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BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

Department of Pharmacology

LTMMC & LTMGH, Sion, Mumbai - 22

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,

I am delighted to put forth this issue of Bulletin on Adverse Drug Reaction.

Oral cavity is a junction of mucosa and cutaneous tissue and is one of the most common sites where Adverse Drug Reactions to large numbers of drugs can be manifested. Even though very few ADRs to oral cavity are life threatening but they still can lead to difficulty in eating and drinking, apart from the cosmetic effects. It is important to know various drugs causing ADR to this tissue, their characteristics with distinctive features and management. The first article deals with the extensive topic and i hope the readers will surely get some valuable information.

The second article also deals with a very important topic of Drugs Induced Seizures, which is preventable to some extent. The article also highlights important aspects on the treatment of this condition.

In this issue we also discuss an interesting case of lithium induced adverse reaction. We have also summarised the ADRs from our institute to provide the glimpse of pharmacovigilance activity at our institute. The puzzle and crossword will surely make it more interesting.

I hope all the readers find this issue informative and interesting.

Finally, I would like to thank all the clinical departments from our institute for their valued contribution to Pharmacovigilance and to the authors for contributing in the bulletin. I would also like to thank all the members of Department of Pharmacology for their efforts in bringing out the current issue of this bulletin.

Thank you.

Dr. Sudhir Pawar

ADVERSE EFFECTS OF DRUGS ON ORAL MUCOSA

Dr Akshil H Mehta*, Dr Supriya D Malhotra, Dr Pankaj R Patel*****

- 3rd year Resident, Dept. of Pharmacology; **- Prof. & Head, Dept. of Pharmacology; *- Dean, Smt. NHL Municipal Medical College, Ahmedabad*

Introduction

Oral mucosa is one of the most common sites where Adverse Drug Reactions (ADR) to large numbers of drugs can be manifested. Drugs causing oral ADRs include nonsteroidal anti-inflammatory drugs (NSAIDs), captopril, methotrexate, antimicrobials (e.g. clindamycin, isoniazid, penicillin and sulphonamides), angiotensin II receptor antagonists, antidepressants and anti-HIV drugs[1-4].

Virtually any drug has potential to cause an untoward reaction but some have a greater ability to do so than others. Pathogenesis of drug reaction may be immunologic or non-immunologic in nature. Three mechanisms have been proposed for immunologic reactions. They could be Ig E mediated, cytotoxic reactions or it could be drug allergy involving circulation of the antigen for extended periods, resulting in sensitization of patient's immune system. Non-immunologic ADRs can occur as extension of pharmacological activity of drugs.

Manifestations of drug reactions are dependent on type of drug, dose and duration of treatment. Oral mucosal membrane may be the only site of ADR involvement or it may involve other areas of the body also. ADRs can be diagnosed by careful history taking and recent use of the suspected drug. Withdrawal of the drug should usually result in improvement in the condition and reinstitution of the drug should exacerbate the condition[5].

Table 1: Common & Uncommon ADRs on Oral Mucosa[6]

Common	Less Common
Oral ulceration	Neoplasms
Mucosal Pigmentation	Pemphigoid reactions
Fixed drug eruptions	Erythema multiforme
Mucositis	Toxic epidermal Necrolysis
Candidiasis	Lupus like disorders
	Lichenoid eruptions
	Leukoplakia
	Hairy leukoplakia

Types of drug related lesions on the oral mucosa

(1) ORAL ULCERATION

This is the most common type of oral lesion due to the ADRs of drug.

The terms 'oral ulceration' and 'aphthous stomatitis' are commonly used synonymously in reports on oral ADRs (OADRs); however, aphthae usually commence in the second decade of life as recurrent oral ulcerations and usually wane during the fourth decade. In contrast, drug-induced ulcerations are present mostly in older age groups and not always as a recurrent pattern. Such lesions are also described as non-specific ulceration. Epithelial necrosis and ulceration may result from direct application to the mucosa of over-the-counter medications such as aspirin, hydrogen peroxide, potassium tablets and phenol-containing compounds. Fixed drug eruptions in the oral cavity often appear initially as areas of oedema and erythema that lead to localized, non-specific ulceration. The labial mucosa is most commonly involved.

A number of drugs are implicated in the development of oral ulcers, including sulphonamides, barbiturates beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), phenolphthalein, nicorandil, dapsone, salicylates and tetracycline. Ulceration of the oral mucosa is a common adverse effect in a wide variety of antineoplastic agents, including methotrexate, melphalan, 5-fluorouracil and doxorubicin.

The key feature of drug-induced oral ulceration is that it does not respond to topical steroid therapy [7-8]. Choosing an alternate drug or decreasing the dosage has been reported to cause remission of the lesion[9].

(a) Drug-related aphthous-like ulceration

Sodium lauryl sulphate may predispose to ulcers similar to aphthous ulceration. There are also case reports of aphthous-like ulceration arising following the use of beta-blockers such as labetalol [10], alendronate, captopril[11-13], nicorandil[14-21], some non-steroidal anti-inflammatory drugs (NSAIDs), mycophenolate or sirolimus[22], protease inhibitors, tacrolimus [23], and sulfonamides, though the exact pathogenic mechanisms are unclear in all of these.

(b) Fixed drug eruptions

Fixed drug eruptions (contact stomatitis) comprise of repeated ulceration at the same site in response to a particular drug and may be caused by anaesthetics, antibiotics, antiseptics, barbiturates, phenacetin, sulphonamides, or tetracyclines. The lesions may be localized to the mouth or can be associated with lesions at other muco-cutaneous sites, and manifest as ulceration, bullae, erythematous patches, or superficial erosions. Initially, the lesions are solitary, but with repeated drug exposure, they may become multiple. A wide range of drugs may cause fixed drug eruption, particularly paracetamol, barbiturates, phenacetin, sulphonamides, and tetracyclines[24].

(c) Drug-related mucositis

Cytotoxic drugs are very commonly associated with mucositis and ulceration, which arises consistently with many chemotherapy regimens, particularly those involving methotrexate, 5-fluorouracil, doxorubicin, melphalan, mercaptopurine, or bleomycin [25]. Such reactions can be so severe as to be treatment-limiting on occasion [26]. Widespread sloughing and ulceration arise within days of commencement of therapy, the associated pain often requiring opioid therapy and/or alteration or cessation of chemotherapy. The ulceration may be a portal of entry for infection and hence a potential cause of septicaemia. Drugs such as phenylbutazone that can cause agranulocytosis may also induce oral ulceration.

Immunosuppressive agents may also cause ulceration. Ulcers in iatrogenically immunocompromised individuals may have a herpesvirus aetiology, or occasionally other infective causes[27-28]. Opportunistic infection secondary to cytotoxic chemotherapy may cause oral ulceration. In particular, herpes simplex virus 1, varicella zoster, and cytomegalovirus give rise to oral ulceration, while, less commonly, ulceration may be due to Gram-negative bacterial infections (e.g., pseudomonas, klebsiella, Escherichia coli, enterobacter, or proteus) or to exogenous bacteria such as tuberculosis[29], or to fungi such as mucormycosis[25].

(d) Drug-related neoplasms and potentially malignant lesions

There is an increased prevalence of dysplastic and malignant lip lesions in immunosuppressed renal-transplant recipients[30-31] and liver transplant recipients[32]. Oral leukoplakia has progressed rapidly to squamous cell carcinoma in some immunosuppressed patients[33], and oral squamous cell carcinoma has been reported in immunosuppressed patients without any recorded precursor lesion.

Post-transplant lympho proliferative disease[34], non-Hodgkin's or MALT lymphoma [35], usually manifesting as ulceration of the gingivae, fauces, or palate [36-37], or, rarely, Kaposi's sarcoma [38-39] may be complications of long-term immunosuppressive therapy, and there have even been reports of the resolution of malignancies where immunosuppression has been reduced[40].

(e) Drug-related pemphigoid-like reactions and other bullous disorders

At least 30 drugs can give rise to conditions resembling bullous or mucous membrane pemphigoid. These drugs belong to a variety of pharmacological groups (thiol sulphonamides, cardio active agents, and penicillin-related antibiotics). The oral mucosa is frequently affected in drug- induced pemphigoid, particularly penicillamine-induced disease, and can be the only affected mucosal surface, although patients often also have cutaneous lesions [41-45]. Other than the high frequency of oral mucosal lesions, the only other clinically distinguishing features of drug-induced pemphigoid are the younger age of affected patients compared with idiopathic (autoimmune) pemphigoid, and the resolution of disease following withdrawal of the causative agent.

