence of hospitalisation especially in elder population.[1] These ADRs resulted in falls due to functional decline, impaired cognition and other adverse events. A prospective study revealed that use of 4 or more medications was associated with increased risk of falling and recurrent falls.[16] This risk of falls is especially increased with use of diuretics, anti-arrhythmics or psychotropic drugs as concluded by a meta-analysis carried out by Leipzig et al.[17]

Measures to prevent polypharmacy and subsequent ADRs[1, 18]:

To avoid detrimental and expensive consequences due to adverse drug reactions associated with polypharmacy,

- Minimising or avoiding prescriptions for minor, non-specific or self-limiting complains.
- Accurate drug history must be taken prior to prescribe any new medication.
- Before prescribing drug following points must be considered
    - Is there really a need of additional drug
    - Efficacy of particular drug in that age group of patient especially for patients at extremes of ages
    - Chances of occurrence of ADRs and drug-drug interactions in that particular patient considering his pathophysiological state
    - Discuss risk-benefit analysis with the patient and then decide new regimen considering every aspect of comorbid conditions and drug PK-PD and side effect profile.
- Monitor the patient very carefully who are taking multiple drugs especially elderly people who are often excluded from clinical trials and have high potential to experience adverse drug reactions. This can be done by using tools like ARMOR, a tool to evaluate polypharmacy in elderly

patients.[18] It is a stepwise approach seen for initial assessment of patients taking multiple drugs and also for falls/behaviours or patients admitted for rehabilitation and includes the following.

- A = Assess the individual for total number of medications and for certain group of medications that have potential for adverse outcome e.g. beta blockers, antidepressants, antipsychotics, pain medications etc.
- R = Review for possible drug-drug and drug-disease interactions.
- M = Minimize nonessential medication and eliminate medications that clearly lack evidence for their usage.
- O = Optimize by addressing duplication, redundancy, adjust drugs according to the hepatic and renal functional status etc.
- R = Reassess heart rate, blood pressure (postural), oxygen saturation at rest and activity.

- Increasing awareness among treating physicians and also patients regarding the polypharmacy and subsequent adverse drug reactions and drug-drug interactions.
- Patients or in general people should be convinced regarding revealing all facts about disease and every drug taken by him from different physicians and also should be discouraged from taking alternative or over-the-counter drugs.
- There should be better communication between physician, pharmacist, nurse and patients
- Multidisciplinary teams, regular medication and reconciliation review can identify and reduce medication related problems.
- Guidelines should be developed regarding use of various drugs in multimorbid conditions for different age groups. The British Geriatrics Society and NICE have declared intentions to develop guidelines that consider multi-morbidity.[19]

Conclusion:

Polypharmacy is a double edged weapon, appropriate use of it with better understanding of the outcomes is always beneficial. Adverse drug reactions are common and costlier complication of polypharmacy need to be dealt appropriately and measures should be taken to minimise at both physician and patient level. Education and strategies that will enable practitioners to attain successful polypharmacy must be developed and shared.

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ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED

(July 2017 to October 2017)

Compiled by Swati Vaidya

Technical Associate, PvPI; Department of Pharmacology, LTMMC and GH, Sion, Mumbai

Total Case Reports: 118

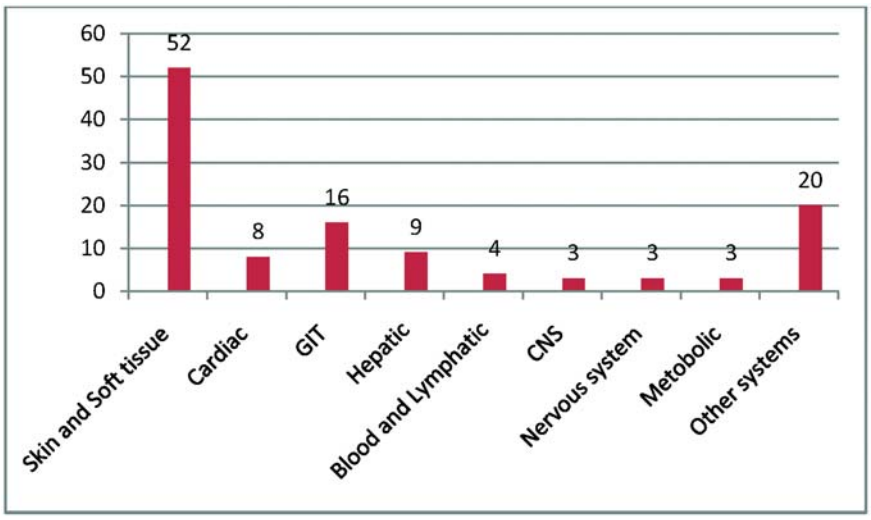
I. Age and Gender distribution:

