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LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

Department of Pharmacology

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Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

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From the Editor's Desk . . . . ✍

Dear Friends and Colleagues,

It gives me great pleasure to present to you yet another issue of Bulletin on Adverse Drug Reactions.

The first article gives an overview of one of the clinical important condition of drug induced psychosis which has an incidence range of 7-25% patients with first episode of psychosis. Many important drugs have been implicated with this condition. The article also gives an overview of prevention and management of this condition.

The second article gives detailed information on drug induced ototoxicity including risk factors, diagnosis, prevention and treatment. Unfortunately there is no effective treatment hence early diagnosis and prevention is more valuable when using those particular drugs.

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

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

Finally, I would like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance, to all the authors for contributing in the bulletin and 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

DRUG INDUCED PSYCHOSIS

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Introduction

Adverse drug reactions (ADRs) have been identified as one of the commonest causes of post discharge complications and accounting for more than 3.5 million physician office visits, approximately 1 million emergency department visits, and almost 125,000 hospital admissions annually.[1] Neuropsychiatric consequences constitute up to 30% of ADRs and are associated with considerable morbidity and mortality.[2]

The term psychosis which represents a disturbance in the perception of reality, was first used in the 19th century to describe an abnormal state of mind.[3] Psychosis is marked by the presence of one or more of the following symptoms: hallucinations, delusions, disorganized thoughts, and unusual, strange, and/or regressed behaviour. The phenomenon now known as medication-induced psychosis was first identified in 1845 by the French psychiatrist Jacques-Joseph Moreau, who described the effects of smoking hashish in his patients as "acute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week; the reaction seemed dose-related whose main feature included paranoid ideation, illusions, hallucinations, delusions, depersonalization, confusion, restlessness and excitement."[4] Since then, many agents have been associated with medication-induced psychosis.

The prevalence of medication-induced psychosis is unknown, but it is estimated that in 7% to 25% of individuals presenting with a first episode of psychosis, the condition may be substance - or medication induced.[5] The Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition, lists several criteria for the diagnosis of drug induced psychotic disorder. The most commonly implicated non-psychiatric medications associated with medication-induced psychosis are anti-parkinsonian agents, cardiac medications, and corticosteroids.[5]

Category	Agents
Antiparkinsonian	Selegiline, amantadine, anticholinergics
Cardiovascular	ACE inhibitors, anti-arrhythmics, beta-blockers, calcium channel blockers, digitalis
Endocrine	Anabolic steroids, corticosteroids
Gastrointestinal	Proton pump inhibitors, H2 blockers
Psychostimulant	Amphetamine
Anti-microbials	Cephalosporins, clarithromycin, linezolid, chloramphenicol, cyclosporine, metronidazole, chloroquine, isoniazid

Table 1: Agents implicated in drug induced psychosis

Antiparkinsonian Agents: In untreated Parkinson's disease (PD) patient's psychotic symptoms usually develop as a complication of drug therapy.[6] Antiparkinsonian agents are associated with the highest risk of medication-induced psychosis, with symptoms developing in up to 60% of patients.[7] Owing to their catecholaminergic or anticholinergic properties, all antiparkinsonian medications have the potential to induce psychosis.[8] Symptoms ranges from abnormal dreams to frank psychosis. Visual hallucinations with or without delirium are most frequently reported; auditory hallucinations, which are less common, are usually accompanied by visual hallucinations.[9,10,11] Delusions -fixed beliefs that are not influenced by clear or reasonable contradictory evidence and are held with great conviction- are less common than hallucinations.[12] In PD, delusions are often paranoid in nature, usually follow hallucinations, and affect up to 14% of patients.[13] Sleep disturbances and abnormal dream phenomena may precede the development of psychosis in PD patients. The action of amantadine on the central nervous system is not well understood. Increasing evidence shows that amantadine enhances dopamine release indirectly via antagonism of the N-methyl-D-aspartate receptor, and this mechanism may be responsible for this rarely exhibited psychotic side effect. N-methyl-D-aspartate antagonists, such as ketamine, can induce the positive, negative, and cognitive symptoms of schizophrenia.[14]

Digoxin has the potential to cause delirium, depression, and psychosis, most likely due to electrolyte imbalances and cerebral hypoxia.[15] These effects are dose-dependent but may be seen at therapeutic levels, especially in elderly patients or in cases when digoxin is used in combination with diuretics that cause potassium loss.[15] The risk of developing psychotic symptoms increases when the plasma digoxin concentration exceeds 1.5 ng/mL. Psychotic symptoms may be the first and only sign of digoxin toxicity, especially when the serum concentration is in the normal range.

Beta-adrenergic receptor blockers are known to cause central nervous system (CNS) effects, including bizarre or vivid dreams, sleep disturbances, delirium, psychosis, and visual hallucinations. Psychosis and delirium have been reported for metoprolol and propranolol.[2,16] These effects are not dose-dependent and appear to be partly due to the medications' lipophilic properties: hydrophilic agents such as atenolol are excreted unchanged by the kidneys, whereas lipophilic agents such as propranolol and metoprolol are metabolized by the liver and are believed to cross the blood-brain barrier.[16] Other factors affecting beta-blockers' penetration of the blood-brain barrier and their ability to cause CNS effects include specific structural details of the molecules, drug-induced increases in plasma catecholamine levels, and decreased melatonin levels.[17]

Neuropsychiatric effects of **ACE inhibitors** are limited; however, visual hallucinations associated with use of these agents have been reported, primarily in elderly patients.[18] Implicated agents include quinapril, enalapril, captopril, lisinopril, ramipril, and perindopril. Hallucination occurred 2 hours to 6 years after initiation of an ACE inhibitor and resolved within 1 to 30 days after discontinuation. Advancing age and underlying CNS disorders may be risk factors for ACE inhibitor-induced psychosis.[18] Other cardiac agents that may induce psychosis include diuretics, calcium channel blockers, and several antiarrhythmic agents.[2,18]

Corticosteroids: The reported incidence of corticosteroid-associated psychiatric reactions ranges from 1.8% to 57%; psychosis related to corticosteroid treatment has an incidence of 3% to 13.9%.[19] The substantial variability in reported incidences reflects the unpredictability of these reactions, differences in dosing, varying treatment durations, and a host of identified risk factors.[19] Emotional liability and irritability, sometimes accompanied by auditory hallucinations and paranoia, are common symptoms experienced by patients receiving corticosteroids. These effects are dose-related, with psychotic reactions more likely to occur in patients receiving dosages of prednisone exceeding 40 mg/day, but even low levels of systemic exposure from inhaled corticosteroids can potentially induce psychiatric adverse effects. The mechanism by which corticosteroids induce psychiatric symptoms such as psychosis and mania remains to be elucidated. The proposed mechanism is due to the wide expression of glucocorticoid receptors in the brain and their long-term modulation can lead to functional and anatomical alteration which may lead to psychosis.

Antimicrobials: Antibiotics are frequently used and are generally well tolerated, but some antibiotics have been associated with neuropsychiatric adverse effects that are usually less recognized.[20]

Fluoroquinolones, particularly ciprofloxacin, have been reported to cause mania, delirium, and hallucinations in 0.9% to 11% of patients.[21] These agents may induce psychosis by binding to GABA receptor and acts as antagonist and possess potential to bind N-methyl D-aspartate receptor which play a role in causing psychosis.

Penicillins: piperacillin has been implicated in an encephalopathy characterized by dysarthria, tremor, behavioural changes, progressive confusion, and finally several generalized tonic-clonic seizures in patients with end-stage renal disease. In addition, it has been demonstrated in rat studies that penicillin can quantitatively reduce benzodiazepine receptors and thus reduced inhibition and altered neuronal excitability.[22]

A few case reports have linked amoxicillin to the development of acute psychosis. Symptoms developed within 2 hours to 10 days after therapy initiation and resolved completely upon cessation.[23]

Trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with the development of psychosis. In one review, 11.9% of HIV-infected patients receiving TMP-SMX for Pneumocystis jirovecii pneumonia developed acute psychosis.[24] In other reports, initiation of TMP-SMX led to altered mental status involving vivid visual and auditory hallucinations, with improvement of symptoms upon discontinuation.[25]

Paranoid-hallucinatory psychosis has been reported with chloramphenicol, streptomycin, cephalosporins, and some anti-tuberculous drugs, such as cycloserine.[25] Isoniazid can induce psychosis through deprivation of Vitamin B complex as well as interferes with the metabolism of biological amines in the CNS.[25]

Antiepileptic: Vigabatrin is one of the most commonly used antiepileptic drugs for the treatment of resistant epilepsy, complex partial seizures, secondary generalized seizures, and for monotherapy use in infantile spasms in West syndrome. The psychotic symptoms could be linked to the effect of VGB on left-hemispheric striatal dopamine metabolism. The other hypothesis suggested that a persistent partial depletion of GABA transaminase with consecutively increased GABA levels. The levels of 4-hydroxybutyric acid in the urine should be monitored.[26] 4-hydroxybutyric acid is one of the main metabolites of GABA.