Drug-induced pemphigoid may be due to thiol-induced local epithelial damage, drugs acting as haptens, or drug- induced immunological dysfunction. Affected patients can have circulating antibodies to the same antigens as idiopathic pemphigoid, hence making diagnosis of drug-related disease so reliant upon the recording of an accurate drug history.

Linear IgA disease (LAD) can be drug-induced, and affected patients have IgA antibodies to bullous-pemphigoid-associated antigen 1 (BPAG or BP1) or other antigens [46]. LAD is especially commonly induced by vancomycin [47], but other drugs such as angiotensin-converting enzyme inhibitors may be involved[25] and even non-thiol and therapeutically targeted groups, including ACE inhibitors, furosemide, NSAIDs, penicillamine, psoralens, sulphonamides, cardio active agents, and penicillin-related antibiotics.

(f) Drug-related pemphigus

Drug-induced pemphigus is not uncommon[48]. Traditionally, drugs that are capable of inducing pemphigus are divided into two main groups according to their chemical structure-drugs containing a sulfhydryl radical (thiol drugs or SH drugs) and non-thiol or other drugs, the latter often sharing an active amide group in their molecules.

Pemphigus vulgaris may occasionally be associated with drugs with active thiol groups in the molecule. Drugs implicated include penicillamine, phenol drugs, rifampicin, diclofenac, and rarely, captopril, other ACE-inhibitors, and other drugs.

The clinical features of drug-induced pemphigus mimic those of pemphigus vulgaris or foliaceus, and affected individuals can have variable levels of circulating antibodies to epithelial components and to expected antigens (e.g., desmoglein 1 and 3) [47]. Besides from epithelial damage due to the action of these antibodies, some of the implicated drugs are thiols that may induce a fall in local levels of plasminogen activator inhibitor, leading to increased plasminogen activation[48]. Thiols such as penicillamine may also interfere in cell membrane cysteine links, potentially leading to antibody generation[49].

(g) Drug-related erythema multiforme

A wide range of drugs-especially barbiturates, cephalosporin, NSAIDs, anti-tuberculosis agents, oestrogens, phenothiazines, progestogens, protease inhibitors, sulphonamides, sulphonylurea derivatives, and tetracyclines-may give rise to erythema multiforme, and it may be clinically impossible to distinguish drug-induced erythema multiforme from disease due to other causes. The distinction of severe erythema multiforme from toxic epidermal necrolysis is quite unclear[24].

Lesions of erythema multiforme typically affect the oral mucosa, the lips, and bulbar conjunctivae. Initial bullae rupture to give rise to haemorrhagic pseudo membrane of the lips and widespread superficial oral ulceration. Other muco-cutaneous surfaces less commonly affected include the nasopharyngeal, respiratory, and genital mucosae.

(i) Drug-related toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN; Lyell syndrome) is clinically characterized by extensive muco-cutaneous epidermolysis preceded by a macular or maculopapular exanthema and enanthema [50,45]. Intra-orally, there is widespread painful blistering and ulceration of all mucosal surfaces. Toxic epidermolysis may be associated with antimicrobials (sulphonamides, thiacetazone), analgesics (phenazones), anti-epileptics, allopurinol, chlormezanone, rifampicin, fluconazole and vancomycin.

(j) Drug-related lupus-like disorders

Systemic lupus erythematosus (SLE) may be induced by a wide variety of different drugs. Indeed, over 70 agents have been implicated in causing drug-induced lupus. The most commonly implicated agents of drug-induced SLE are procainamide and hydralazine, although drugs less commonly associated include chlorpromazine, isoniazid, methyldopa, penicillamine, and quinine, as well as whole groups of drugs such as anticonvulsants, beta-blockers, sulphonamides, and others.

(2) DRUG-RELATED WHITE LESIONS

(a) Lichenoid eruptions

Since the advent of antimalarial therapy, there have been an ever-increasing list and spectrum of drugs that may give rise to muco-cutaneous lichen planus (LP)-like eruptions (lichenoid reactions) [51-52]. However, many of the reports claiming associations have been single case reports, and many of the drugs implicated in cutaneous lichenoid reactions have not been shown to be associated with oral lesions.

The possible association of drugs with lichenoid reactions was noted when quinacrine and mepacrine, used as antimalarial during World War II, were seen to cause lichenoid lesions. Apart from these drugs, gold was probably the most common agent recognized as initiating a lichenoid reaction[53]. Gold salts can cause a range of mucocutaneous lesions[54] of which oral lichenoid lesions may be the first[55].

The drugs now most commonly implicated in lichenoid reactions are the non-steroidal anti-inflammatory drugs and the angiotensin-converting enzyme inhibitors [56]. Lichenoid reactions also may follow the use of HIV protease inhibitors, antihypertensive agents, antimalarials, phenothiazine, sulphonamides, tetracyclines, thiazide diuretics, and many others[57-61], but the list of drugs implicated lengthens almost weekly and, interestingly, includes several agents which have also been used in the therapy of lichen planus, particularly dapsone (Downham, 1978), levamisole [62], tetracycline and interferon. Occasionally, there are lichenoid reactions to multiple drugs[63].

Several questions remain regarding drugs as causal agents of these reactions. For example, why can the same drug bring about different clinical manifestations? How can different chemical structures coincide in the clinical expression of their side-effects? and How can some drugs belonging to the same family (such as antimalarials) produce a lichenoid reaction and at the same time find some use in the treatment of oral lichen planus (LP)?

The exact pathogenic mechanism by which drugs may cause LP-like disease are not known. Some of the agents implicated (e.g., penicillamine, captopril, and gold sodium thionalate) are thiol-like and hence implicated in pemphigus-like disease. However, in LP, quite different immunological mechanisms are involved. It is likely that Grinspan's syndrome simply represents a drug-induced disorder [64], and drug therapy may occasionally account for the co-occurrence of LP with lupus erythematosus or bullous-like disease [65]. Clinical identification of lichenoid drug reactions has been based largely on subjective criteria: There does seem to be sometimes a tendency for these oral lesions to be unilateral [66] and erosive, but these features are by no means invariable. Histology may help; lichenoid lesions may have a more diffuse lymphocytic infiltrate and contain eosinophils and plasma cells, and there may be more colloid bodies than in classic LP, but there are no specific features [67], and immunostaining is usually non-contributory, though basal cell cytoplasmic antibodies may be found[66], but this has not been con- firmed [68] and surely occurs less reliably than in cutaneous drug reactions.

(b) Lupoid reactions

Drugs causing lupoid reactions include ethosuximide, isoniazid, phenytoin, sulphonamides, gold, methyldopa, phenothiazines, tetracyclines, griseofulvin, para-aminosalicylate, procainamide, hydralazine, penicillin and streptomycin.

(c) Candidiasis

Pseudomembranous candidiasis arises secondary to therapy with broad-spectrum antibiotics[69], corticosteroids and other immunosuppressive regimens (e.g., cyclosporin) and cytotoxic therapies.

(d) Papilloma

Human papillomavirus infection manifesting as warty-like growths may arise in patients on long-term immunosuppressive therapy.

(e) Hairy leucoplakia

Oral hairy leucoplakia, usually affecting the dorsum and lateral borders of the tongue and floor of mouth, may be a consequence of Epstein-Barr virus infection, associated with therapy with corticosteroids (topical and systemic), cyclosporine, or other long-term immunosuppressive regimens[70].

(f) Leucoplakia

Tobacco and alcohol use are important risk factors for leucoplakia[71-72] and oral epithelial dysplasia[73]. An increased frequency of lesions with epithelial dysplasia of the lips (but not oral mucosa) has been observed in some but not all iatrogenically immunosuppressed patients[31,74].

(3) Drug related mucosal pigmentation

Table 2. Drug-related oral mucosal pigmentation of different colors[24]

Blue	Brown (hypermelanosis)	Black	Grey	Green
Amiodarone	Aminophenazone	Amiodiaquine	Amiodiaquine	Copper
Antimalarials	Bismuth	Bismuth	Chloroquine	
Bismuth	Busulphan	Methyldopa	Fluoxetine	
Imatinib	Clofazimine	Minocycline	Hydroxychloroquinine	
Mepacrine	Contraceptives		Zinc	
Minocycline	Cyclophosphamide			
Phenzopyridine	Diethylstilbestrol			
Quinidine	Doxorubicin			
Silver	Doxycycline			
Sulphasalazine	Fluorouracil			
	Heroin			
	Hormone-replacement therapy			
	Ketoconazole			
	Methaqualone			
	Minocycline			
	Phenolphthalein			
	Propranolol			
	Zidovudine			

Management of ADRs on oral mucosa:

Several oral lesions and symptoms caused by drug reaction can simulate systemic diseases and be treated with local or sometimes systemic medical treatment. The first step is to find out whether the oral manifestation started after the use of a specific medicinal product, and it is then necessary to determine whether the illness could be due to the drug.