Age groups	Number of patients	Males	Females
<3 yrs	8	5	3
3 - 17 yrs	36	15	21
18 - 44 yrs	49	16	33
45 - 60 yrs	18	8	10
>60 yrs	7	2	5
Total	118	46	72

II. Seriousness of the reaction:

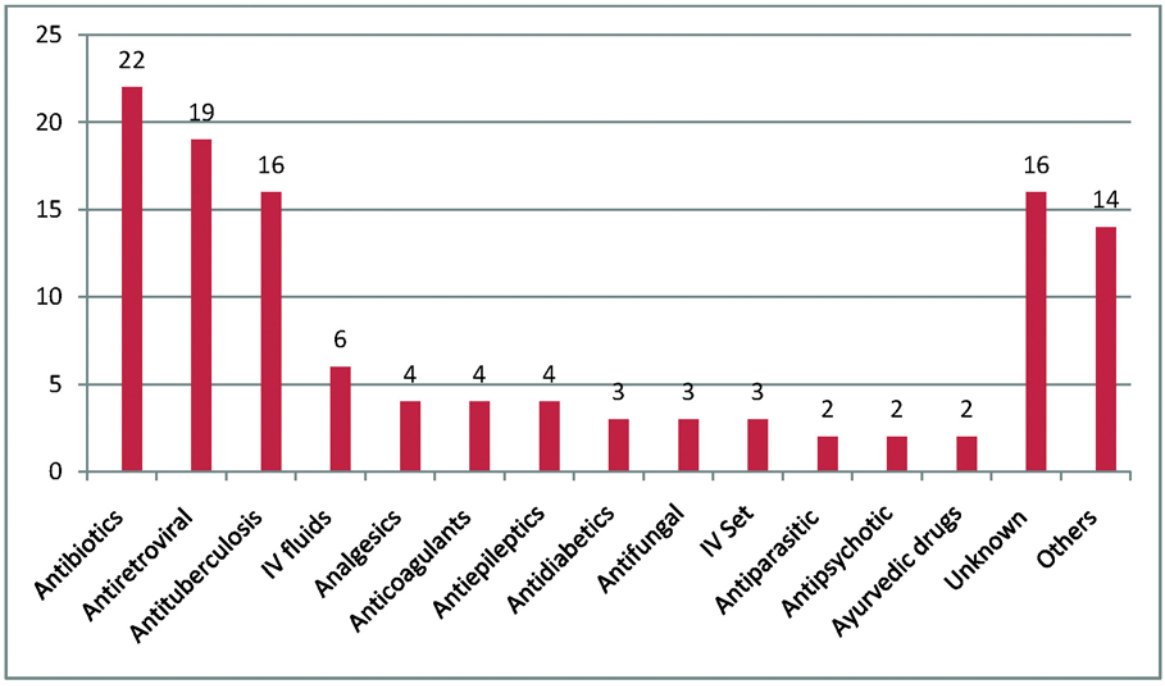
Seriousness of the ADR	No. of Cases (N=118)
Yes	100
No	18

III. System involved in the ADR : N=118



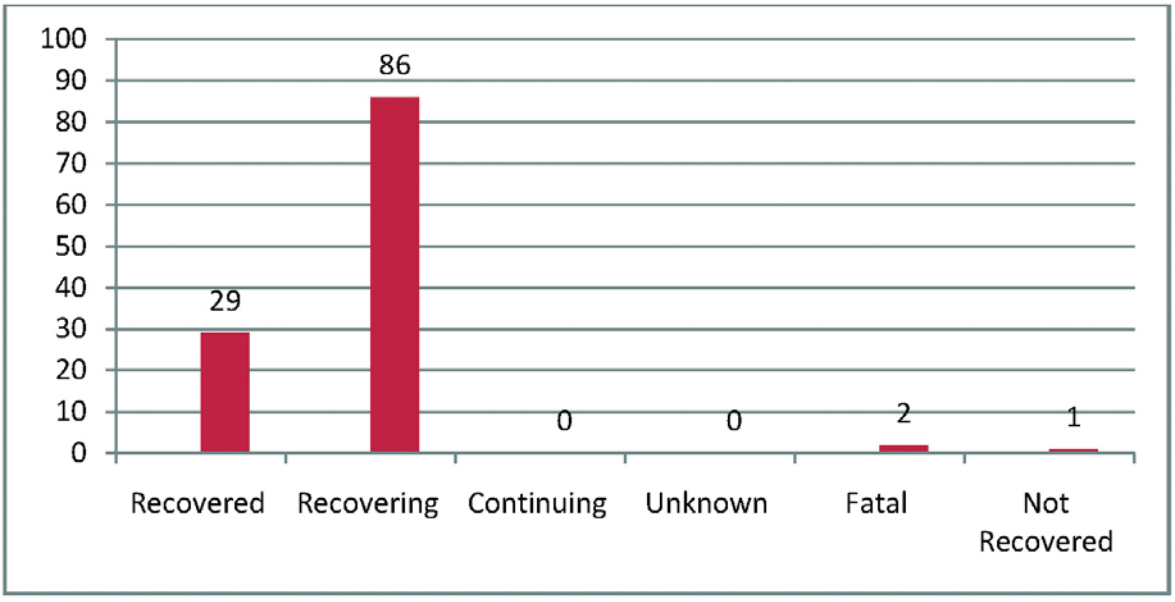
Other system fever with or without chills, immunological, renal system, respiratory system, electrolyte disorder and ocular system.