Psychostimulants: These agents are well known to cause psychosis. Amphetamine increases glutamate release in the cortex, excess of cortical glutamate likely to damage GABAergic interneurons leading to dysregulation of cortical signals and which ultimately results in psychosis.[27]

Antiretrovirals: The prevalence of new-onset psychosis in HIV-infected patients ranges from 0.5% to 15%. Antiretroviral therapy (ART), which is a mainstay of HIV treatment, may be a contributing factor.[28] ART initiation may be associated with onset of psychotic symptoms within 1 month ofinitiation; resolution of symptoms frequently occurs following discontinuation of the offending agent. The most commonly cited agents are efavirenz, zidovudine, abacavir, nevirapine, and drug combination of lamivudine and zidovudine.[28]

Antidepressants: Antidepressants have been recognized as potential inducers of mania and psychosis since their introduction in the 1950s. The neurobiological mechanism responsible for antidepressant exacerbation of manic and psychotic symptoms largely is unknown. Proposed mechanism is differential affect in monoamine efflux leading to increase in extracellular dopamine, additionally chronically it increases in presynaptic dopamine prefrontal cortex. Majority studies conclude greater risk of manic or psychotic exacerbation with TCA (tricyclic antidepressants) compared to SSRI's (Selective serotonin reuptake inhibitors).[29]

Anticholinergic: Central nervous system (CNS) manifestations result from central cortical and subcortical muscarinic receptor antagonism. The degree of CNS manifestation is related to the drug's ability to cross the blood-brain barrier.

In 2014, the American Association of Poison Control Centers (AAPC) National Poison Data System Annual Report documented 8271 single exposures to anticholinergic drugs. Unintentional ingestions accounted for 7774 presentations. Moderate morbidity (requiring specific treatment) was reported in 200 cases, major morbidity (life-threatening) in 16, and 1 death was reported. Patients with severe central manifestations (eg, hallucinations, psychoses, seizures, coma) have the highest morbidity rates.[30] eg: atropine, scopolamine.

Non-prescription Medications: Many non-prescription medications can cause psychotic symptoms. Sympathomimetics like ephedrine and pseudoephedrine used in most cold products and nasal sprays have been associated with psychotic symptoms; even at usual dosages.[31] Histamine (H2)-receptor

antagonists and proton pump inhibitors, although considered relatively safe, have been associated with serious neuropsychiatric events (including mental confusion and agitation, insomnia, and hallucination), especially in elderly patients, severely ill patients, and those with impaired hepatic or renal function.[32,33]

Clinical Presentation

Medication-induced psychosis may present in a similar manner as idiopathic psychosis. The essential features are prominent delusions and/or hallucinations that are found to be due to the physiological effects of a medication. The hallucinations are usually tactile, visual, and/or gustatory. The patient may also present with paranoia, anxiety, agitation, grandiosity, and disorganized speech and/or behaviour.

There are no definitive tests to determine whether a patient is experiencing medication-induced psychosis. A thorough history is needed to establish a temporal relationship. It is important to determine the onset of psychotic symptoms; medication-induced psychosis is usually related to an increase in dosage or changes to medication regimens, with symptoms appearing within days of drug initiation, dosage change, or discontinuation.[3] Abrupt onset or the appearance of symptoms in patients older than 35 years with no known psychiatric history should suggest medication-induced psychosis.[3,5] In certain cases, such as with corticosteroids, symptom onset can occur as long as 3 months later. Symptom duration also can help determine the aetiology of a patient's symptomatology; if symptoms persist for more than 4 weeks after discontinuation of the suspected medication, other causes of psychosis must be evaluated.

Risk Factors and Prevention

Certain factors increase a patient's risk of medication-induced psychosis, including age (young children and the elderly), altered hepatic or renal function, female gender, polypharmacy, and previous psychiatric history.[3,5] It is important to obtain a thorough medical history to determine past and current psychotic illness. In addition, a complete medication history including all prescription and non-prescription drugs, herbal products, and supplements is essential. Illicit drug use and alcohol consumption must be addressed as well. Polypharmacy, especially in the elderly, may be associated with an increased risk of medication-induced psychosis; this population is more likely to be treated for Parkinsonism, cardiovascular disease, and other conditions that have the potential to induce psychosis. In initiating drug therapy, it is always best to use the lowest dosage possible, taking into consideration the patient's weight and age. Awareness of potential drug interactions also is important for preventing medication-induced psychosis.

Management

Medication-induced psychosis is typically self-limiting, usually resolving within a day (in some cases, several days) after discontinuation of the offending agent. Treatment involves discontinuing the suspected

agent or, when discontinuation is not possible, lowering the dosage to below psychomimetic levels and/or using antipsychotic medications to treat symptoms.[3] Ideally, the patient should be in an environment where he or she can be observed and contained, if necessary, to avoid self-harm or harm to others.[6] Medical management is usually unnecessary if the offending agent is discontinued. Short-term treatment with antipsychotics or benzodiazepines during a period of psychosis may be warranted for patients in danger of harming themselves or others.[3]

In PD-treated patients, the drug with the greatest psychosis-inducing potential and the least antiparkinsonian activity should be eliminated first.[9] PD medications should be eliminated in the following order: 1) adjunctive drugs such as anticholinergics, amantadine, and selegiline; 2) dopamine agonists; and 3) levodopa-carbidopa.[9] If an antipsychotic medication is utilized to treat chronic and bothersome psychosis in a PD patient, the potential effect of worsened motor symptoms caused by dopamine blockade must be weighed against the potential benefit. Typical antipsychotics and most atypical antipsychotics are not recommended for this reason. Clozapine and quetiapine have been shown to be the most efficacious agents with the least likelihood of worsening motor symptoms.[33] However, their side-effect profiles have prompted investigations into finding alternative agents that are effective in reducing hallucinations in PD patients. The most promising medications are the cholinesterase inhibitors rivastigmine and donepezil.[34]

A medication retrial may be appropriate in certain situations, such as when the patient's psychosis developed because of a high dosage or when the agent was used in combination with other psychotomimetics. If a retrial is attempted, the medication should be initiated at a lower dosage, with careful monitoring of the patient for early signs of psychosis.[3]

Conclusion

Medication-induced psychosis has been associated with many non-psychiatric medications. It is important to be aware of the psychotropic ADRs of many common non-prescription and prescription medications. Educating patients and caregivers about potential ADRs of psychotomimetic drugs and inquiring about ADRs at each patient encounter will aid in the early detection and prevention of medication-induced psychosis. Patients should be instructed to consult their pharmacist or other healthcare provider prior to using any non-prescription medication and to avoid excessive consumption of caffeinated products when taking psychotomimetic agents. Preventive strategies directed at avoidance of high-risk medications, appropriate dosing regimens based on age and weight, reduction of polypharmacy, and close follow-up can improve patient outcomes.

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DRUG INDUCED OTOTOXICITY

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Use of the term "ototoxicity" could be traced back to 18th century when it was recognised that quinine and acetylsalicylic acid provoked dizziness, tinnitus, and hearing loss. Ototoxicity refers to impairment of hearing and balance. It may be "cochleotoxic" when there is impairment of hearing or "vestibulotoxic" which involves balance impairment.[1] Literature search has revealed that more than 130 medications can cause ototoxicity.[2] The hearing loss may be transient, progressive, or permanent. Loop diuretics (furosemide), salicylates and phosphodiesterase type 5 inhibitors (sildenafil) can cause transient hearing loss, the severity of which may range from slight to profound. Aminoglycosides, platinum based chemotherapeutic agents and quinine usually lead to permanent hearing loss.[3] Different drugs causing hearing loss or leading to ototoxicity have been enlisted in **Table 1**

Table 1 :Examples of drugs known or reported to be ototoxic

Ototoxic drug class	**Examples**
Aminoglycosides	Streptomycin, Amikacin, Tobramycin, Gentamycin, Kanamycin, Capreomycin
Other antibiotics	Vancomycin, Erythromycin
Platinum-based chemotherapy	Cisplatin, Carboplatin, Oxaliplatin
Loop diuretics	Furosemide, Torasemide, Bumetanide, Piretanide
Antimalarials	Quinine
Salicylates	Aspirin
Phosphodiesterase type 5 inhibitors	Sildenafil, Tadalafil, Vardenafil
Environmental chemicals and other substances	Lead, Mercury, Carbon Monoxide, Arsenic, Carbon Disulfide, Tin, Hexane, Toluene, Alcohol
Other drugs	Deferoxamine, Interferon

The hearing loss is usually bilateral and symmetrical. It may be manifested with a single dose or it may take several weeks to months after completion of the treatment with an ototoxic drug. Since benefits of these drugs prevail over the risks, their use can be defensible in certain medical conditions. Therefore, it is of utmost importance to understand different mechanisms of ototoxicity which may aid in developing new strategies either to prevent or to cure drug-induced hearing loss or to develop new drugs or molecule having same efficacy but with fewer side effects. Different mechanisms of drugs leading to hearing loss have been discussed in detail below:

1. Aminoglycoside-induced ototoxicity

Aminoglycosides associated vestibular toxicity or cochleotoxicity is reported in 10% of patients receiving these drugs intravenously out of which 33% has occurred in adults and in 3% of cases damage becomes permanent.[4] Gentamicin, tobramycin and streptomycin are mainly responsible for vestibulotoxicity, whereas amikacin and kanamycin are primarily cochleotoxic. Ototoxicity is commonly associated with the use of ear drops, particularly in the presence of tympanic membrane perforation or tympanostomy tubes.[5]