The initial history should include a recording of all prescription and non-prescription drugs taken within the last month, including dates of administration and dosage. The temporal relationship between drug intake and the onset of clinical symptoms is critical. Unless the patient has been previously sensitized to a drug, the interval between starting therapy and the onset of reaction is rarely less than 1 week or more than 1 month. [25]

Most of the ADRs of oral mucosa could be controlled by withdrawing the culprit drug. Though in some cases additional medical management may be required e.g. folic acid supplement along with methotrexate therapy. Some ADRs like pigmentation are non-aggravating which may not need medical intervention. Papilloma and candidiasis due to long term immunosuppressive therapy can be prevented by proper hygiene and care. Neoplasms, TEN, erythema multiforme needs glucocorticoids and other medical and or surgical interventions.

Conclusion:

As oral mucosa is a site where many drugs cause adverse drug reaction with varying characteristics with distinctive features. It is advisable for clinician to be appraised of them. They can be very useful in diagnosing early signs of ADRs and thus preventing serious ADRs by allowing to discontinue treatment and planning alternate course of treatment. Most of these ADRs can be cured by withdrawing causative drug. Very few are life threatening but as they make difficulty in eating and drinking, they are important.

Conflict of interest: None declared.

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DRUG INDUCED SEIZURES

Dr Pooja Vaidya
Specialty Medical Officer, Dept of Pharmacology, LTMMC & GH, Sion, Mumbai-22

Seizures in a patient taking a medically prescribed drug is a serious adverse drug reaction.[1, 2] Drug induced seizures occur either due to exposure to or withdrawal from a medication, drug or a toxin.[3] The vital characteristics of the drug responsible for a seizure include class, dose and route of administration. Whereas, the patient factors that predispose to drug induced seizures include pre-existing neurological illness, concomitant medical illnesses, old age, liver failure, renal insufficiency, family history of epilepsy, non-compliance with antiepileptic treatment, use of concomitant drugs, stress, sleep deprivation, and alcohol abuse.[2] These factors together lower the seizure threshold.

Majority of these seizures are self-limited and do not cause permanent sequelae. Nonetheless, repeated or prolonged seizure activity can cause irreversible neurological injury and life-threatening complications including hypoxia, hypotension, pulmonary aspiration, hyperthermia, rhabdomyolysis and metabolic acidosis.[3] Data about drugs commonly responsible for drug-induced seizures is limited, particularly in children. Moreover, thorough acquaintance with the likely causative agents would be valuable to clinicians and could potentially guide the therapeutic approach.

Epidemiology

In published literature, 6% of new-onset generalized tonic clonic seizures in individuals older than 16 years presenting to the emergency department at a single centre over a five year period were ascribed to drug exposures, excluding alcohol withdrawal which accounted for 17.6% cases.[4] Whereas, in an urban hospital, 9% of adults treated for status epileptics had drug induced seizures.[5]

The drugs causing seizures also vary geographically. Two studies in USA showed that antidepressants were the most common drug class implicated, with bupropion being the most commonly identified drug followed by anticholinergics.[6, 7] In Switzerland, mefenamic acid and citalopram were the most commonly implicated drugs in seizures.[8] In Iran and Australia, tramadol overdose was the common cause of seizures and herbicides and insecticides were implicated in developing countries.[3] A study in the USA recognised that the drugs responsible for seizures showed rapid transition from cocaine, benzodiazepine withdrawal, and tricyclic antidepressants to atypical antidepressants.[6]

Pathophysiology

Typically, sudden onsets of disparity between the excitatory and inhibitory forces result in activity in the cerebral cortex resulting in uncontrolled neuronal stimulation. The primary neurotransmitters involved are acetylcholine, gamma-aminobutyric acid (GABA), and glutamate.Periodic oscillations of these neuro-transmitters occur in the thalamic cortical circuit and are regulated by serotonergic, noradrenergic and cholinergic brainstem pathways.[9]

Drugs can decrease the inhibitory GABA neurotransmission and lead to over activation resulting in seizures due to membrane depolarization.[3] For e.g. isoniazid or cephalosporin overdose causes seizures by decrease in GABAergic neurotransmission[10].

The release of excitatory neurotransmitter glutamate is mediated by three main receptors: NMDA, AMPA/kainite, and metabotropic. Chronic ethanol use leads to an increase in NMDA receptors. On sudden cessation of alcohol use, the increased neuroexcitatory tone is unmasked which may trigger convulsions.[11]

However, no single mechanism can explain all cases of drug-induced seizures.[3] Certain drugs cause secondary seizures through indirect effects on brain perfusion, oxygenation or metabolic disturbances. Narcotics induce hypoxaemia and seizures by direct injury to lung parenchyma or by pulmonary aspiration of gastric contents.[9] Carbon monoxide and cyanide interfere with cellular oxygen utilization resulting in hypoxia and seizures. Even electrolyte disturbances such as hyponatraemia, hypomagnesaemia and hypoglycaemia can lead to seizures. For e.g. sulfonylureas induce seizures via hypoglycaemia, 3, 4-Methylenedioxymethamphetamine (MDMA) via hyponatremia, salicylates via cerebral oedema.[1, 2, 6]

Some toxins such as strychnine can induce spinal seizures characterized by involuntary muscle contraction, myoclonus, hyper-reflexia and opisthotonus without loss of consciousness. Strychnine competitively inhibits the action of glycine, a major inhibitory neurotransmitter in the spinal cord and brain stem and results in seizures. Similarly, tetanus toxin prevents the release of glycine from the pre-synaptic membrane and induces seizures.[3]

Drugs frequently implicated in drug induced seizures

Drug related factors that contribute to the condition include intrinsic epileptogenicity of the substance, dose, route, and central nervous system (CNS) levels. Drugs with a high lipid solubility, low molecular weight, low protein binding and weakly polar are more likely to enter the CNS.[2, 9]

Drugs which induce seizures are classified as psychotropic and non-psychotropic agents. Seizures may also occur as an indirect effect of antiepileptic drugs, miscellaneous agents and drug-drug interactions. Psychotropic drugs include antidepressants, antipsychotics and anti-epileptics, whereas non-psychotropic agents include narcotics, methylxantines, anticholinergics and several miscellaneous drugs as described herewith (Table 1).[1]

Table 1: Drugs frequently implicated in causing seizures

Class of drugs	Examples
Anti-epileptics	Phenytoin, carbamazepine, lamotrigine, tiagabine, vigabatrin
Antidepressants and Antipsychotics	Tricyclic antidepressants, citalopram, escitalopram, bupropion, SSRI, venlafaxine, lithium, chlorpromazine, phenothiazines, clozapine, olanzapine, quetiapine
Analgesics	Propoxyphene, tramadol, mefenamic acid, salicylates, meperidine, phenylbutazone
Antibiotics	Carbapenems (meropenem, imipenem/cilastatin), cephalosporins, erythromycin, gentamicin, fluoroquinolones (ciprofloxacin, enoxacin, norfloxacin, ofloxacin), nalidixic acid, penicillins, antimalarials
Drugs of Abuse	Cocaine, amphetamines, MDMA, phencyclidine, ketamine
Withdrawal	Ethanol, baclofen, sedatives - hypnotics
Miscellaneous agents	Methylxanthines, isoniazid, anticholinergics, organochlorine pesticides, organophosphate pesticides, camphor, lindane, nerve agents, carbamates, chloroquine, quinine, asphyxiants, Iron
Natural Substances	Gyomitra esculenta (mushrooms), jimson weed (Datura stramonium), ephedra

Psychotropic agents inducing seizures

Anti-epileptics: Seizures after anticonvulsant overdose is a rare finding and can occur after exposure to phenytoin, carbamazepine, vigabatrin, tiagabine, and lamotrigine.[12] The elderly are at a higher risk of confusion and medication misuse, thus increasing the likelihood of seizures. Moreover, exacerbation of pre-existing seizures may ensue because of acute or chronic toxicity, sudden withdrawal or by an indirect mechanism. For e.g. Carbamazepine can lead to seizures via inappropriate anti-diuretic hormone secretion and hyponatraemia. [12]