IV. Class of the Suspected drug: N=120

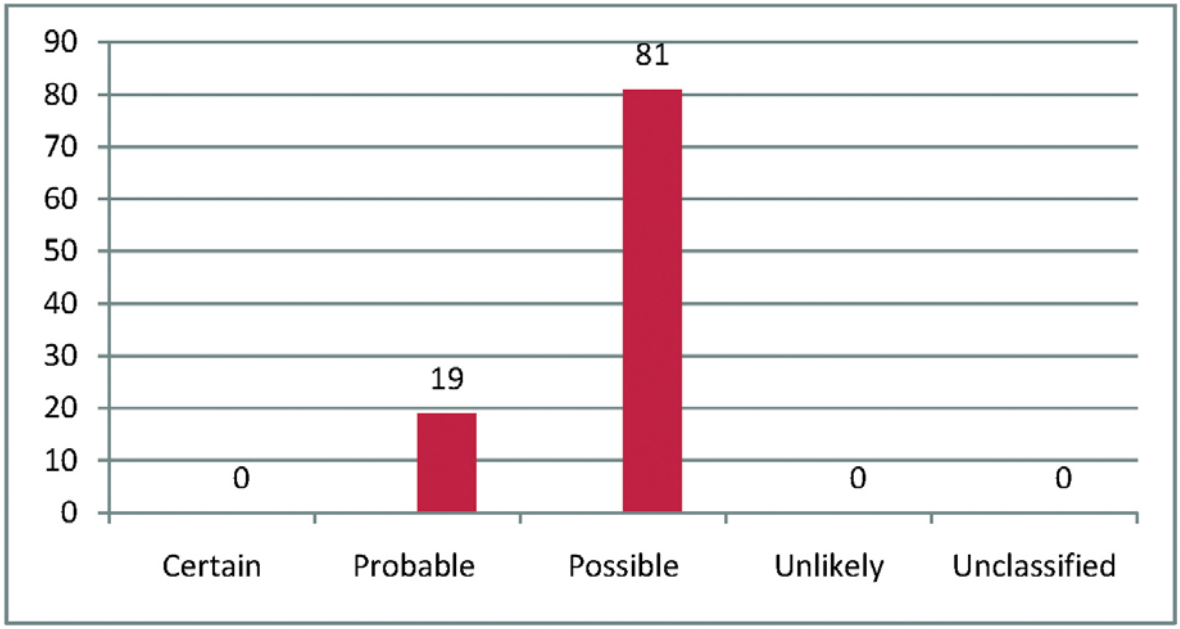


Others include one ADR each of anesthetic agent, antigout agent, antihypertensive agent, antimalarial agent, antiplatelet agent, antisnake venom, blood products, bronchodialater, corticosteroids, hematinic, thyroid hormone replacement, proton pump inhibitor and vitamin supplement.