Aminoglycoside ototoxicity is multifactorial. Slow clearance of aminoglycosides from inner ear fluids compared to serum is responsible for accumulation of the drug in inner ear fluid. This latency or delayed clearance is responsible for progressive hearing loss. About 4% to 15% of patients receiving streptomycin (1 g/day for > 1 wk) develop considerable hearing loss, which usually occurs after a short latent period (7 to 10 days) and slowly worsens if treatment is continued. At cellular level, mitochondrial protein synthesis disruption and the formation of free oxygen radicals are responsible for destruction of cochlear hair cells, specifically the outer hair cells. Generated free radicals within the inner ear activate inducible nitric oxide synthetase and subsequently increase nitric oxide concentrations. By reacting with oxygen radicals, it forms the destructive peroxynitrite radical, which directly stimulates mitochondrial-mediated apoptotic cell death resulting in permanent hearing loss.[6] Other suggested mechanisms, being the presence of specific mitochondrial DNA mutations (e.g. A1555G). Exposure to sub-detrimental doses of aminoglycosides aggravates noise induced cochlear damage and can have direct effects on cellular membrane potentials through interference with potassium channels.[7] Ultimately, individually, or collectively these mechanism leads to permanent loss of sensory hair cells in both the cochlea and vestibular apparatus, resulting in permanent hearing loss and balance dysfunction.

Susceptibility and genetic predisposition of patients to aminoglycosides:

Mutations in the mitochondrial DNA often results in increased susceptibility to aminoglycoside induced toxicity. This may be because of reduction and inhibition of mitochondrial protein synthesis. Though these drugs preferentially target bacterial ribosomes, some cellular mechanisms of inner ear get damaged resulting in ototoxicity which occurs even after a single dose in patients who are genetically susceptible.[8,9]

Prevention:

Therapeutic drug monitoring is one of the best ways to prevent aminoglycoside ototoxicity by carefully monitoring the serum drug levels. Also monitoring renal and auditory functions before, during and after treatment may sometimes prove beneficial; (however, this is not always possible in acute scenario). Frequent monitoring decreases incidence of ototoxicity and should be considered whenever possible. It can also be prevented by proper family history and DNA analysis. One can select alternative

antibiotics for high-risk patients. Since clearance of aminoglycosides from cochlea takes much longer even after cessation of therapy, patients are instructed to avoid noisy environments for about 6 months as there are high chances of noise-induced cochlear damage. Single daily dosing of aminoglycoside induces higher peak serum concentrations, lower ototoxicity is observed compared to multiple daily dosing.

Literature reveals that antioxidant N-acetyl-cysteine (NAC) can protect against amikacin ototoxicity. In a study conducted by Kocyigit et al 46 patients who received amikacin for peritoneal dialysis-related peritonitis, (half of patients received NAC while other half placebo).[10] NAC protected cochlear function, particularly at higher frequencies. Also, oxidative stress measurements indicated that antioxidant status was significantly improved in the NAC patients. Another study by Kranzer et al also indicated that NAC has an otoprotective effect when administered with aminoglycosides.[11]

2. Platinum Compounds Induced Ototoxicity

Platinum drugs are frequently used as chemotherapeutic agents for the treatment of a variety of adult and paediatric cancers. Among the platinum compounds, cisplatin is more ototoxic than other platinum-based drugs with the incidence of 60% permanent bilateral hearing loss among children[12] Carboplatin at myeloablative doses for autologous bone marrow transplantation was also found to be ototoxic.[13]

Mechanism of ototoxicity:

Platinum compounds mainly cause damage to the stria vascularis which secretes endolymph in scala media and it also causes outer hair cell death beginning at the basal turn of the cochlea. The underlying mechanism here is free radical production through inhibition of NOX3 (NADPH oxidase 3), is a particular form of NADPH oxidase that is highly and selectively produced in the inner ear, which ultimately leads to mitochondria-mediated and caspase (protease)-mediated apoptotic cell death and permanent hearing loss.[14]

Prevention of ototoxicity

Antioxidants like vitamin E (α-tocopherol), sodium thiosulfate, D-methionine and N-acetylcysteine were found to be useful in preventing platinum induced ototoxicity by reducing the formation of free radicals. Dexamethasone is also found to have otoprotective effect.[14]

3. Loop diuretics

Diuretics are mainly used in reducing oedema of cardiac, hepatic, or renal origin, mild to moderate hypertension, oliguria due to intrinsic renal failure and in patients suffering from hypercalcaemia. The incidences of ototoxicity associated with furosemide and ethacrynic acid are 6% and 0.7% respectively. Ototoxicity occurs most frequently with rapid intravenous administration than oral administration. Sensory hearing loss due to the loop diuretics may be transient or permanent. Sensorineural hearing

loss may present with vertigo, indicating that vestibular toxicity is also present. Furosemide associated ototoxicity is noticed particularly when doses exceed 240 mg per hour. Bumetanide has a decreased risk of ototoxicity as compared to furosemide. Furosemide and other loop diuretics are sulphonamides excluding ethacrynic acid; hence ethacrynic acid is used only in patients with sulpha allergies. However, it is more ototoxic compared to another loop diuretic.

Mechanism of ototoxicity:

Loop diuretic produce morphological alterations such as extensive outer hair cell loss in the basal turn of the cochlea, cystic changes in the stria vascularis, rupture of endothelial layers, and edema of the marginal cells of the stria vascularis. Death of the hair cells in the organ of corti results in permanent hearing loss. When loop diuretics are given with aminoglycosides, morphologic changes occur within 1 hour.

Na+/K+/2Cl- transporter present in stria vascularis presumably binds to both ethacrynic acid and furosemide. Pre-treatment with organic acids such as salicylic acid reduces the ototoxic effects of furosemide, but not of ethacrynic acid therefore it is uncertain whether inhibition of this transporter is responsible for the ototoxicity. Therefore, it is suspected that, ethacrynic acid ototoxicity may involve the production of an ototoxic metabolite.[15]

4. Nonsteroidal anti-inflammatory drugs (NSAIDs):

NSAIDs such as ibuprofen, diclofenac, indomethacin, aspirin (at therapeutic dosages) and mefenamic acid are used for musculoskeletal and inflammatory conditions. Elders are most commonly prone to develop 'ototoxicity'. Temporary hearing loss and tinnitus are seen in patients taking high doses of salicylates (> 12 tablet of 325-mg tablets of aspirin per day).

Mechanism of ototoxicity

NSAIDS impair sound amplification of the outer hair cells which ultimately results in mild to moderate sensorineural hearing loss. At high doses, it leads to degeneration of the spiral ganglion neurons, with impaired auditory neural activity of the cochlea. Due to inhibition of prostaglandin synthesis, levels of arachidonic acid increases which enhances/stimulates N-methyl-D-aspartate receptor currents in the spiral ganglion neurons causing tinnitus.[14]

5. Quinine

Quinine, an antimalarial drug is specifically used to treat Plasmodium falciparum. It is also used as a muscle relaxant in the management of myotonic contractions and nocturnal leg cramps.

Mechanism of ototoxicity

Quinine results in reversible hearing loss due to hyperpolarisation, followed by depolarisation of the hair cell membrane potential in a dose-dependent manner. It may also lead to reduction in the cochlear

blood flow, with possible vasoconstriction. Quinine triggers the complement cascade. By binding to plasma proteins, it may lead to disseminated intravascular coagulation, thrombocytopenic purpura and haemolytic anaemia in susceptible individuals. This can be attributed to the microvascular changes in the cochlea. Quinine may produce reversible hearing loss, however, permanent hearing loss that interferes with conversational frequencies has been reported.[14]

Ototoxicity due to hydroxychloroquine is rare but well established. Sensorineural hearing loss following chloroquine therapy has been reported to be dependent on dose and duration of treatment and observed to be reversible by many while some have reported it to be irreversible.[16]

6. Phosphodiesterase-5 inhibitors

First case report of phosphodiesterase-5 inhibitor (PDE5i) leading to ototoxicity was published in 2007. Use of this class of drug results in sudden sensorineural hearing loss (SSNHL) which involves inner ear and/or central auditory pathway. SSNHL may be of variable intensity and frequency, ranging from a mild feeling of packed ear, tinnitus, to total hearing loss in approximately 80% of the cases.[17]

Mechanism of ototoxicity

Ototoxicity may occur due to decrease in the number of outer hair cells of the organ of Corti and excess nitric oxide in the auditory organs such as the cochlea and the auditory nerve. Though direct evidence regarding mechanism of PDE5i induced ototoxicity is still not clear, it is postulated to be related to the prolonged effects of cyclic guanosine monophosphate (cGMP) within the cochlea.[18] However, deafness is reversible with the discontinuation of the drug and there is improvement in hearing thresholds later.

7. Heavy metals[19]

Heavy metals such as lead, arsenic, mercury, and manganese used in industry or for some medicinal purpose may cause ototoxicity.