Antidepressants and Antipsychotics: Incidence of seizures at therapeutic doses of antidepressants and antipsychotics range from 0.1-1.5%. In overdose, the risk increases to 4 to 30%. Skowron et al has categorized the antidepressants in order of their probability to precipitate seizures. (Table 2)

Table 2. Antidepressant precipitated seizures [13]

Probability of inducing seizures	Antidepressants
High	Clomipramine, amoxapine, maprotiline, bupropion
Intermediate	Amitryptiline, imipramine, desipramine, nortryptiline, protriptyline, doxepin
Low	Fluoxetine, sertraline, paroxetine, fluvoxamine, trazodone
Minimal	Tranylcypromine, phenelzine

Tricyclic antidepressants (TCA): Most of TCA induced seizures are associated with acute overdose with an incidence of 10% with drug overdose. The mortality rate from overdose remains significantly

more up to 10% than other antidepressants. A study of TCA induced seizures has shown that seizures are generalized, brief, and occur within 1.5 hours of ingestion. Sustained seizures may occur in up to 17% of TCA overdoses. Of all the TCA's, clomipramine has been reported to have a greater seizure risk at doses greater than 300 mg/day. [14]

Bupropion: Monocyclic antidepressant was initially withdrawn from the U.S. market due to possibility of seizures, but was reintroduced later. Thundiyil et al has demonstrated that bupropion is the most common cause of new onset seizures attributable to drug exposures.[7] In studies of bupropion overdoses, the seizure incidence ranges from 11- 15%, and this rate was highest among those taking an extended release preparation. A significant number of patients experienced seizures greater than 8 hours post ingestion.[15]

Citalopram and Escitalopram: Seizures occur in 5-15% of overdose cases. Citalopram causes QT prolongation, sedation, bradycardia, and hypotension leading to convulsions. [16]

Venlafaxine: Seizures are observed in 0.26% of patients at therapeutic doses, whereas in overdose, it has a dose dependent pro-convulsant effects with an incidence up to 14%. Doses of 900-1500 mg are associated with seizures.

Antipsychotics: First generation anti-psychotics have a low incidence of seizures. A retrospective cohort study showed that second generation antipsychotics carry significant risk. The seizure incidence appears to be highest with clozapine (2.8%) and olanzapine (2%). Clinical reports imply that haloperidol, molindone, pimozide, thioridazine, thiothixene and risperidone exhibit lowest seizurogenic effects. Factors implicated in the occurrence of seizures in patients receiving antipsychotics include elderly age group, high dose therapy and rapid titration. Moreover, risk of seizure is greater in epileptics as competitive enzyme inhibition by the anti-psychotics decrease anticonvulsant serum concentrations and can precipitate convulsions. [1]

Specific stimulants: Cocaine, amphetamines, MDMA exhibit proconvulsant effect probably attributed to increase in norepinephrine and serotonin levels. Stimulant induced seizures are associated with a higher mortality rate. A case series determined that 3 out of 7 deaths were attributed to stimulant abuse induced seizures. [7]

Cocaine can trigger seizures in patients with epilepsy and in alcoholic patients during the detoxification period. Though less common, but a single dose of amphetamines or analogous substance (e.g., ephedra) can trigger seizures cluster. Amphetamines are the fifth leading cause of drug induced seizures due to their direct effects on serotonin and indirect effects of hyponatremia. Mortality due to MDMA is directly linked with number of seizures.[17]

Non-psychotropic agents inducing seizures

Antimicrobials: The various antimicrobials differ in their potency to cause neurotoxicity. Among the beta lactam antibiotics, penicillin G, cefazolin and imipenem/cilastatin have a greater potential than others. Myoclonus and grandma seizures were the most frequent types associated with penicillin toxicity. Seizure like activity due to imipenem and cilastatin has been increasingly reported in the literature and with a higher predisposition in elderly. Other agents reported to cause drug induced

seizures are reported in the table 1 above. Drugs like aminoglycosides, metronidazole and quinolones have reduced clearance in the elderly predisposing them to neurotoxicity due to drug accumulation.[1,2] Mefloquine and chloroquine constitute antimalarial quinolones. Seizures have been reported with both prophylactic and therapeutic dose of mefloquine and is not recommended in patients with epilepsy. Rarely seizures have been reported in patients on chloroquine. However, it is not contraindicated in patients with epilepsy.[2]

Narcotics: An estimated incidence of seizures in opioid abusers in 12.5%. Seizures occur in as many as 20.2% of patients presenting with propoxyphene abuse. Of these seizures, 87% were generalized tonic-clonic and typically manifest in 2 hours. The metabolite of meperidine, normeperidine, is highly epileptogenic. There exists an increased risk with high doses or in patients with compromised kidney function.[18]

In case of tramadol, seizures occur not only in overdoses but even in therapeutic dose. The convulsions are not dose dependent. A study revealed 13.7% incidence of seizures in patients on tramadol and chronic use increased risk. Seizure activity also has been reported when reversing the effects of tramadol by using naloxone.[19]

Methylxanthines: Seizures can occur even at therapeutic doses and are more likely to occur with serum levels of greater than 100 mg/dL in acute exposures and 60 mg/dL in chronic toxicity. Preclinical data suggest that blockade of the adenosine A1 receptor is the mechanism for theophylline induced seizures.[20]

Isoniazid: In case of overdoses, deficiency of pyridoxine which is required to convert glutamate to GABA is suggested as the causative factor for seizures. A retrospective review of 52 cases of INH overdoses reported that seizures were found in 100% cases. A natural substance, the false morel mushroom (Gyromitra esculenta) acts by similar mechanism. It is metabolized into monomethylhydrazine, which is structurally same as isoniazid and results in a functional depletion of vitamin B6 and GABA. [10]

Anticholinergic Drugs: These are reported to account for up to 10% of drug induced seizures. [7] Diphenhydramine is the most commonly ingested anticholinergic agent and can cause seizures in overdose.

Jimson weed (Datura stramonium) is a common weed consumed for its hallucinogenic and euphoric effects in the United States, and toxicity often results due to intentional ingestion by teenagers. It contains the belladonna alkaloids atropine, L-hyoscyamine, and L-scopolamine, causing anticholinergic toxicity and seizures. [7, 9]

Household toxins like camphor and phenol can be ingested accidentally. Khine et al. reported a cluster of camphor-induced seizures in children associated with imported or illegally sold camphor products. [21]

Local Anaesthetics: Toxicity can be seen when excessive doses are administered (> 4.5 mg/kg lidocaine). Higher dose symptoms include CNS excitation, seizures followed by respiratory depression, coma.[22]

Drug withdrawal inducing seizures

The common drugs causing seizures via withdrawal include alcohol and sedative-hypnotics. Drug withdrawal causes decrease in GABA and subsequent loss of NMDA receptor inhibition. The result is increased glutamate stimulation, excitatory and a hyperadenergic state with potential for seizure activity. In ethanol withdrawal, seizures occur typically within 6-48 hours after cessation of drinking. The onset of symptoms after benzodiazepine withdrawal, is not as predictable due to varying half-lives and pharmacokinetics of the various agents.[1, 7]

Clinical Presentation of Drug Induced Seizures

Differentiating drug and toxin induced seizures from other causes is a difficult task unless there is a history of overdose of any specific drug. In conditions wherein there is no history of epilepsy, patient is not hypoxic or hypoglycaemic, the physician should maintain a high index of suspicion to consider drugs or toxins as the aetiology. Conversely, in case of focal seizure, if there is no alteration in level of consciousness or a post ictal period, then the seizure is unlikely to be drug related.