V. Outcome of the reaction : N=118



VI. Causality Assessment (WHO UMC Classification): N=118



No Causality assessment was done for unknown drugs - 18

EVALUATION OF A CASE

Dilated Cardiomyopathy induced by Zidovudine-based Antiretroviral Regimen

Dr. Nayana Nair

Second Year Resident, Department of Pharmacology, LTMMC and GH, Sion, Mumbai

Introduction

Cardiomyopathy is a general term that refers to the various abnormalities of the heart muscle. Dilated cardiomyopathy (DCM) is a progressive disease of heart muscle that is characterized by ventricular chamber enlargement and contractile dysfunction.[1] Dilated Cardiomyopathy is idiopathic on most cases or could have be related to genetic mutations, certain toxins, viral infection, drug induced, etc. Acquired immunodeficiency syndrome (AIDS) patients treated with HAART (Highly active antiretroviral therapy) have shown significantly reduced morbidity and mortality, but has also resulted in an increase in cardiac and skeletal myopathies[2]. In a study, Patel et al found that during the HAART era (1996-2007) there was decrease in the incidence of cardiomyopathy by 6-fold among children infected perinatally with human immunodeficiency virus (HIV) when compared to the pre-HAART era (1993-1995). Later it was documented that with use of Nucleoside reverse transcriptase inhibitors (NRTI's) like (Zalcitabine) there was 80% higher incidence of cardiomyopathy. Zidovudine-containing antiretroviral regimen has also shown increased risk of cardiomyopathy.[3]

The present case describes details of a 7-year-old boy who developed cardiomyopathy 4.5 years after initiating antiretroviral therapy.

Case

A 7-year-old immunocompromised patient presented with dyspnoea on exertion, decreased appetite and irritability since the last 10 days. He was diagnosed with HIV at 3 years of age. He was started on fixed dose combination of zidovudine 60 mg and lamivudine 30 mg twice daily along with efavirenz 300 mg once a day orally. His father was seropositive and mother's status was unknown. On further examination he was detected positive for pulmonary tuberculosis for which he was started on Cat-1 regimen simultaneously. Patient successfully completed full course of antitubercular treatment 2 years ago.

On general examination patient was afebrile and having generalised weakness and pallor. Blood pressure was 92/70 mm Hg, pulse rate was 84 beats/min and respiration rate were 26 breaths/min. Urine output was decreased. Arterial oxygen saturation measured noninvasively by pulse oximetry was 99% while on room air breathing. Auscultatory findings for heart sounds were normal with no murmur. Laboratory parameters for liver function test were normal except for serum aspartate transferase, alkaline phosphatase and lactate levels which were raised. CD4 count was significantly decreased. (Table No 1)

Table 1. Laboratory investigations at the time of admission

Laboratory parameters	Value	Normal range[4]
Aspartate transferase (AST)	80 IU/L	10 - 40 IU/L
Lactate	2.5 mmol/L	0.5-1 mmol/L
Alkaline phosphatase	797 IU/L	108 - 306 IU/L
Blood bicarbonate levels	36.9 mEq/L	24 - 34 mEq/L
CD4 absolute count	56 cells/mm^3	500-1,500 cells/mm^3
CD4%	1.64%	25% to 65%

Chest radiography revealed cardiomegaly and pulmonary vascular redistribution. ECG changes revealed sinus tachycardia, left atrial enlargement, left ventricular hypertrophy, deep Q waves with ST segment depression. Echocardiography findings were suggestive of marked left ventricle dilatation with global hypokinesia. Left ventricular ejection fraction was 15 - 20% and diffuse left ventricular hypokinesia was observed. Left ventricular walls were thin and areas of dyskinesis were observed with severely compromised left ventricular systolic function. The left atrium was dilated, and mitral valve leaflets showed sluggish movement. Doppler studies showed varying degrees of mitral regurgitation secondary to left ventricular dilation and papillary muscle dysfunction which was suggestive of dilated cardiomyopathy.

Congenital and acquired heart diseases leading to cardiomyopathy secondary to severe aortic stenosis, coarctation of aorta or congenital mitral valve dysplasia, and anomalous left coronary artery arising from pulmonary artery (ALCAPA) were excluded. Serological tests for cardiotropic viruses (coxsackievirus, adenovirus, herpes simplex virus, respiratory syncytial virus, and Epstein-Barr virus), toxoplasma gondii, chlamydia trachomatis and chlamydia pneumoniae were all negative. The results of blood cultures and tests for cytomegalovirus antigenemia were also negative, ruling out the infectious aetiology leading to dilated cardiomyopathy.

Patient recovered 6 months after changing the antiretroviral regimen to lamivudine 30 mg, abacavir 60 mg, and efavirenz 300 mg. Patient was also given injection dobutamine 10mcg/kg/min once a day for 3 days, furosemide 13mg IV BD, injection ondansetron 2 mg IV SOS for the management of DCM related symptoms.

Although AIDS itself could be associated with cardiomyopathy, development of DCM showed reasonable temporal relationship to zidovudine intake in this case. Concomitant administration of lamivudine to this patient along with zidovudine is known to increase the plasma concentration of zidovudine contributing to its mitochondrial toxicity.[5] Considering these factors causality of this adverse

drug reaction is POSSIBLE as per WHO UMC (World Health Organization Uppsala Monitoring Centre) causality scale & NARANJO scale.