Lead (Pb): It has been found that longer the exposure to lead greater is the severity of the hearing loss. Though all frequencies are lost, it has been observed that there is more loss in high frequencies. Mechanism for ototoxicity lies in demyelination of VIII cranial nerve.

Arsenic (As): Arsenic is most commonly found in the manufacturing of parasite and micro-organism inhibitors. It leads to hearing loss which commonly affects lower frequencies. Sometimes problem with balance is also noted. Over exposure to arsenic can cause damage to Organ of Corti beginning at the apex.

Mercury (Hg): Mercury is used in the manufacturing of thermometers and detonators. Hearing loss is in the entire range with greater losses in the high frequencies and in early or middle stage it affects

cochlea with sensory cell destruction. In later stages, the injury is retro cochlear as well.

Manganese (Mn): It is used in battery manufacturing, electroplating, and the processing of ferrous metals . The auditory site of lesion is unknown. However, it results in a loss of both the low and high frequencies with the mid range showing better hearing.

8. Other drugs

a. Interferon:

Literature reveals several reports on interferon induced ototoxicity especially in patients receiving treatment for hepatitis B and C infection. PEGylated IFN α-2a treatment uncommonly causes ototoxicity (1%).[20] Several factors are responsible for sensorineural hearing loss like direct toxicity of the auditory nerve hairy cells, immunoregulatory and antiviral activity can also explain this sensorineural pathology. Other investigators reported anti-endothelial-cell antibodies in an HCV patient with sudden hearing loss during interferon therapy.[21] These antibodies cause microvascular damage during therapy for vasculitis. In addition, interferon-induced thrombocytopenia may cause a microvascular insult in the inner ear.

Clinicians are continuously required to monitor balance between effectiveness and safety of the drug and to optimise pharmacological/therapeutic ratio to obtain clinical advantages and avoid undesired side effects.

b. Desferrioxamine:

Desferrioxamine (DFO)is a chelating agent, used to treat chronic iron overload usually seen in patient having thalassemia receiving frequent blood transfusions or iron poisoning. It was seen in 3.8 - 57% of patients of beta thalassemia. The hearing loss was postulated due to the effect of DFO on cochlear ciliated cells. Tinnitus is the commonest otological symptoms and may be the early alarming sign. Proper dosing of desferrioxamine and transfusion therapy, along with regular monitoring of body iron burden and haemoglobin, regular otolaryngologic and audiometric follow-up with special care to include the frequencies of 3 and 6 kHz may help recognize and prevent permanent ototoxicity.[22]

Risk Factors for ototoxicity[23]

There are certain factors that may put patients at increased risk for ototoxicity:

- Dose and duration of therapy
- Infusion rate and cumulative lifetime dose
- Impaired kidney function, which can lead to rapid accumulation of the ototoxic drug

- Concurrent administration of another ototoxic drug (e.g. aminoglycosides and loop diuretics)
- Age- Most hearing loss from age will occur beyond age 60.
- Pre-existing hearing loss, sensorineural hearing loss or any previous injury to middle or inner ear
- Exposure during pregnancy
- Previous exposure to head and neck radiation (for chemotherapeutic agents)
- Genetic susceptibility e.g. in aminoglycoside ototoxicity specific mitochondrial DNA mutations (e.g. A1555G)
- Family history of ototoxicity

Symptoms[23]

The most common symptoms experienced from ototoxicity are:

- Tinnitus or ringing in the ears
- Bilateral or unilateral hearing loss
- Dizziness
- Inco-ordination in movements
- Unsteadiness of gait
- Oscillating or bouncing vision

Progression

Symptoms of ototoxicity may present rapidly or take months following administration of causative drug. In early stages, ototoxicity goes unnoticed when hearing loss is very minimal or restricted to high pitched sounds. It is usually diagnosed, when hearing loss reaches the lower frequencies, and by that stage permanent damage has already occurred.

Aminoglycosides cause permanent hearing loss, normally preceded by high pitched tinnitus and a gradual loss of hearing that begins in the higher frequencies. Symptoms of aspirin and quinine toxicity are dependent on dose and are usually reversible. Permanent hearing loss occurs in patients who take large doses of quinine particularly in elderly patients who consume it long-term. Hearing loss associated with chemotherapeutic agents usually begins as a loss of high frequencies in both ears, and progresses to a loss of all frequencies. Hearing loss presents as a sensation of hearing muffled voices. Vestibular effects (e.g. loss of balance, in-coordination and vertigo) are also common. Hearing loss usually occurs after 1-2 weeks of treatment, although it can often be delayed for up to 6 months post treatment.[2]

Diagnosis:

To identify and prevent ototoxicity is still a challenge in clinical practice. Early detection of ototoxicity includes direct auditory function assessment, though it may not detect early ototoxic changes, it evaluates the patient's hearing in the speech frequency range for communication, calculates word recognition ability and middle-ear functioning via tympanometry, and detects whether there is a co-existing pathology.

- Pure tone air conduction test: Can detect very small changes even before onset of tinnitus, as most ototoxic agents produce hearing loss in the highest frequencies first. Early detection permits modification of treatment before speech frequencies are affected.
- Pure tone bone conduction: Used to determine sensorineural function.
- Word recognition tests
- Romberg's test: Balance test to detect vestibular damage.

For infants and critically ill patients who are bed-bound or comatose, alternative tests are available.

The audiological monitoring of patients receiving potentially cochleotoxic drugs is now standardized. For diagnosis of suspected vestibulotoxic effects, the video head impulse test and vestibular evoked myogenic potentials seem to be suitable procedures for objective assessment. These should be conducted prior to the beginning of treatment with a known ototoxic agent, as well as during treatment and after treatment has stopped. Transient evoked otoacoustic emission (TEOAE) and distortion product otoacoustic emission (DPOAE) tests are used for examination in ototoxicity control, allowing assessment of cochlea function at high frequencies and Brainstem evoked response audiometry (BERA) is considered as gold standard test especially for paediatric population.[24]

Otoacoustic emission (OAE): OAEs provide an objective evaluation of the cochlear outer hair cell system. OAE is a sensitive test for detecting and monitoring even small changes in the inner ear due to ototoxicity. The outer hair cells are amongst the first inner ear structures that are damaged by aminoglycosides. Early changes in OAEs may reflect subclinical cochlear damage that could progress to a clinically relevant hearing loss if treatment is continued.[14]

Auditory brainstem response (ABR): It measures auditory function that utilises responses produced by the auditory nerve and the brainstem and it helps to differentiate sensory from neural hearing loss.

Prognosis

Ototoxicity, although not life-threatening, may cause considerable discomfort to patients , and in some cases drug discontinuation may be necessary to prevent permanent damage.

Recovery of patients from ototoxicity is dependant on the type of drug and the dose and duration of

treatment. Usually hearing loss from cisplatin treatment is irreversible, whereas that occurring from salicylates and quinine is most often reversible. Most environmental chemicals are associated with permanent hearing loss. Mercury has been associated with permanent balance problems. If symptoms are detected early, then the chance of recovery is much higher. However, most patients do not notice any significant changes until it is too late.

Treatment:

Currently no treatment is available for drug induced ototoxicity. Prevention by avoidance of ototoxic medications and in time withdrawal of suspected medication is the best possible option. In patients who are at high risk, frequent hearing and balance tests should be conducted. Ototoxic drugs should not be prescribed to pregnant women as it may affect foetal labyrinth and may cause impairment of hearing. The management of cochlear toxicity includes appropriate schedules of therapy, the association of supposed protectors, monitoring and referral for hearing aids, cochlear implants, and/or assistive technology options.[14]

Prevention

Taurine or another antioxidant (e.g. Vitamin E, sodium thiosulfate, D-methionine, N-acetylcysteine) and Dexamethasone with the ototoxic drug may be able to reduce toxicity. Inhibitors of cell death pathways as well as gene therapy for aminoglycoside ototoxicity are also being investigated.[25]

Conclusion

Despite many efforts, ototoxicity still occurs and considering the unavailability of the cure, research is still required to investigate all the possible causes and mechanisms of ototoxicity and to prevent this complication in terms of hearing loss and tinnitus in the future.