If there is suspicion for drug induced seizures, the patient's past and family history, current illness and certain clinical clues can prove useful. The patient's access to medications should be assessed. Previous medical history of tuberculosis or epilepsy may suggest isoniazid or tiagabine induced seizures respectively. Prolongation of QRS on ECG points towards TCA, propoxyphene, venlafaxine, or diphenhydramine overdose. A sympathomimetic toxidrome prior to seizure activity suggest stimulant or drug withdrawal. Serum levels of certain medicines or toxins and sometimes drug screens may help clarify the aetiology. [2, 9, 23]

Management of Drug induced seizures

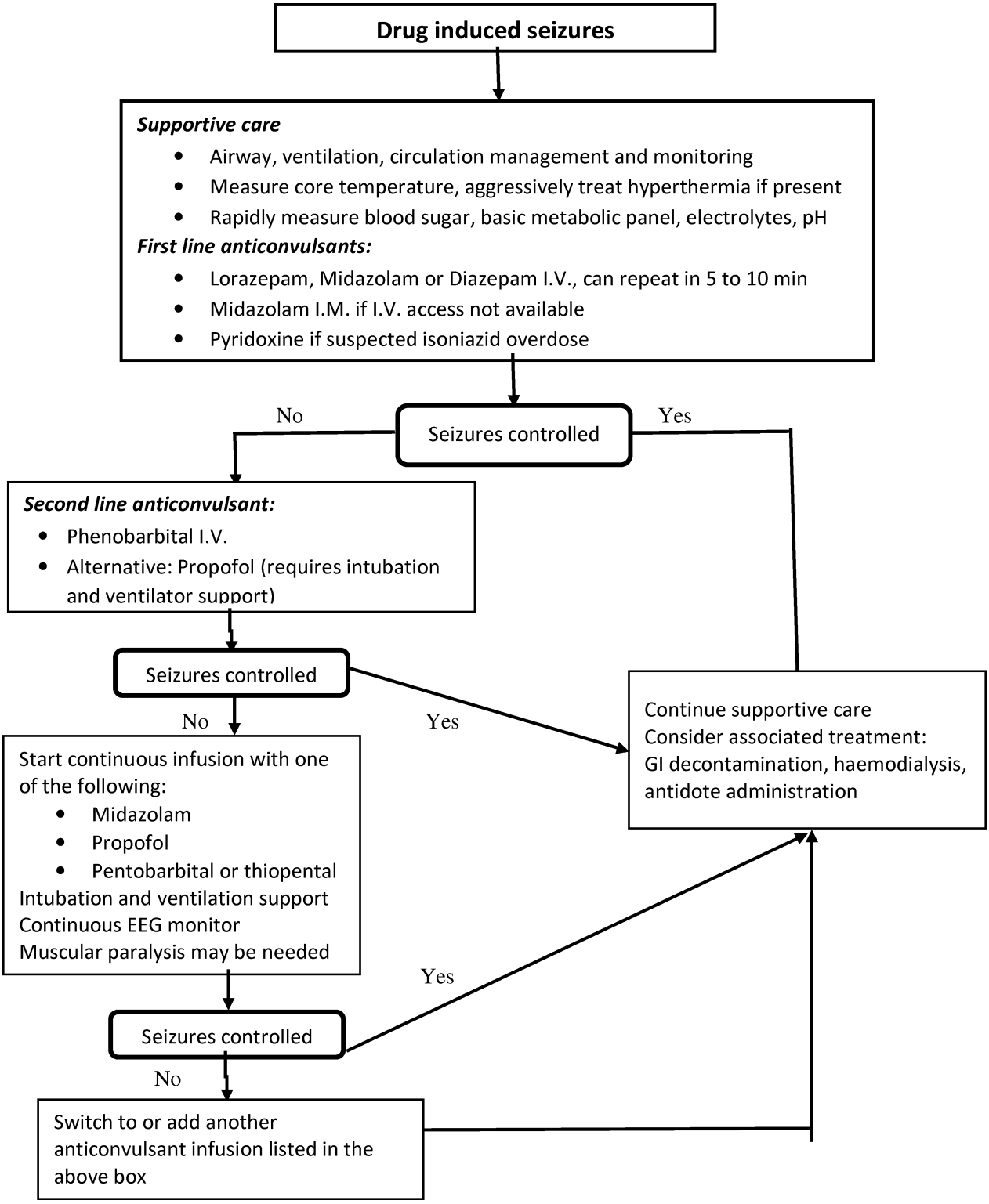
Majority of drug induced seizures present as generalized tonic clonic motor activity. It is often self-limited, however, prolongation of the convulsive muscle activity can lead to hypoxia, hypercarbia, pulmonary aspiration of gastric contents, lactic acidosis, hyperthermia and rhabdomyolysis.

Initial treatment consists of airway management with adequate oxygenation and ventilation, stabilization of the blood pressure and heart rate and rapid testing of serum glucose concentration and core body temperature. [3]

The recommended treatment approach for drug induced seizures is as depicted in the figure 1 below. The recommended first line anticonvulsant therapy in drug-induced seizures is benzodiazepines.[3] Pyridoxine (vitamin B6) is an essential cofactor in GABA synthesis and is the drug of choice for seizures due to suspected isoniazid toxicity, and can also be used in poisoning by certain Gyromitra mushrooms.[10] If benzodiazepines are ineffective, phenobarbital is recommended as the second line treatment. Studies have reported effectiveness of barbiturates in fluvoxamine-induced seizures resistant to benzodiazepines. Moreover, preclinical studies also suggest superiority of phenobarbital over phenytoin in prevention of theophylline-induced seizure and death.[3, 9, 23]

Propofol with an additive or synergistic effect is an alternative second line treatment. However due to high cost, potential to cause hypertriglyceridemia, propofol infusion syndrome and neuroexcitatory events, it is reserved for patients with refractory status epilepticus.[3] The doses of the first and second line anticonvulsants for the treatment of drug induced seizures is as given in the figure 2.

Figure 1: Recommended treatment approach for drug induced seizures [3]



The role of phenytoin in drug induced seizures is questionable and not recommended. Pre-clinical studies and case reports have shown that phenytoin did not effectively terminate seizures produced by a variety of substances. Moreover, phenytoin may be harmful and exacerbate cardiac conduction abnormalities when used to treat seizures induced by lidocaine, theophylline, isoniazid, local anaesthetics and tricyclic antidepressants. Phenytoin was also ineffective in preventing recurrent alcohol withdrawal seizures in various studies.[3]

Figure 2: Anticonvulsants for drug induced seizures [3]

Drug	Initial/ Loading dose	Continuous infusion
Diazepam	5 - 10 mg IV (children: 0.2 to 0.5 mg/kg) over 2 to 5 min (max 10 mg/day); may repeat every 5 - 20 min	Note: contains propylene glycol
Lorazepam	2 - 4 mg IV (children: 0.05 to 0.1 mg/kg, max 4 mg/day); may repeat every 5 - 10 min (max rate: 2 mg/min)	Note: contains propylene glycol
Midazolam*	I.V.: 0.05 - 0.2 mg/kg (children: 0.1 - 0.3 mg/kg) over 20 - 30 sec (max 10 mg) I.M.: 0.1 - 0.2 mg/kg (max 10 mg)	0.05 to 2 mg/kg/hr titrated to EEG
Pentobarbital	5 - 15 mg/kg I.V. (children: 3 -15 mg/kg) no faster than 1 mg/kg/min	0.05 to 2 mg/kg/hr titrated to EEG
Phenobarbital	15 - 20 mg/kg I.V. no faster than 1 mg/kg/min. An additional 5 - 10 mg/kg dose may be given 10 min after initial dose	Note: contains propylene glycol
Propofol $	1 -2 mg/kg I.V.	1.5 - 10 mg/kg titrated to EEG
Thiopental	2 - 7 mg/kg I.V. no faster than 1 mg/kg/min	0.5 - 5 mg/kg/hr titrated to EEG

*Consider I.M. route when there is no I.V. access

$ - Propofol is not recommended for infants and young children.

Other anticonvulsants such as valproate are not recommended in certain conditions such as prophylaxis of clozapine-induced seizures. Studies have shown to increase the threshold for theophylline- induced seizures in preclinical study. Ketamine was useful in tetramine poisoning in which seizures were refractory to benzodiazepines and thiopental. Levetiracetam has been reported effective in patients with nerve agent and pilocarpine neurotoxicity. Other potentially effective therapies still in development include adenosine analogues and cannabinoid receptor agonists.[3, 9]

Prevention of Drug induced seizures

Awareness about the potential of various drugs to cause seizures is important for all physicians,

particularly those in emergency, neurology, or intensive care settings. Premarketing studies, case reports of adverse outcomes, post-marketing surveillance and physician alert notices educate physicians to be aware of the potential hazards of a drug. Moreover, in a therapeutic set-up, identification of patients at increased risk is an important and potentially preventative step. Those with history or presence of progressive neurological disease, extremes of age, renal impairment (where relevant to the drug pharmacokinetics e.g., antibiotics) and co-administration of other drugs with neurotoxic or epileptogenic potential have an increased risk of seizure precipitation. In an epileptic patient, it is prudent to optimise anticonvulsant drug therapy first. In some cases, anticipatory treatment may be possible. For example, using pyridoxine with isoniazid and avoiding theophylline or clozapine in patients with a history of epilepsy. It is easy to misattribute a changing mental status to other factors in acutely unwell, particularly older patients and in case of doubt, neurological clinical assessment and, if indicated, EEG should be considered.