Discussion

Overall incidence of dilated cardiomyopathy in HIV patients in India is around 9.25 %.[6] In HIV-infected patients receiving HAART therapy that includes zidovudine has shown an increased prevalence of DCM.[7]

Dilated cardiomyopathy can appear as a spectrum of no symptoms, subtle symptoms or can develop life-threatening problems such as arrhythmias, congestive heart failure. Infants and young children usually have irritability, failure to thrive, increased sweating especially with activities, pale colour, faster breathing and/or wheezing. Our patient presented with the similar symptoms.

Several mechanisms have been proposed for HIV-associated cardiomyopathy. The presence of HIV can cause cardiac damage because of direct infection of cardiac myocytes.[8,2,9,10] Mitochondria are the primary target of the toxic effects of zidovudine as shown in many studies.[11,12] The zidovudine-induced cardiomyopathy is thought to be a mitochondrial toxicity caused by depletion of mitochondrial DNA. Mitochondrial toxicity inhibits HIV reverse transcriptase and DNA polymerase gamma. These enzymes are responsible for mitochondrial DNA replication.[13,14] High concentration of lactate suggested mitochondrial damage, probably induced by zidovudine.[14] The rank order of the effects of NRTIs inhibiting DNA polymerase gamma varies within different human tissues but relatively consistent, with zalcitabine, which are no longer in use, associated with the greatest degree of mitochondrial toxicity, followed by didanosine, stavudine, and zidovudine[13] Concomitant use of lamivudine with zidovudine increase the plasma concentration of zidovudine and can cause mitochondrial toxicity.[5] Use of lamivudine along with zidovudine is a risk factor which was present in our patient along with the history of tuberculosis infection.[9]

While making the treatment plan, benefits of medications must be weighed against their potential side effects. Even with the significant declines in mortality observed with improved HAART therapy, there is ongoing problem of cardiomyopathy among HIV-infected children. zidovudine may cause progression to cardiomyopathy and thus its risks and benefits should be carefully balanced for each child, and alternative NRTI may be considered. Additionally, long-term monitoring of cardiac function among HIV-infected children may be warranted.

The main goal of treating drug induced cardiomyopathy includes -withdrawal of suspected drug and its replacement with better alternative, controlling signs and symptoms, stopping the disease progression, reducing complications and the risk of sudden cardiac arrest.

Blood pressure can be lowered by giving ACE inhibitors, angiotensin II receptor blockers, beta blockers, or calcium channel blockers. Beta blockers, calcium channel blockers, or digoxin can be

used to maintain the heart rate. Antiarrhythmics help prevent arrhythmias. Diuretics used to relieve oedema and anticoagulants can be used to prevents ischemia.[1]

Coenzyme Q10 is an endogenously synthesised and diet-supplied lipid-soluble cofactor that functions in the mitochondrial inner membrane to transfer electrons from complexes I and II to complex III. It also acts as a membrane antioxidant. Myocardial Coenzyme Q10 has been shown to be deficient in myocardial tissue biopsies taken from DCM hearts when compared with normal hearts. Therapy with coenzyme Q10 is in phase 4 clinical trial.[15] MYK-491, an orally available small molecule allosteric activator of myosin, is designed to increase cardiac contractility in patients with dilated cardiomyopathy.MYK-491is in phase 1 clinical trial.[16]

Surgical management for patients with disease refractory to medical therapy includes left ventricular assist devices, cardiac biventricular pacing, automatic implantable cardioverter-defibrillators, ventricular restoration surgery, heart transplantation.[1]

To summarize, the patient was diagnosed to have AIDS in the last 4.5 years was on zidovudine, lamivudine, efavirenz. He gradually developed dyspnoea on exertion, decreased appetite and irritability for the last 10 days. After ruling out congenital and acquired heart diseases as a cause of dilated cardiomyopathy, it was diagnosed as zidovudine induced dilated cardiomyopathy. Suspected drug (zidovudine) was withdrawn and replaced with abacavir and with the supporting treatment patient recovered in 6 months.

Conclusion

Dilated cardiomyopathy can present with no symptoms or it can cause life-threatening problems such as arrhythmias, congestive heart failure. So along with the anaemia this side effect of the zidovudine should be kept in the mind if a child presents with irritability, increased sweating, pale colour, failure to thrive and he/she is on zidovudine containing antiretroviral regimen one should always rule out zidovudine induced DCM before commencing further on the management of the patient.

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PUBLISHED CASE REPORTS ON ZIDOVUDINE INDUCED CARDIOMYPATHY

Compiled by Dr Smita Mali
Assistant Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai-22.