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ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED IN LTMMC AND GH

(March 2017 to June 2017)

Compiled by Swati Vaidya

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Total Case Reports: 86

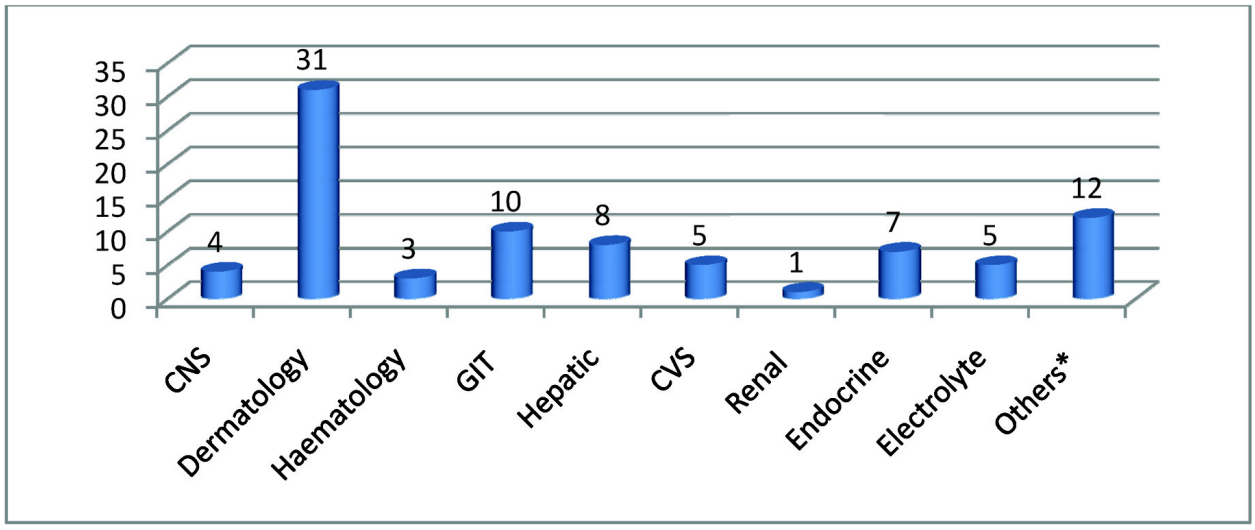
I. Age and Gender distribution:

Age groups	Number of patients	Males	Female
<3 yrs	14	7	7
3-17 yrs	24	11	13
18-44 yrs	26	10	16
45-60 yrs	15	9	6
>60 yrs	7	5	2
Total	86	42	44

II. Seriousness of the reaction:

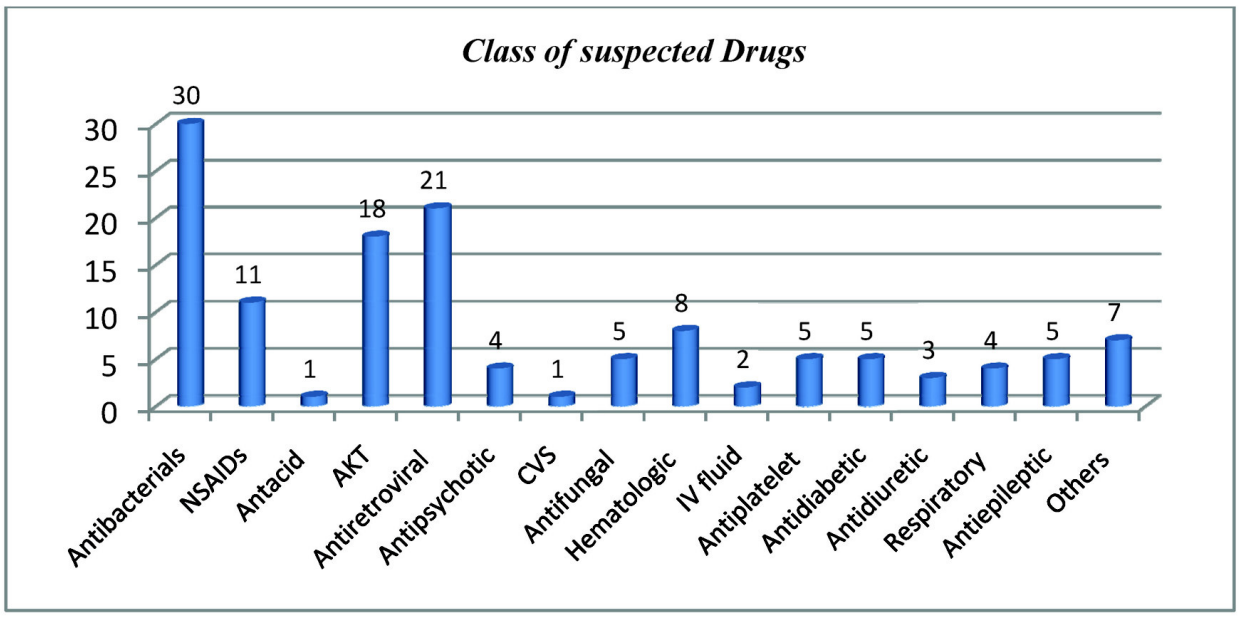
Seriousness of the ADR	No. of cases (N=86)
Yes	72
No	14

III. System involved in the ADR: N=86



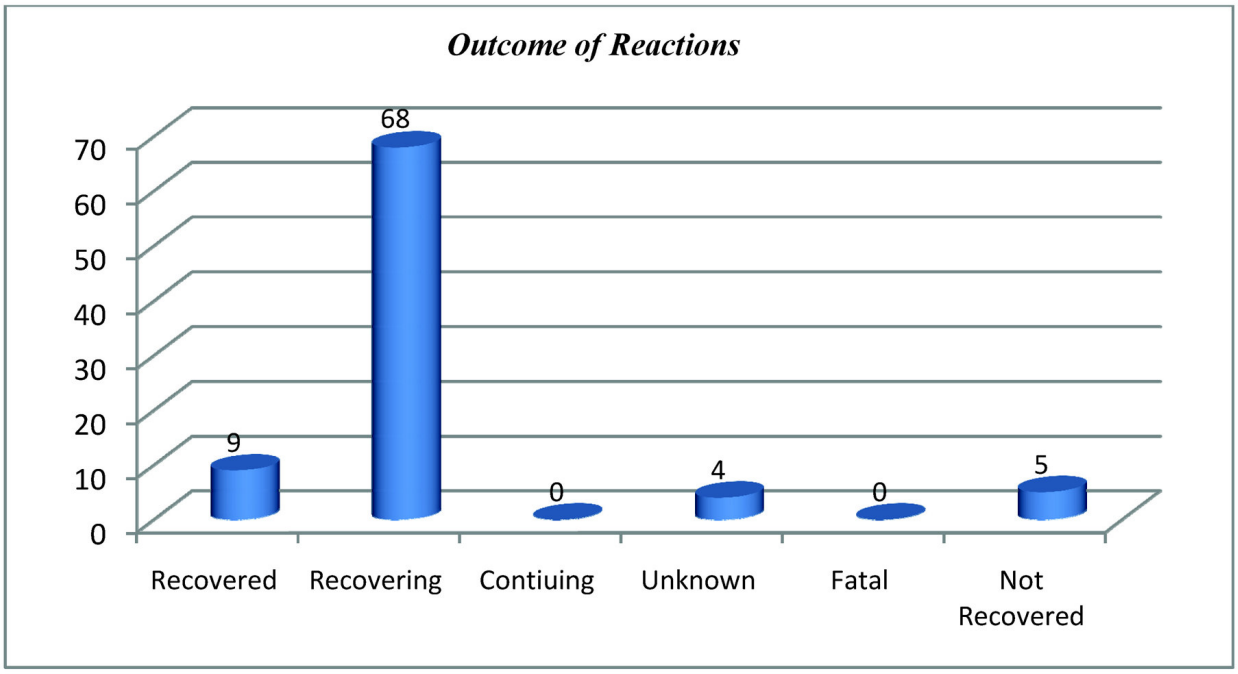
Others include hypersensitivity reaction (angioedema), dapsone poisoning (accidently taken), fever and respiratory problems (cough)

IV. Class of the Suspected drug: N=123

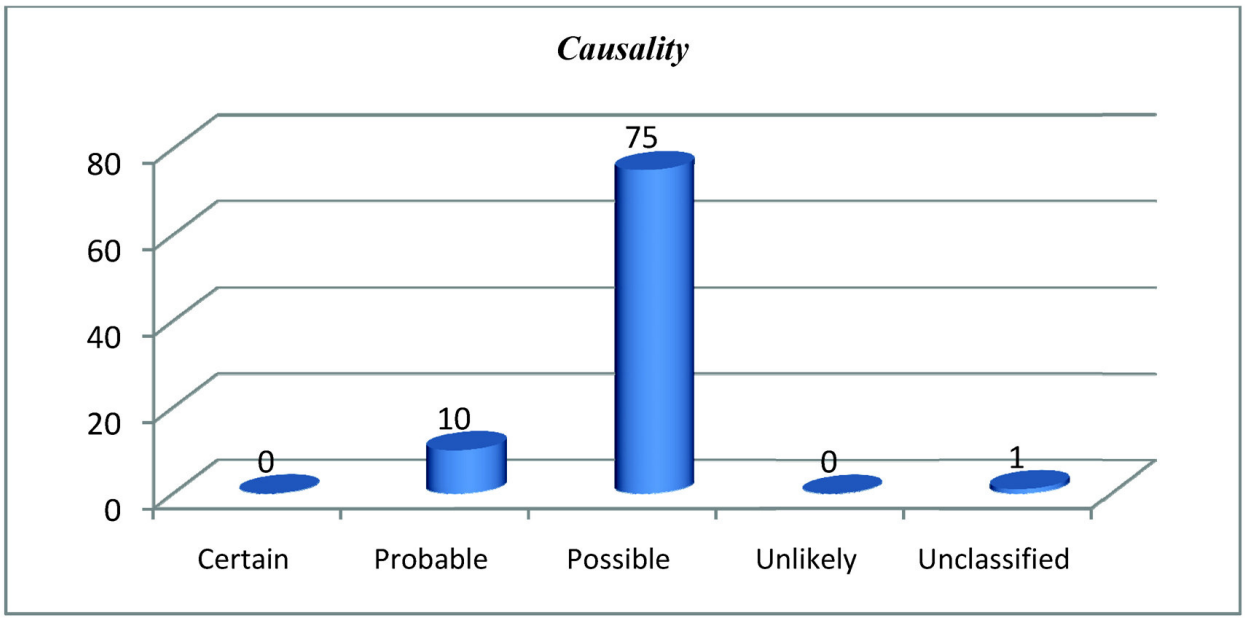


Other drugs include anthelminthic, antihistaminic, corticosteroid, anti snake-venom, hematopoietic (filgrastim), antileprotic (dapsone poisoning) and antispasmodics.