The patients should also be advised to inform their physicians of additions or changes in medications made either by other physicians or by patient using over the counter and/or complementary medicines. Additionally, periodic review of the necessity for, and the benefits and adverse effects of, the prescribed drugs should be made. Thus, rational prescribing and patient education are the best strategies to prevent drug-induced seizures. [1, 2]

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SUMMARY OF ADRs IN LTMMC & LTMGH

(July 2016 to October 2016)

Compiled by Swati Vaidya

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

Total Case Reports: 133

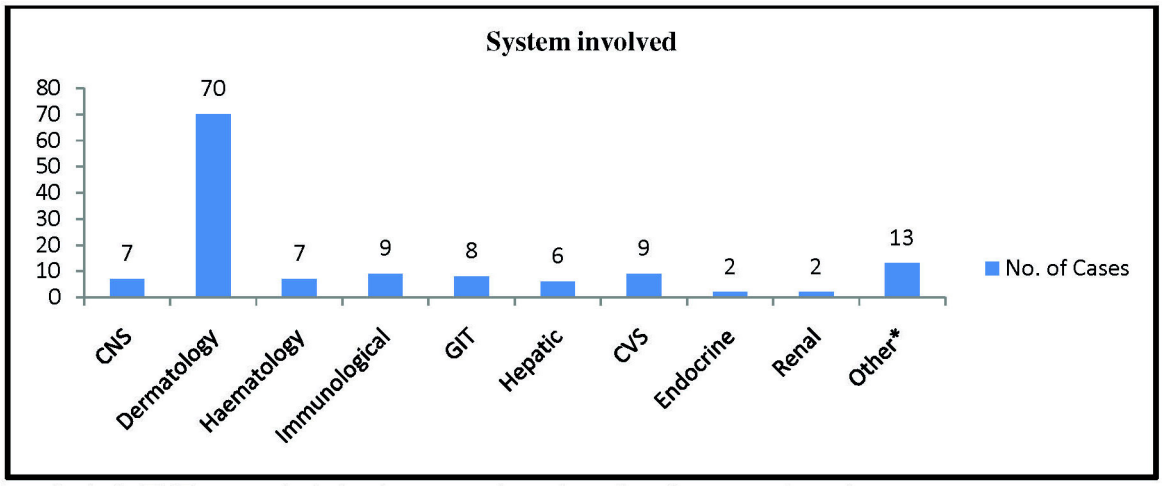
I. Age and Gender distribution:

Age groups	Number of patients	Males	Females
<3 yrs	21	10	11
3 - 17 yrs	32	26	6
18 - 44 yrs	58	30	28
45 - 60 yrs	17	10	7
>60 yrs	5	4	1
Total	133	80	53

II. Seriousness of the reaction:

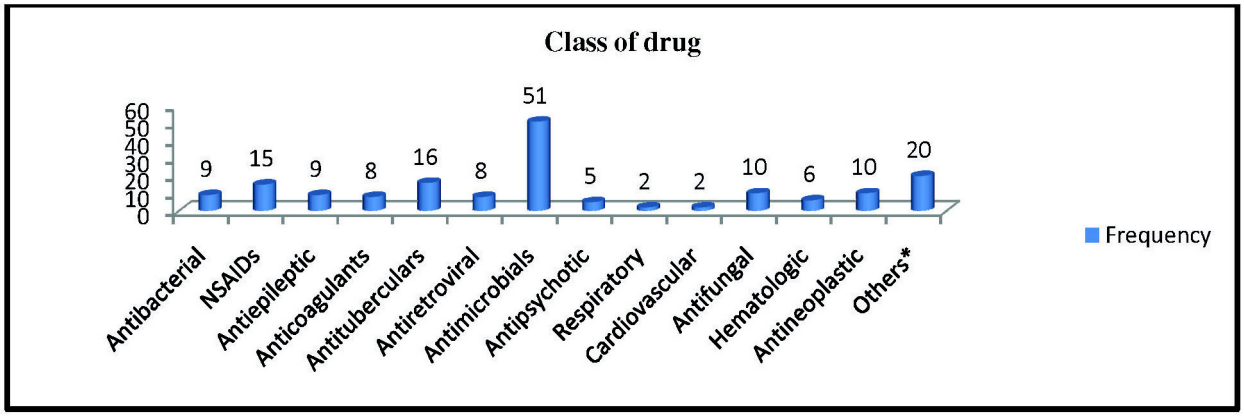
Seriousness of the ADR	No. of Cases (N=133)
Yes	106
No	27

III. System involved in the ADR : N=133



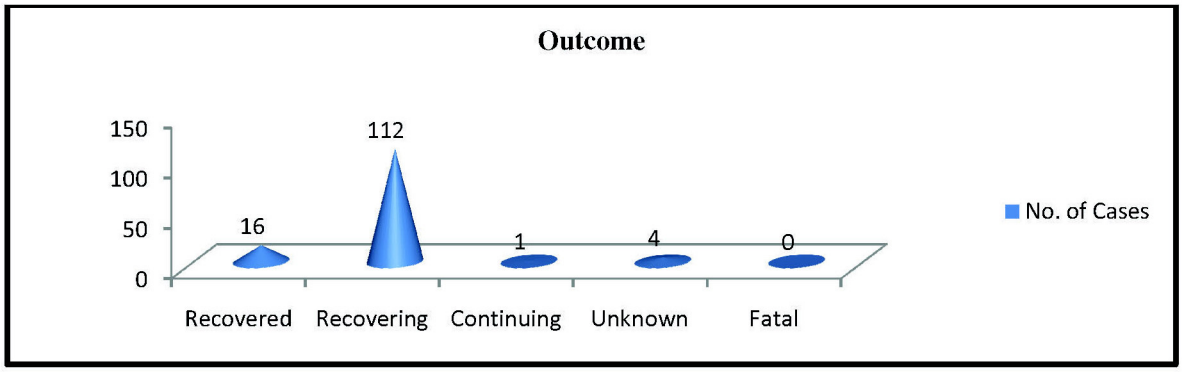
*Others include ENT, musculoskeletal system, electrolyte disturbances and respiratory system.

IV. Class of the Suspected drug: N=133

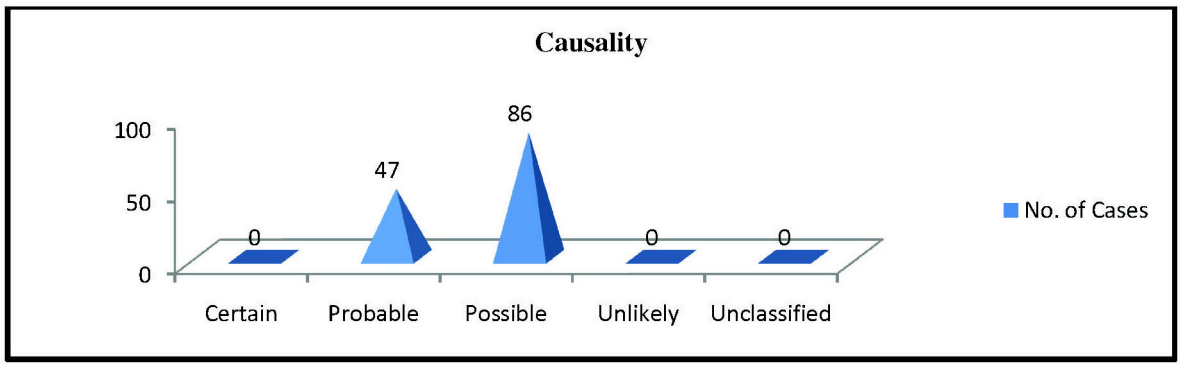


*Other drugs includes antifungals, antivirals, antihypertensives, antipsychotic, haematinics, diuretics, radiocontrast media, sedatives, prokinetics and antispasmodics.

V. Outcome of the reaction : N=133



VI. Causality assessment (WHO UMC Classification): N= 133



EVALUATION OF A CASE

The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT)

***Dr. Trupti Jadhao, #Dr. Kshitija Jain, ##Dr. Trupti Trivedi, ###- Dr. Nivedita Moulick**
****Dr. Neha Kadhe, ***Dr. Sudhir Pawar**

-Second year resident,- Additional Professor, ***-Professor & Head-Department of Pharmacology, LTMMC & GH, # - Third year resident, ## - Associate Professor, ###-Professor & Head, Department of Medicine LTMMC & GH.*

Introduction

Lithium is widely used in the treatment of psychiatric and neurologic disorders, such as bipolar disorders and cluster headache.[1-3] Since it has a low therapeutic index, toxic levels are frequently seen in clinical practice[4-5]. In fact, lithium's adverse effects occur not only during acute drug intoxication, but also at therapeutic levels. Several neurologic disturbances are related to lithium, most commonly tremor[6]. Fortunately, these adverse effects are reversible upon drug discontinuation in most cases. Rarely, however, lithium-induced persistent neurologic disorders have been reported, particularly cerebellar dysfunction[7-8].