1. Dilated Cardiomyopathy in an Adult Human Immunodeficiency Virus Type 1-Positive Patient Treated with a Zidovudine-Containing Antiretroviral Regimen.

Clinical Infectious Diseases 2003; 37:e109-11

Tanuma J, Ishizaki A, Gatanaga H, Kikuchi Y,Kimura S, Hiroe M, Oka S.

Tanuma J et al has described a 36-year old woman infected with human immunodeficiency virus type 1 (HIV-1) who developed dilated cardiomyopathy (DCM) with histologically confirmed mitochondrial damage while receiving anti-HIV-1 combination therapy that included nelfinavir, lamivudine, and zidovudine. DCM resolved after discontinuation of the regimen, and cardiac function remained normal after initiation of treatment with nelfinavir, lamivudine, and abacavir, which indicates that DCM was induced by mitochondrial toxicity, most likely caused by zidovudine.

This case of histopathologically confirmed dilated cardiomyopathy was probably caused by zidovudine. The reasons for suspecting that zidovudine was the cause of the cardiac pathologic findings are as follows: (1) the clinical symptoms appeared after the commencement of HAART that included zidovudine, (2) the clinical signs and symptoms gradually improved 3 months after discontinuation of the zidovudine-containing HAART regimen, and (3) cardiac function remained normal after the introduction of new HAART regimen that included lamivudine, abacavir, and nelfinavir. Previous stavudine treatment, which had been administered for 11 months before the change to zidovudine, might have contributed to the development of the cardiomyopathy. However, the clinical symptoms appeared 20 months after the switch from stavudine to zidovudine. Therefore, zidovudine seemed to have played a key role in the pathogenesis of this case.

The mechanism of zidovudine-induced cardiomyopathy is thought to be mitochondrial toxicity caused by zidovudine, made evident by depletion of mitochondrial DNA levels. In our case, we also found severely altered mitochondria on an electron micrograph. These changes and the high concentration of lactate suggested mitochondrial damage, probably induced by zidovudine. Physicians should be aware of the possibility of zidovudine- induced cardiac toxicity.

2. Cardiomyopathy with Mitochondrial Damage Associated with Nucleoside Reverse-Transcriptase Inhibitors.

N Engl J Med. 2002;347(23):1895-6.

Frerichs F, Dingemans K, Brinkman K.

In July 2000, a 58-year-old man infected with the human immunodeficiency virus (HIV) began treatment with highly active antiretroviral therapy, which initially consisted of zidovudine, lamivudine, and ritonavir-

boosted indinavir. After three months, a buffalo hump, anemia, and proximal muscle weakness developed, and the regimen was therefore switched to stavudine, lamivudine, and nevirapine. Because of pain in his legs, stavudine was replaced with abacavir three months later.

In February 2001, the patient was admitted to our hospital because of progressive exertional dyspnea and peripheral edema. Echocardiography showed severe dilated cardiomyopathy. Left-sided catheterization showed normal coronary arteries, and a myocardial-biopsy specimen was obtained through right-sided catheterization. Histologic examination showed hypertrophic myocardial tissue without any signs of inflammation or infection. Electron microscopy findings were highly suggestive of selective mitochondrial damage.

Since the nucleoside reverse-transcriptase inhibitors with the greatest mitochondrial toxicity (stavudine and zidovudine) had already been withdrawn shortly before admission, treatment with an angiotensin-converting-enzyme inhibitor, furosemide, and digoxin was started. The patient's condition improved slowly. Later echocardiographic study showed improvement in the cardiac dimensions.

Dilated cardiomyopathy is also believed to be caused by a direct action of HIV on the myocardial tissue or an autoimmune process induced by HIV or possibly other cardiotropic viruses. In animal models, there is clear evidence of cardiomyopathy due to the use of zidovudine, but in humans, such an association has been described only in children. In general, nucleoside reverse-transcriptase inhibitors are not believed to cause cardiomyopathy. However, nucleoside reverse - transcriptase inhibitors - in particular, zalcitabine, didanosine, stavudine, and zidovudine - can have mitochondrial toxic effects in several other tissues.