V. Outcome of the reactions: N=86



VI. Causality Assessment (WHO UMC Classification): N=86



EVALUATION OF A CASE SERIES

Amphotericin induced Hypokalaemia

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Introduction:

Opportunistic fungal infections are becoming increasingly common. Because there is a compromised immune defence mechanism, immunocompromised patients are prone for various fungal infections. Empirical treatment with antifungal drugs is initiated in many cases prior to confirmation of a definitive diagnosis of a fungal infection.[1]

Amphotericin B is a polyene group of anti-fungal drugs. It is obtained from Streptomyces Nodosus. It possesses broad spectrum anti-fungal activities. Spectrum involves *Candida, Aspergillus, Histoplasma, Blastomyces and Cryptococcal* species. Amphotericin B is mostly used to treat systemic fungal infections caused by these species.[2]

Fungal cell membrane contains ergosterol. Amphotericin B binds to ergosterol and brings about an aggregate in cell membrane. This aggregate leads to formation of a transmembrane channel through which fungal cell contents leak out causing death of fungus.[3]

Various adverse drug reactions are seen with amphotericin B. These reactions are classified into 2 groups - acute reactions and chronic reactions, based on the time of their appearance after starting Amphotericin B.

Acute reactions are those which occur in short duration of time (within few hours) after its infusion.[4] These reactions are fever, chills, headache, anorexia, hypotension etc. Cause of these reaction is release of proinflammatory cytokines, which is an infusion related response of innate immunity.[3]

Chronic reactions are late appearing (3-4 weeks) reactions which include nephrotoxicity, hepatotoxicity, cardiotoxicity, neurological symptoms like confusion, delirium which occur in 1-10% of patients.[4] Most common amongst them is the nephrotoxicity.[5] This nephrotoxicity manifests in the form of azotaemia, reduced glomerular filtration rate, acidosis, electrolyte imbalance in the form of hypokalaemia, inability to concentrate urine.[5]

Here we are presenting a case series of Amphotericin induced hypokalaemia. In these 3 cases, we found that amphotericin B was causing depletion of serum potassium levels without any change in other serum electrolytes. Reaction appeared after a short time of amphotericin B administration and prompt treatment resolved the serum potassium levels back to normal within a few days.

Case I

A 13 years old boy weighing 35 kg was a known case of aplastic anaemia. He was scheduled to undergo bone marrow transplant in this institute. His investigations (complete blood count, liver and kidney function test, serum electrolytes) were within normal limits, except white blood cell count which was 3500/mm3, (4500 - 11000/mm3).

Patient was started prophylactically on inj. meropenem 1gm, inj. acyclovir 50mg, inj. amphotericin B (75mg i.v. twice day) to decrease the risk of opportunistic infections. Other concomitant drugs were inj. ondansetron 4mg and inj. pantoprazole 40mg.

On 2nd day after starting the treatment, patient presented with tingling sensation in hands and feet. Patient also complained of numbness and weakness in the limbs. On CNS examination patient was oriented in time, place, and person. Muscular strength was reduced but deep tendon reflexes were normal. Patient's blood investigations done showed decreased serum potassium level of 2.70mEq/l (Normal range 3.5-5.0mEq/l).

Suspecting amphotericin B and meropenem to cause hypokalaemia, both were stopped. Scheduled bone marrow transplant was delayed for getting the serum potassium levels back to normal. Patient improved symptomatically on same day and his serum potassium level came to normal on the next day which was 3.57mEq/l.

On applying the WHO UMC causality assessment scale we can see the presence of temporal association between the drug and reaction, the reaction can also explained by other cause (meropenem can cause hypokalaemia in <1% patients) and de-challenge was positive. Hence the causality is considered as "Possible". Also on applying Naranjo scale to this data we get a score of 4 which falls under causality category of "Possible".

Case II

A 9-year-old boy weighing 26 kg was suffering from acquired immune deficiency syndrome since age of 5 years. Patient was on fixed dose combination of drugs zidovudine, lamivudine and nevirapine.

He came with the chief complaints of dry mouth, difficulty in swallowing, nausea, and vomiting. Patient was cachexic and oral cavity examination revealed white lesions of cottage cheese appearance. Lesions showed bleeding on removal, suggesting oral muco-cutaneous candidiasis. Gastro-oesophagoscopy revealed lesions in oesophagus as well.

Patient was admitted for oesophageal candidiasis and started on inj. amphotericin B (70mg i.v. once a day). Other concomitant drugs were inj. ondansetron 4mg and inj. pantoprazole 40mg. Laboratory investigations were done for complete blood count, liver and kidney function test and serum electrolytes. All these test reports were normal.

On 4th day after starting the treatment with amphotericin B patient developed muscular weakness, constipation, fatigue, inability to walk and pain in calf muscles. Physical examination revealed dehydration and abdominal distension. He was conscious, oriented in space, time, and person. Blood sample sent for analysis showed decreased serum potassium levels to 1.74mEq/l.

Suspecting amphotericin B as a causative agent, it was stopped and patient was started on i.v. fluids and potassium replacement in the form of oral potassium bicarbonate syrup 2mEq/kg. Patient improved symptomatically on the same day and his serum potassium levels raised to 3.70mEq/L by the next day.

On reviewing the case we see that there is a temporal association between drug administered and the reaction, there was no other apparent cause for the hypokalaemia and de-challenge was positive. Thus according to WHO-UMC scale, the causality for this reaction was "Probable". On applying the Naranjo scale, the score was calculated as 7 which also falls under "Probable" category.

Case III

The 3rd case is of a baby boy of 2.5 years, weighing 12 kg and suffering from acute myeloblastic leukaemia from the age of 3 months. The patient was admitted with the chief complaints of fever not resolving since last 3 days to the treatment given by private practitioner.

On admission to this institute blood samples were collected for complete blood count, liver and kidney function tests and serum electrolytes. Reports of all these tests were normal. Patient was put on inj. paracetamol 325mg, inj. ceftriaxone 250mg, Inj. ondansetron 4mg. Fever did not respond to this treatment hence suspecting systemic fungal infection, patient was added on amphotericin B (10mg/day).

On 10th day of starting treatment with amphotericin B patient was unable to pass stools and was incessantly crying. Patient's blood report on the same day showed decreased serum potassium values i.e.(2.80mEq/l). Urinary potassium was high (48mEq/l, normal range is 10-40mEq/l).

Suspecting amphotericin B as a causative agent it was stopped. No replacement therapy was given. Symptoms resolved in 2 days after stopping the amphotericin B. Potassium values came to normal on day 4 after stopping amphotericin B.

As per the WHO-UMC causality assessment scale, there is a temporal relation between drug administration and hypokalaemia, the reaction cannot be explained by other drug or disease condition and de-challenge was positive.Thus according to above, the causality is "Probable". Applying the Naranjo scale the score is 7 which also fall under "Probable" category.

Discussion :

Amphotericin B is available in many formulations e.g. amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B colloidal dispersion, amphotericin B lipid complex etc. Amongst these deoxycholate formulation is the most commonly used since its cheaper than others.[5] However, this formulation has the greatest risk of side effects. In all 3 cases described above, amphotericin B deoxycholate was used.[3]

It has been estimated that the incidence of hypokalaemia secondary to amphotericin B administration is as high as 75-90%.[9] Amphotericin B - induced hypokalaemia has been reported to be dose-dependent. Three separate mechanisms mentioned below may be involved in the potassium wasting associated with amphotericin B administration.[6]

1) Amphotericin B may induce intramembranous pore formation, or vacuolation, of the epithelial cells in the distal convoluted tubule of the kidney and in peripheral red blood cells by binding to cell membrane cholesterol.

2) Amphotericin B therapy may result in a defect in the distal tubule proton pump (type 1 renal tubular acidosis), which increases the elimination of potassium.

3) Amphotericin B affects ion transport in the distal colon in humans to enhance sodium reabsorption in the colonic epithelium, with resulting potassium excretion in the feces.