Although the first report on persistent sequelae of lithium ion intoxication appeared in 1965 (Verbov et al.,1965)[9-10], there has been a general lack of awareness about irreversible complications of lithium treatment. So we are presenting a case of Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT).

Case report

A 47 year old male was admitted to medicine ward with history of vomiting and diarrhea since 16/7/16. On 18/07/16 patient had an episode of seizure followed by hyperreflexia, confusion state, tremors. Patient was known case of bipolar mood disorder since 1990 and was on Tab. Lithium 400 mg BD. Tab. Olanzapine 5 mg BD and, Tab. Propranolol 10mg TDS were added since last 6 months. On 22/7/16, he had a second episode of seizure. Lithium toxicity or Neuroleptic malignant syndrome was suspected and therefore lithium and antipsychotics were withheld.

On examination, he was febrile, hypertensive, disoriented in time, place and person. He had coarse tremors of all four extremities, myoclonic jerks, dysarthria, and muscular incoordination were present. He had vertical nystagmus, rigidity, and hyperreflexia. The sensory system and ocular findings were normal. There were no signs of meningeal irritation.

His laboratory investigations revealed hypernatremia, deranged renal function and hypothyroidism. The serum lithium level was found to be 1.5mmol/L (normal range about 0.8 and 1.2 mmol/L)

Laboratory investigations revealed hemoglobin 13.8g/dL, TLC 15400/mm3 with 86% neutrophils, and ESR 24 at the end of 1 hr. BUN 28mg/dl and serum creatinine 1.9mg/dl were elevated. Blood sugar (random) was 194 mg% and Na and K were 161 mmol/L and 4.2 mmol/L respectively. Chest radiograph, EKG and EEG were normal. Routine urine examination and culture were normal. CSF R/M - 04 cells/cu.mm (L-04, P-00); Protein- 18 mg/dl, Sugar 52mg/dl, CSF C/S - No growth. MRI was not suggestive of encephalopathy.

On 23/7/16 serum lithium levels were 1.5 mmol/L and he received two cycles of dialysis following which lithium level decreased to 0.4 mmol/L. Concomitantly, his sensorium started improving after about a week. Cerebellar signs and symptoms, however, persisted. Tremors and muscular incoordination decreased considerably, but dysarthria and gait ataxia continued unabated. Patient was admitted in MICU for more than 60 days and died because of septic shock on 19/09/2016.

According to WHO causality assessment criteria, the causality of this case comes out to be "possible" as -

- there was a reasonable time relationship between the event and drug intake
- reaction was likely to be caused by other disease or drugs.
- response to withdrawal was clinically reasonable.
- rechallenge was not required.

Discussion

In 1987, Adityanjee et al. proposed the acronym SILENT, i.e. Syndrome of Irreversible Lithium-Effectuated Neurotoxicity, to describe patients in which the neurologic symptoms induced by lithium toxicity persisted for at least two months after the discontinuations of the drug in the absence of previous neurological impairment. Cognitive side effects and lack of coordination are also common among patients taking lithium and may occur even in therapeutic range, but are almost always tolerable and not disabling. At earlier stages of lithium intoxication, ataxia, coarse tremor, dyskinesias, dysarthria, hyperreflexia and muscle weakness can be seen[11-12]. Usually, this acute toxicity is not persistent and gradually improves with reduction of the lithium's plasma levels. Peripheral manifestations of lithium toxicity include myasthenia-like syndrome, rhabdomyolysis and proximal muscles weakness.

Persistent neurologic dysfunction associated to lithium can occur after acute intoxication. Even if the lithium levels are within normal range, chronic use can also result in persistent neurological dysfunction. Cerebellar symptoms are most frequently reported. A number of risk factors have been reported to predict the development of persistent, lithium-induced neurological dysfunction, including high serum levels during acute lithium-intoxication; presence of fever; concomitant use of other drugs (e.g. antipsychotics, tricyclicantidepressants, and anticonvulsants); rapid correction of hyponatremia or

lithemia; and coexistent illness, such as hypertension, chronic renal failure, heart failure, acute gastroenteritis, and epilepsy[13-14].

In our case, the presence of fever, concomitant administration of antipsychotic and gastroenteritis may have contributed to the poor outcome exhibited by the patient. Although plasma lithium levels were found to be elevated in our case as well as several cases of SILENT reported in the literature, normal values have also been reported, thus suggesting that blood levels do not exhibit a linear relation with intracellular level[15-16]. Another common feature associated with lithium induced persistent neurologic damage is fever, which can be caused by the intoxication itself, thus showing some resemblance to neuroleptic malignant syndrome, or by secondary infection. Infection can also be an independent risk factor for persistent neurological damage. The mechanism underlying this phenomenon is unknown, but it has been hypothesized that fever may induce a rise in blood brain-barrier permeability and an increase in the uptake of lithium by cerebellar cells.

Concomitant use of psychotropics was frequently reported in cases of lithium-induced persistent neurologic damage, mainly antipsychotics. Antipsychotic drugs, especially phenothiazines, might increase lithium influx in red bloodcells (RBC), thereby leading to neurotoxic effects. Other drugs, such as amitryptiline, aspirin, verapamil, valproate, erythromycin, diuretics, beta blockers, and nonsteroidal anti-inflammatory may also be associated with increased risk of developing lithium neurotoxicity[17].

Neurologic sequelae have been reported with lithium. In one of the reported case of SILENT, a 51-year-old obese female who was on lithium 800mg/day had dysarthria and gait disturbance even after 17 days of hospitalization. After one year follow up also she was only able to walk with support on a broad base. In most of the published cases sequelae were present at one-year follow-up, though milder. Occasionally, neurologic sequelae have been reported as long as five years after cessation of lithium therapy[18].

Complete neurological recovery in SILENT is uncommon, but patients may respond to rehabilitative measures with significant functional gains, and may return to their previous lifestyle[19].

Conclusion:

The presence of fever, concomitant administration of antipsychotic and gastroenteritis may have contributed to the poor outcome exhibited by this patient. It remains to be clarified, however, whether then after-mentioned risk factors are independent from each other. Since the information on lithium intoxication are generally provided by sparse case reports, there is an urgent need to gather data on lithium intoxication in a more systematic way, thus prompting the identification of independentrisk factors for SILENT and allowing their timely correction.

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PUBLISHED CASE REPORTS ON SYNDROME OF IRREVERSIBLE LITHIUM - EFFECTUATED NEUROTOXICITY (SILENT)

Compiled by Dr. Jaisen Lokhande

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

The syndrome of irreversible lithium-effectuated neurotoxicity: Clinical case and review

Leite F., Salgado H., Viveiros S., Coya P.

European Psychiatry. March.2016;33(supple): S167

Objectives: To present a clinical case of a probable Syndrome of Irreversible Lithium-effectuated Neurotoxicity (SILENT) and a review of the literature concerning this rare syndrome.

Methods: Psychiatric and psychological evaluation of a probable clinical case of SILENT and review of the literature using the key words "lithium neurotoxicity" and "Syndrome of Irreversible Lithium-effectuated Neurotoxicity".

Results: A 54-year-old female patient was admitted in our hospital due to involuntary lithium intoxication, with acute renal and cardiovascular failure, neurological, metabolic and electrolytic dysfunction in an acute confusional state and in need of dialysis. The patient clinical picture rapidly improved although, when she achieved normal lithium serum levels, it was observed a worsening of the preexisting confusional state followed by two consecutive generalized tonic-clonic convulsions and a partial convulsion. A short time after, it was recognized the development of a persistent catatonic state. It was detected urinary incontinence and repetitive, monosyllabic, incoherent, short phrased speech featuring echolalia, together with emotional lability and incongruous affect. The patient slightly improved with the introduction of anti-Parkinson's pharmacotherapy.

Conclusions: This clinical case raises several differential diagnoses due to its psychiatric and neurologic characteristics. We conclude that the most probable diagnosis is SILENT.

Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (Silent): Break the Silence

Kodadhala V, Ganji J, Hemmings S, Anwukah U, Mahajan A, Michael M

Meeting: SHM Annual Meeting 2015

A 60 y/o African American Female with history of Manic-depressive disorder was brought to emergency room for altered mental status of three day duration. Her home medications included Lithium, Trazadone, Paliperidone. She had no history of alcohol abuse. Positive physical exam findings: Dry mucous membranes, disorientation to place and time with GCS of 13/15, nystagmus, dysarthria, tremors of both hands, past pointing, hypertonic reflexes and babinski sign. Serum lithium levels were elevated at

2.4 mEq/L. Serum alcohol, tylenol, salicylate levels were undetectable. CT head and MRI of brain did not reveal any acute pathology. Lithium was stopped and patient was started on high infusion of normal saline. Hemodialysis was not initiated as her lithium levels trended down to normal range within a few hours of admission. Patient was admitted to the intensive care unit for further care. Gradually her altered mental status improved but her neurological signs persisted, so Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT) was considered. Patient was discharged after one week under family care. Lithium and other anti psychotic medications were discontinued. Three months after initial presentation, physical exam was still positive for tremors, nystagmus and other cerebellar signs. She was therefore diagnosed with SILENT.

The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT): One-year follow-up of a single case

Porto FH, Leite MA, Fontenelle LF, Marrocos RP, Szczerback NF, de Freitas MR.

Journal of the Neurological Sciences.2009;277:172-173

In this article, we report the case history of a 44-year-old female patient with bipolar disorder who developed the so-called Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT). A detailed description of our patient's neurologic status is provided at baseline (i.e. during lithium intoxication) and after one year of follow-up, confirming the persistency of cerebellar signs and symptoms. Although rare, our report - which shows a severe and disabling form of SILENT - underscores the need to perform a strict control of the putative risk factors argued to be associated with the development of this syndrome. In our case, the presence of fever and the administration of multiple doses of antipsychotics may have contributed to the poor outcome exhibited by the patient.

Unusual manifestation of therapeutic dose of lithium as syndrome of irreversible lithium-effectuated neurotoxicity

Singh H, Ganjekar S, Kalegowda A, THyloth M

J Mental Health Hum Behav 2015;20:80-1

Lithium is a commonly used mood stabilizer. However, because lithium has a low therapeutic index, lithium-induced drug toxicity is frequently seen in clinical practice. While most side effects of lithium use reverse after the drug is discontinued, in rare cases patients develop a persistent neurological side effect known as a syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). We report a case where the patient developed SILENT even when given a therapeutic dose of lithium. Our case also supports the biological mechanism of SILENT, which involves demyelination at multiple sites in the brain.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr. Jaisen Lokhande
Assistant Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Changes in Package inserts for inclusion of new adverse reactions

1. **Allopurinol - Risk of drug-induced hypersensitivity syndrome:** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA), Japan, have announced that the package inserts for allopurinol have been updated to include the risk of drug-induced hypersensitivity syndrome (DIHS) as a clinically significant adverse reaction.

2. **HMG-CoA reductase inhibitors - Risk of immune-mediated necrotizing myopathy:** The MHLW and the PMDA, Japan, have announced that the package inserts for HMG-CoA reductase inhibitors (fluvastatin, pravastatin, simvastatin, atorvastatin, pitavastatin, rosuvastatin) and their combination preparations have been updated to include the risk of immune-mediated necrotizing myopathy as a clinically significant adverse reaction.

3. **Zoledronic acid - Risk of Fanconi syndrome:** The MHLW and the PMDA, Japan, have announced that the package inserts for zoledronic acid have been updated to include the risk of Fanconi syndrome as a clinically significant adverse reaction.

4. **Olanzapine - Risk of urinary retention:** Health Canada has updated safety information for olanzapine. At the time of the review, Health Canada had received 38 Canadian reports related to urinary retention and the use of atypical antipsychotics. Most patients recovered or were recovering from the adverse effect after stopping the antipsychotic medication. In some cases, urinary retention re-occurred after the drug was re-administered.

5. **Alogliptin containing products, teneligliptin and linagliptin -Risk of pemphigoid:** The MHLW and the PMDA, Japan, have announced that the package inserts for alogliptin, teneligliptin and linagliptin have been updated to include the risk of pemphigoid as a clinically significant adverse reaction.

Reference: WHO Pharmaceuticals Newsletter.2016 [cited 2017 Jan 25].(6) Available from:http://www.who.int/medicines/publications/WHO_Pharm_Newsletter_6_2016.pdf?ua=1

MATCH THE FOLLOWING DRUG WITH ITS SPECIFIC ADR

Dr. Sharmada Nerlekar*, Dr. Abhilasha Rashmi*

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

1.	Lithium	A)	Raised intraocular Pressure
2.	Halothane	B)	Cardiomyopathy.
3.	Dipyridamole	C)	Hyperuricemia
4.	Gatifloxacin	D)	Prostate Cancer
5.	Sitagliptin	E)	Cytokine release Syndrome
6.	Fomivirsen	F)	Renal Toxicity
7.	Thiazides	G)	Contraindicated in MI and epileptic patients.
8.	Trastuzumab	H)	Dose related pulmonary toxicity
9.	Nefopam	I)	Coronary Steal Phenomenon in elderly
10.	Antithymocyte Globulin	J)	Fatal Ventricular Tachycardia
11.	Cisplatin	K)	Excessive Hypotension
12.	Amiodarone	L)	Foetal goitre
13.	Droperidol	M)	Nasopharyngitis
14.	Nesiritide	N)	Dysglycemia
15.	Finasteride	O)	Hepatotoxicity

ANSWERS

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

ALPHABET 'N' PUZZLE

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

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

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

1. Use of this COX 2 selective, sulfanilide NSAID is limited to 15 days due to the risk of hepatotoxicity.
2. Though having better efficacy in severe Psoriasis than Adalimumab, neutralizing antibodies may develop against its chimeric structure, which is not seen with Adalimumab.
3. This calcium sensor mimetic drug is approved for the treatment of secondary hyperparathyroidism owing to chronic renal disease and for patients with hypercalcemia associated with parathyroid carcinoma.
4. Also known as Marinol, this naturally occurring cannabinoid is approved as a useful prophylactic agent in patients receiving cancer chemotherapy when other anti-emetic medications are not effective.
5. This short acting perioperative opioid analgesic exhibit elevated plasma concentrations when co-administered with Azole anti-fungal agents because of their hepatic enzyme inhibiting action.
6. This Antigout drug is ineffective in patients with renal insufficiency and should be avoided in those with creatinine clearance of <50 mL/min.
7. Due to its higher specificity for mineralocorticoid receptors, the incidence of progesterone-related adverse effects (gynaecomastia, hirsutism etc.) are lower than that of Spironolactone.
8. Nausea-vomiting (1-20%) and seizures (1.5%) in high doses are the most common adverse reactions seen with Imipenem which belongs to the group _____.
9. Chronic administration of this oldest antiretroviral drug has been associated with nail hyperpigmentation, skeletal muscle myopathy and rare but fatal hepatic toxicity, with or without steatosis and lactic acidosis.
10. 10% cream and lotion of _____should be used in patients suffering from scabies and lice, in whom lindane or permethrin are contraindicated and also in pregnant or lactating females.

ALPHABET 'N' PUZZLE: ANSWERS :

1. Nimesulide
2. Infliximab
3. Cinacalcet
4. Dronabinol
5. Alfentanil
6. Probenecid
7. Eplerenone
8. Carbapenem
9. Zidovudine
10. Crotamiton

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

Please feel free to contact us for the same.

Names	Phone No.	E-mail
Dr Sudhir Pawar	2406 3162	dr.sudhirpawar@gmail.com
Dr Neha Kadhe	2406 3206	nehakadhe@yahoo.com
Dr Manjari Advani	2406 3205	manjari.advani@gmail.com
Dr Jaisen Lokhande	2406 3164	dr_jaisen@yahoo.co.in,
Dr Swati Patil	2406 3161	drswati246@gmail.com
Dr Swapnil Meshram	2406 3161	swapmd4@gmail.com
Dr Swapnil Jamdade	2406 3161	drswapniljamdade@gmail.com
Dr Trupti Jadhao	2406 3161	truptijadhao90@gmail.com

Address for correspondence :

Dr. Sudhir Pawar

Department of Pharmacology,

College Building, LTMMC & LTMGH,

Sion, Mumbai-400022.

Tel.: 022-2406 3160 • E-mail: ltmghbulletin@yahoo.com

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