3. Dilated cardiomyopathy in two adult human immunodeficiency positive (HIV+) patients possibly related to highly active antiretroviral therapy (HAART)

Eur J Med Res (2005) 10: 395-399

Breuckmann F, Neumann T, Kondratieva J, Wieneke H, Ross B, Nassenstein K, et al

Highly active antiretroviral therapy (HAART) has substantially improved the survival of patients with acute immunodeficiency syndrome (AIDS) what resulted in a significant reduction of morbidity and mortality of HIV+ patients. But prolonged survival of HIV+ individuals is also associated with an increase of adverse effects by the treatment itself. An association between AIDS and dilated cardiomyopathy has been well-established. Severe stages of cardiomyopathy represented by NYHA functional classes III-IV could be observed in a high number of patients especially in the pre-HAART era. Simultaneously, the use of antiretroviral drug therapy has been suggested to contribute to cardiac adverse effects including acute onset heart failure, chronic dilated cardiomyopathy, coronary heart disease and arrhythmias. Following are two cases of severely reduced left ventricular function detected in the screening of 132 HIV+ individuals of the German heart failure network.

Features	Patient 1	Patient 2
Age	48	51
Gender	Male	Male
Duration of AIDS	10 years	7 years
Highly active antiretroviral therapy (HAART) regimen	zidovudine 300 mg + lamivudine 150 mg (twice daily)+atazanavir sulfate 400 mg (once daily)	zidovudine 300 mg + lamivudine 150 mg (twice daily) + nelfinavir 750 mg (thrice daily)
Clinical presentation	Progressive exercise-induced dyspnoea (NYHA III-IV), extensive central and peripheral oedema and a poor overall condition.	Progressive angina pectoris, exercise-induced dyspnoea (NYHA II-III) and lymphadenopathy.
Medical history	Interstitial plasma cell pneumonia, cytomegalovirus retinitis and colitis, infectious hepatitis B	NIL
Electrocardiograghy results	Left bundle branch block	Left bundle branch block, ventricular arrhythmia
Echocardiography features	Left ventricular systolic dysfunction with an ejection fraction of 22%	Severely dilated left ventricle with a highly reduced ejection fraction of 28%, a global left ventricular hypokinesia
Myocardial biopsy	Hypertrophy, myocyte degeneration and increased diffuse interstitial fibrosis, without any signs for acute or chronic myocarditis.	Myocardial fiber hypertrophy and myocyte degeneration without any signs for acute or chronic myocarditis.
Brain natriuretic peptide levels (normal level < 100 pg/ml)	1270 pg/ml	339 pg/ml
Serum lactate levels (normal range: 0.5 - 2.2 mmol/L)	4.9 mmol/L	1.2 mmol/L
Diagnosis	HAART-associated dilated cardiomyopathy	HAART-associated dilated cardiomyopathy
Change in HAART regimen	Not made as per genotypic resistance analysis	Not made as per genotypic resistance analysis
Therapy for cardiac ailment	Biventricular implantable cardioverter defibrillator	Biventricular implantable cardioverter defibrillator

4. Dilated cardiomyopathy in a zidovudine-treated AIDS patient.

Cardiovasc Pathol. 1992 Oct-Dec;1(4):317-20.

d'Amati G, Kwan W, Lewis W.

The pathogenesis of dilated cardiomyopathy in acquired immunodeficiency syndrome (AIDS) is poorly understood. We report a case of an HIV-positive, 45-year-old homosexual male treated with high-dose azidothymidine (AZT, 1,200 mg/day) for two years prior to development of AIDS. He subsequently manifested symptoms of congestive heart failure with left ventricle dilation and a 20% ejection fraction. An endomyocardial biopsy showed no active myocarditis, but intramyocytic vacuoles were found. Transmission electron microscopy revealed mitochondrial cristae with distortion and myofibrillar loss. The clinical consideration was dilated cardiomyopathy in AIDS. His AIDS worsened and he died in October 1991. Autopsy revealed a 100-ml pericardial effusion, cardiomegaly, and biventricular dilation. Vacuolar changes in cardiac myocytes were present. Pathologic findings support a diagnosis of AZT-induced cardiotoxicity.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr Jaisen Lokhande

Assistant Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

The following are the list of the adverse effects recently identified by the respective heath agencies and the recommendations given for changes in the product information sheets.

1. Atypical antipsychotics: Potential risk of sleep walking and sleep-related eating disorder

Based on the review of the cases worldwide, Health Canada recommended that the product safety information for all atypical antipsychotics should be updated to include risks of sleep walking (SW) and sleep-related eating disorder (SRED).

2. Azithromycin: Risk of acute generalized exanthematous pustulosis

The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for azithromycin has been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction.

3. Doxycycline: Risk of fixed drug eruptions

The Saudi Food and Drug Authority (SFDA) has updated the summary of product characteristics and patient information leaflet for doxycycline to include the risk of fixed drug eruptions (FDE).

4. Palivizumab: Risk of thrombocytopenia

The MHLW and the PMDA have announced that the package insert for palivizumab has been updated to include the risk of thrombocytopenia as a clinically significant adverse reaction.