Management of hypokalaemia is done by supplementation of potassium rich food. Potato, sweet potato, white beans, yogurt are the food products which are very rich source of potassium in diet. All the patients which are on amphotericin B treatment should be monitored for serum potassium levels from the beginning of therapy. Liposomal formulations of amphotericin B have better adverse effect profile but these are also known to cause hypokalaemia.[7]

Various potassium supplements are available in market for use in a hospitalised patients e.g. potassium bicarbonate, potassium citrate, potassium chloride. Replacement should be given in the doses of 1-2 mEq/kg/day in 2 divide doses for both potassium bicarbonate and potassium citrate.[8] Rapid recovery occurs in the patients those who are given potassium supplementation.[7]

Amphotericin B lipid preparations are the new gold standard of polyene therapy. These molecules are better tolerated. But their high cost limits their use in resource limited places.[9] Amiloride is a diuretic which is found to be preventive of both hypokalaemia and hypomagnesaemia.[10] Spironolactone a potassium sparing diuretic also has been shown to reduce urinary potassium loss in patients on amphotericin B.[11]

Conclusion:

Invasive opportunistic fungal infections are a serious cause of morbidity and mortality for most of the patients. Therefore, amphotericin B adverse effects management is essential. Clinicians must be aware of this adverse effect. Symptoms suggestive of hypokalaemia should not go un-noticed. Supplementary potassium formulations should be kept ready to administer as soon as the symptoms are noticed. Thus, early recognition, and correction of potassium levels as well as concurrent administration of some potassium sparing agents like spironolactone, amiloride are warranted.

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PUBLISHED CASE REPORTS ON AMPHOTERICIN B INDUCED HYPOKALEMIA

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Liposomal amphotericin B and delayed presentation of renal tubular acidosis: a case report.
MOJ Clin Med Case Rep. 2017;7(1):00189
Muhammad A, Naeem A, Nasr R.

26 years old patient with medical history of HIV (CD4 count <20 and viral load >54,000) was admitted with severe frontal headache of 10 days. After having a negative CT scan for SOL and raised ICP, LP was done and CSF analysis was suggestive of cryptococcal meningitis. Patient received Liposomal formulation of Amphotericin B (AmBisome) and Flucytosine for 2 weeks in the hospital. Patient was found to have persistent hypokalemia with the lowest nadir value of 2.6 mEq/L (Lab normal 3.5-5.0 mEq/L) on day 9 of receiving Liposomal Amphotericin B and serum creatinine (S.Cr) worsened from 0.7mg/dl to 1.5mg/dl at the time of discharge (Lab normal for S.Cr 0.5-1.5 mg/dl). He was discharged on Fluconazole 400mg once a day. One month later, patient came back with complaints of severe generalized body aches and weakness. At the time of admission, he was found to have potassium level of 1.7mEq/L, lowest serum potassium level on the day of admission was 1.3 mEq/L and serum creatinine 1.3mg/dl. Anion gap was 14. Spot urinalysis showed urine Ph of 7.0 (Lab Normal 6.00-8.00). 24-hour urine collection showed urine potassium 27.4 mEq/L (Lab normal 22-160 mEq/L) and urine creatinine 57 mg/dl (Lab normal 20-320 mg/dl), Urine potassium-creatinine ratio was 26.9. Patient was given intravenous potassium supplement and his symptoms improved significantly. He was started on oral potassium chloride and sodium bicarbonate supplementation, observed clinically and on labs, remained stable and was discharged home with K supplements. The impression was renal tubular acidosis type I secondary to recent AmBisome use. There was documented evidence of normal anion gap metabolic acidosis, renal wasting of potassium and hypokalemia in the setting of recent AmBisome.

The AmBisome related nephrotoxicity can present right after the start of medication or it may be delayed and can persist for months as in this case. The cause of this delayed presentation is unknown. The physicians must be aware of the possible delayed presentation of AmBisome induced nephrotoxicity and must monitor patient renal profile after giving AmBisome to their patients.

Amphotericin B induced hypokalemia in a diabetic patient with rhino-orbitocerebral mucormycosis.
Anaesth Pain & Intensive Care 2017;21(1):90-93
Sharma R, Bairagi S, Das S, Kumar J.

Rhino-orbito-cerebral mucormycosis is an aggressive and potentially lethal invasive fungal infection. Surgical debridement and amphotericin B remains the mainstay of treatment, however, associated side effects of amphotericin B like nephrotoxicity, hypokalemia, hypertension and arrhythmias need to be addressed. We discuss the anesthetic management of a 47 year old male with uncontrolled diabetes diagnosed with left sinoorbital mucormycosis posted for surgical debridement. The patient received amphotericin B and insulin preoperatively since the day of admission. Liposomal AmB was not available

initially and could be added a day before surgery only. The serum K^+ level decreased to 2.6 meq/l and Creatinine increased to 1.8 mg/dl which may be due to the nephrotoxic effect of AmB.

Studies indicate that renal function is impaired in more than 80% of patients treated with AmB, with 15% of patients requiring hemodialysis. The anesthetic management of patients with acute tubular necrosis leading to development of acute renal failure is of particular concern for anesthesia providers. Anesthetic management aims at maintenance of an adequate mean arterial pressure while concomitantly avoiding further renal insults. A heightened awareness for renal, electrolyte, hemodynamic, and respiratory aberrancies is warranted for anesthesia providers when treating patients receiving AmB therapy. AmB induced hypokalemia may enhance the effect of skeletal muscle relaxants when administered concomitantly serum potassium levels should be closely monitored.

Hypokalemia can lead to prolonged duration of action of non depolarising neuromuscular blocking agents and lead to delayed or incomplete recovery after the surgery. Hypokalemia also predisposes to arrhythmias and paralytic ileus. We used neuromuscular monitoring (Train of four: TOF) to give optimum doses of rocuronium to avoid these complications.

Since, hypokalemia denotes an intracellular deficit of K+, it important not to aim at its rapid correction in short time period. There were no ECG changes of hypokalemia and we did not aim to correct the levels in the 90 min duration surgery. The patient received oral K+ supplementation preoperatively and low concentration of potassium chloride was given as part of GKI regimen (Glucose-Potassium-Insulin) for diabetes mellitus. AmB lipid preparations are more tolerable, more efficacious and less nephrotoxic. But due to high cost and relative paucity of clinical data lipid formulations are generally used as second line therapy.

Role of diuretics and lipid formulations in the prevention of amphotericin B-induced nephrotoxicity.

Eur J Clin Pharmacol (2013) 69:1351-1368

Karimzadeh I, Khalili H, Farsaei S, Dashti-Khavidaki S, Sagheb MM.

This article gives the result of study done to define the role of diuretics and lipid formulations in the prevention of amphotericin B (AmB)-induced nephrotoxicity (AIN) in human populations.

A literature search was performed in the relevant databases, including Scopus, Medline, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database Systematic Reviews. The key words used were "amphotericin (B) and nephrotoxicity", "amphotericin (B) and renal failure", "amphotericin (B) and renal damage", "amphotericin (B) and renal dysfunction", and "amphotericin (B) and renal impairment". Randomized clinical trials, prospective or retrospective human studies, case series, and case reports were included in this review.

Co-administration of mannitol failed to show any clinically significant benefit in preventing AIN. Potassium-sparing diuretics, such as Amiloride and spironolactone, have been shown to have beneficial effects as an alternative or adjunct to oral/- parenteral potassium supplements in preventing hypokalemia due to AmB. Lipid-based formulations of AmB are clinically effective and safe in preventing AIN. However, due to their high cost and limited accessibility, these formulations are generally used as

second-line antifungal therapy in cases of conventional AmB refractoriness and/or intolerance or pre-existing renal dysfunction. The potential effects of other nephroprotective agents, such as N-acetylcysteine, AIN merit further considerations and investigations.

Acute renal failure in patient treated with ATRA and amphotericin B: case report.

J Bras Nefrol 2011;33(2):276-281

Moresco G, Martinello F, Souza LC.

This is a report of the case of a 47-year-old female patient diagnosed with APL with translocation t(15;17). The patient was pallor, and presented fever (38.6ºC), asthenia, headache and rectal bleeding along with clinical pictures of febrile neutropenia and anemia. For which oral dipyrone 500 mg and intravenous cefepime 2g were administered every eight hours as empiric therapy, for the infection agent had not been isolated. Concomitantly, cytostatic therapy with cytarabine 370 mg/m2/day EV was administered for seven days, mitoxantrone 20mg/ m2/day EV for three days and ATRA 40 mg/ m2/day (continuous oral administration). Repeat hemoculture and uroculture done on the seventh day remained negative. On the same day, the patient presented mouth ulcer and white lesions in the oropharynx at clinical examination, both characteristics of candidiasis. For that, antifungal fluconazole 200 mg/day (oral route) was used. The patient continued to have fever peaks (37.5 to 38.1ºC), and fluconazole was replaced by AB 30 mg/ day EV (6 hours of infusion) on the 13th day. On the 17th day, cefepime (antibiotic) was replaced by meropenem 1 g EV every eight hours, as empiric therapy. Despite the use of hydroelectrolytic replacement therapy from the beginning, potassium values were still decreasing. On the 19th day, the patient was referred to the Intensive Care Unit (ICU) with respiratory failure due to pulmonary hemorrhage, oliguria and intense hypokalemia. From the 17th to the 21st day, diuresis decreased (urinary output was not registered in the file), and urea and creatinine increased, which indicates severe renal damage, leading to the discontinuation of AB therapy on the 21st day.

The patient's renal function was aggravated by the administration of 240 mg of AB (cumulative dose), which can be observed by the fast increase of creatinine and urea, besides the decrease in serum potassium, despite steroid and hydroeletrolytic therapy. Among the drugs that are famous for causing renal damage, antibiotics and non steroidal anti-inflammatories may be cited, and among the most important agents of acute tubular necrosis are aminoglycosides, radiologic contrast agents, cyclosporine and AB. Actually no reports were found in literature regarding the interaction between cefepime and ATRA, therefore, the aggravation of renal function was attributed to AB.

Nephrotoxicity is the most common adverse effect of AB, and it is aggravated when there is already some degree of renal impairment. The main nephrotoxic mechanism is the increase of afferent arteriole resistance and/or tubular permeability. The increase of afferent arteriole resistance decreases renal blood flow and glomerular filtration, and it is a probable explanation for the increase in the plasma creatinine concentration. The high permeability of the luminal tubular membrane to K+ and H+ cations is a result of the formation of intra-membranous pores after AB is connected to the cholesterol of the membrane, enabling K+ loss through urine and plasma K+ decrease. The patient had a decrease in renal blood flow, which led to oliguria, elevation of creatinine and decrease of serum potassium during the administration of ATRA and AB. Another mechanism of renal damage related to ATRA and AB is hypotension-induced endothelial lesion.

In this manner, renal toxicity was not only a consequence of AB therapy. It is likely that ATRA and/or ATRA associated with cefepime or fluconazole have impaired the renal function, making it prone to AB damage. They might have been responsible for the development of renal toxicity, maintained by AB.

Refractory hypokalemia due to conventional amphotericin B in patients with leukemia.

Indian J Cancer 2009;46:76

Bamba AV, Jadhav MP, Prabhu R, Ray S, Gogatay NJ, Jijina FF, Kshirsagar NA.

Parameters	CASE I	CASE II
Age (years)	12	21
Gender	Male	Female
Diagnosis	B-ALL & febrile neutropenia	AML & febrile neutropenia
Absolute neutrophil count	440/mm3	00/ mm3
Conventional amphotericin B dose and day of start of therapy	1 mg/kg/day on Day 5	1 mg/kg/day on Day 4
Baseline serum potassium level	3.8 mEq/l	3.18 mEq/l
Potassium supplement	60 mEq/l	60 mEq/l
Serum Potassium levels	Day 10: 2.8 mEq/l Day 14: 2.9 mEq/l Day 17: 1.6 mEq/l Day 19: 0.9 mEq/l Day 23: 1.9 mEq/l	Day 7: 1.8 mEq/l Day 8: 2.1 mEq/l Day 9: 1.4 mEq/l
Symptoms	Vomiting, diarrhoea, USG abdomen: bulky kidneys, multiple lesions indicative of tubular lesions; anasarca	Severe vomiting, cardiac arrest, ECG: U wave, USG abdomen: medical renal disease, metabolic acidosis
Correction	Potassium supplement: 40 mEq/l tid Amiloride therapy Amphotericin B stopped on day 28	Amphotericin B (AmpB) stopped on day 10. Liposomal (AmpB) 1 mg/kg/day was started. It was stopped due to second cardiac arrest on day12. Potassium supplement: 40 mEq/l tid given
Normalization of potassium levels	Though fever and neutropenia resolved potassium levels normalized only after 45 days	Ten days after stoppage of amphotericin B drug withdrawal.

Both reported cases developed severe refractory hypokalemia in spite of adequate correction due to which amphotericin B had to be stopped. Contributory factors could be AmpB, prednisolone, vomiting and diarrhoea. In leukaemia, hypokalemia occurs as abnormal WBCs take up large amount of potassium and increased urinary loss accompanying blast cell waste. In both patients, Naranjo's probability scale scored the adverse drug reaction as probable association with amphotericin B.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by **Dr Jaisen Lokhande**

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

The following are the selected Signals Reported in the recent WHO Newsletter 2017

Pregabalin and visual colour distortions: 25 reports of pregabalin related changes in colour vision have been reported in the VigiBase based on which it is recommended to add changes in colour vision to the product information leaflet of pregabalin. Pregabalin is used for the treatment of pain due to nerve injury, fibromyalgia, epilepsy, and anxiety disorders. Pregabalin related disturbances in colour vision may occur within hours to days after starting the drug. The adverse reaction appears to be reversible as reported in seven cases who regained normal colour vision after stopping pregabalin.

Although changes in colour vision can have other causes, the relationship with pregabalin is strengthened by the fact that changes in colour vision is a known adverse reaction of other drugs (vigabatrin and tiagabine) which exert their effects in a similar way as pregabalin.

Reference: WHO Pharmaceuticals Newsletter.2017 [cited 2017 August 8].(3) Available from: http://www.who.int/medicines/publications/WHO-Pharmaceuticals_Newsletter_No3_2017.pdf?ua=1

Panic attacks with Levothyroxine: Close to 200 reports in VigiBase has been described in patients who have suffered panic attacks while on levothyroxine treatment. The panic attacks may be reversed upon stopping levothyroxine treatment or lowering the dose which sometimes recurred after repeated exposure.

Reference:WHO Pharmaceuticals Newsletter.2017 [cited 2017 May 1].[2] Available from:http://www.who.int/medicines/publications/WHO_Pharmaceuticals_Newsletter_No2_2017_Rev.pdf

Lamivudine and hearing decreased: Lamivudine is indicated in combination for the treatment of HIV/AIDS, and for the treatment of hepatitis B. VigiBase described 45 reports of lamivudine and hearing decreased which is not labelled as an adverse drug reaction. In most of the reports, lamivudine was mostly co-prescribed with other ARTs, notably stavudine, zidovudine, ritonavir, and nevirapine. The time to onset ranged from 4 days to 5 years (median 9 months) mostly within 2 to 10 months. The biological plausibility includes mitochondrial toxicity of lamivudine and the exposure to event time observed. Even though Lamivudine was co-administered with other ARTs, the evidence is suggestive of a possible causal effect relationship of the lamivudine-hearing decreased combination.

Reference: WHO Pharmaceuticals Newsletter.2017 [cited 2017 May 1].[2] Available from:http://www.who.int/medicines/publications/pharm_news_no1_2017.pdf

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.	Methotrexate	a)	Nephrogenic Diabetes Insipidus
2.	Ethambutol	b)	Pancreatitis
3.	Amphotericin-B	c)	Cardiotoxicity
4.	Ganciclovir	d)	Capillary Leak Syndrome
5.	Fomivirsen	e)	Pseudo-Lymphomatous Reaction
6.	Halofantrine	f)	Pericardial Effusions
7.	Busulfan	g)	Hyperlipidaemia
8.	Gefitinib	h)	Nephrolithiasis
9.	Filgrastim	i)	Pharyngo-Laryngeal Dysaesthesia
10.	Indinavir	j)	Acneiform Skin Rash
11.	Sirolimus	k)	Nephrotoxicity
12.	Oxaliplatin	l)	Cataract Formation
13.	Clofarabine	m)	Myelosuppression
14.	Didanosine	n)	Iritis
15.	Demeclocycline	o)	Retrobulbar Neuritis.

Answers: 1-e; 2- o; 3-k; 4-m; 5-n; 6-c; 7-l; 8-j; 9-f; 10-h; 11-g; 12-i; 13-d; 14-b; 15-a

ALPHABET 'P' PUZZLE

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

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

1. Bone marrow toxicity, especially neutropenia, is the primary toxic effect of this mitosis inhibitor anticancer drug prescribed as combination therapy in the treatment of metastatic ovarian and breast cancer.
2. Being a vesicant, intravenous injection of this Anthracycline antitumor antibiotic can cause extensive tissue damage & blistering if it escapes from the vein.
3. Reduced estradiol plasma concentration occurs with concurrent use of this antiepileptic drug, suggesting the need of higher doses of oral contraceptives when administered with it.
4. Adverse effects like breast tenderness, constipation, loss of libido, hot flushes, sweating, rise in blood glucose levels etc. are commonly seen with the use of this GnRH agonist for treatment of advanced prostate cancer.
5. With this NSAID, fluid retention and raised plasma creatinine concentration are commonly seen in patients receiving diuretics & in those over the age of 60 for which renal function tests should be regularly monitored.
6. Immunoglobulin light chain proteinuria is seen in about 85% of patients of tuberculosis treated with this first line antitubercular drug, which can lead to renal failure.
7. Used to treat schizophrenia or bipolar disorders, this atypical antipsychotic can lead to rise in serum prolactin levels which causes enlarged breasts, missed menstrual periods and loss of libido in females.
8. Severe hypertriglyceridemia is a contraindication to the use of this bile acid sequestrant because of its tendency to increase serum triglyceride levels.
9. 20% of patients receiving this antihypertensive drug develop positive Coombs test, of which 1-5% develop hemolytic anemia which requires prompt discontinuation of the drug.
10. Cardiovascular side effects like deep vein thrombosis, hypertension, myocardial infarction, pulmonary embolism & tachycardia have been reported with Aprepitant, a _____ antagonist, when given in highly emetogenic cancer chemotherapy.

ALPHABET 'P' PUZZLE: ANSWERS :

1. Paclitaxel
2. Epirubicin
3. Topiramate
4. Leuprolide
5. Ketoprofen
6. Rifampicin
7. Quetiapine
8. Colestipol
9. Methyldopa
10. Substance P

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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