5. Warfarin: Risk of calciphylaxis

The MHLW and the PMDA have announced that the package insert for warfarin has been updated to include the risk of calciphylaxis (a syndrome of calcification of the blood vessels, blood clots and skin necrosis) as a clinically significant adverse reaction.

6. Methylprednisolone injections containing lactose: Contraindication to patients allergic to cow's milk proteins.

As per the European Medicines Agency (EMA), the product information for methylprednisolone injections containing lactose will be revised to include a contra-indication in patients allergic to cow's milk proteins.

7. Paracetamol (modified- or prolonged-release): Modified- or prolonged-release preparations should be suspended from marketing

The EMA has recommended that modified- or prolonged-release paracetamol products should be suspended from the market. This is in view of the risks to patients from the complex way these medicines release paracetamol into the body after an overdose.

Reference: WHO Pharmaceuticals Newsletter.2017 [cited 2017 December 11].(2) Available from:http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No5_2017.pdf?ua=1

MATCH THE FOLLOWING DRUG WITH ITS ADVERSE EFFECT.

Dr. Sharmada Nerlekar*, Dr. Abhilasha Rashmi*

**- Associate Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai-22.*

1.	Loracarbef	A.	Hot flushes
2.	Ifosfamide	B.	Osteonecrosis of jaw
3.	Raloxifene	C.	Goiter
4.	Gatifloxacin	D.	Rashes in kids
5.	Zoledronate	E.	Drug induced Lupus
6.	Mianserin	F.	Rickets
7.	Amiodarone	G.	Neurotoxic
8.	Sildenafil	H.	Unpredictable hypoglycemia
9.	Hydralazine	I.	Ataxia in elderly
10.	High dose corticosteroid	J.	Blood dyscrasias
11.	Prolonged phenytoin use	K.	Arthralgia
12.	Midazolam	L.	Splenomegaly
13.	Anastrozole	M.	Kidney damage
14.	Vancomycin	N.	Sudden loss of vision
15.	Filgrastim	O.	Necrosis of femur head

Answers : 1 -D; 2 - G; 3 - A; 4 - H; 5 - B; 6 - J; 7 - C; 8 - N; 9 - E; 10 - O; 11 - F; 12 - I; 13 - K; 14 - M; 15 - L

ALPHABET 'P' PUZZLE

Dr. Abhilasha Rashmi*, Dr. Sharmada Nerlekar**

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Department of Pharmacology, LTMMC & GH, Sion, Mumbai - 22

1 Q									
2	Q								
3		Q							
4			Q						
5				Q					
6					Q				
7						Q			
8							Q		
9								Q	
10									Q

1. Among all antimalarial drugs used for treatment of resistant cutaneous lupus, _____ is the only one which does not cause retinopathy.
2. With minor side effects like dry mouth, thirst and polyuria, _____ like Tolvaptan and Conivaptan are found efficacious in treating hyponatremia associated with SIADH, CHF and cirrhosis.
3. Though the soft gelatin capsule formulation of this HIV protease inhibitor has threefold greater oral bioavailability, nausea/ vomiting/diarrhea and other gastrointestinal side effects are more prevalent with this formulation.
4. Atovaquone, a highly lipophilic analog of _____, should not be coadministered with Tetracycline as it leads to 40% reduction in plasma concentration of Atovaquone.
5. Minor skin reactions are the only adverse reactions seen with this Imidazoquinoline, topically given immune response modifier, which is having orphan drug status in the treatment of Cutaneous T Cell Lymphoma.
6. Bulaquine, a congener of _____, developed in CDRI, Lucknow, is found safe in patients with G-6PD deficiency, as compared to _____.
7. Due to its _____ consistency, aspiration of Paraffin may take place, particularly if taken at night for prolonged period, leading to lipoid pneumonia.
8. Among all _____ substances, Gadolinium based contrast agents (GBCA) should be avoided in patients with severe kidney disease because of the risk of nephrogenic systemic fibrosis.
9. _____depletion results in mitochondrial dysfunction, activation of apoptotic pathways & promotion of oxidative stress, which are regarded as possible mechanisms of myopathies associated with Statin use.
10. Also known as Nociceptin, this novel opioid receptor is involved in inhibition of pain- facilitating as well as analgesia-facilitating neurons in Rostral Ventromedial Medulla.

ALPHABET 'P' PUZZLE: ANSWERS :

1. Quinacrine
2. Aquaretics
3. Saquinavir
4. Ubiquinone
5. Resiquimod
6. Primaquine
7. Oily Liquid
8. Radiopaque
9. Coenzyme Q10
10. Orphanin FQ

NOTES

We would like to request all the clinical departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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