

BULLETIN ON ADVERSE DRUG REACTIONS

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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 deals with the topic of drug-induced peripheral neuropathies, including chemotherapy-induced peripheral neuropathies (CIPNs), which has an important impact on patients' quality of life and compliance. CIPNs in particular are important because of their dose-limiting side effects and are often related to the choice of anti-cancer drugs and the cumulative doses. In recent years, significant progress has been made in understanding some of the pathophysiological mechanisms of neuropathy and the article gives an overview on some development of prophylactic and therapeutic measures for this condition.

The second article is a review on drug induced salivary disorders and deals with the monitoring, prevention and management of this important condition.

Other features in this issue include analysis of the ADRs from our institute for your quick review, an interesting case report of drug induced peripheral neuropathy and other topics.

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

OVERVIEW OF DRUG INDUCED PERIPHERAL NEUROPATHY

Dr Patil Swati*, Dr Smita Mali*

*Assistant Professors, Department of Pharmacology, LTMMC & GH, Sion, Mumbai-22.

Introduction

Peripheral neuropathy and polyneuropathy is defined as the clinical syndrome of weakness, sensory loss and impairment of reflexes caused by diffuse lesions of peripheral nerves.^[1] Toxic neuropathy refers to neuropathy caused by drug ingestion, drug or chemical abuse, or industrial chemical exposure from the workplace or the environment.^[2] Of these, medication-induced neuropathies are uncommon (2-4% of cases in one outpatient neurology setting), but crucial to recognize because intervention can lead to significant improvement or symptom resolution.^[3]

Amongst the different classes of drugs that are implicated, anticancer drugs are the ones which have been extensively studied. Anti-cancer drugs such as vincristine, paclitaxel, oxaliplatin, cisplatin and bortezomib are well reported, to exert direct and indirect effects on sensory nerves to alter the amplitude of action potential, conduction velocity and induce pain.^[4] Streptomycin causes ototoxicity by affecting cochlear part of eighth nerve. Isoniazid produces polyneuropathy by creating pyridoxine deficiency whereas phenytoin on prolong use frequently produces subclinical symptoms of neuropathy. In August 2013, the US Food and Drug Administration (FDA) announced that oral or injected fluoroquinolone antibiotics can cause permanent peripheral neuropathy (PN) and that labels on the drugs will be updated to reflect this finding though topical fluoroquinolones have not been associated with this condition.^[5] Thus, not only anticancer drugs but other classes of drugs are also incriminated in causing peripheral neuropathy. This review focuses mainly on salient features related to medication induced neuropathy rather than toxin related neuropathies.

Causative drugs

Drugs associated with peripheral neuropathy are mentioned in the table 1.

Table 1: Drugs commonly associated with peripheral neuropathy^[6]

Drug class	Examples
Chemotherapy	5-azacytidine, 5-fluouracil, cisplatin and analogs, cytarabine (high dose), etoposide, gemcitabine, ifosphamide, misonidazole, suramin, taxanes, vinca alkaloids

Antibiotics	nucleoside analogs, chloroquine, chloramphenicol, clioquinol, dapsone, ethambutol, fluoroquinolones, griseofulvin, isoniazid, mefloquine, metronidazole, nitrofurantoin, podophyllin resin, sulphonamides
Cardiovascular	amiodarone, enalapril, hydralazine, statins, perhexiline, propafenone
Drugs acting on CNS*	amitriptyline, phenytoin, chlorprothixene, gangliosides, glutethimide, lithium, nitrous oxide, phenelzine, thalidomide
Miscellaneous	allopurinol, almitrine, botulinum toxin, cimetidine, clofibrate, colchicine, cyclosporin a, dichoroacetate, disulfiram, etretinate, gold salts, interferons -2a & 2b, penicillamine, pyridoxine abuse, sulphasalazine, tacrolimus, zimelidine

*central nervous system

Epidemiology

The literature regarding exact incidences of peripheral neuropathy with each drug is sparse. The frequency of chemotherapy induced peripheral neuropathy (CIPN) is increasing partly because of the wider use of high-dose chemotherapy, longer survival for many patients with cancer who experience CIPN as a lasting symptom and new agents and delivery routes that target the nervous system.^[7]

The incidence of neuropathy varies between reports and according to dose, but is roughly 12% at conventional dose and 70-100% with higher cumulative doses (540-600 mg/m²) and may be lower (14%) if used as a sole agent.^[8] But this incidence can increase to 38% with poly chemotherapy regimens.^[7]

Neuropathy with the use of nucleoside-analogue antiretroviral drugs such as didanosine (ddI), stavudine (d4T) and zalcitabine (2' - 3' – dideoxycytidine, ddc) is dose-dependent and is estimated to occur in 15±30% of patients receiving each of these drugs.^[9] A 10% incidence of PN was observed for patients commenced on triazole therapy for chronic aspergillosis.^[10] Shin et al has reported that peripheral neuropathy was encountered in 13% of their cohort of MDR-TB treated patients.^[11] Pertaining statins, at present there are insufficient evidences to conclusively implicate statin therapy as a common cause of peripheral neuropathy; however, it is plausible that its occurrence associated with statin therapy is rare and idiosyncratic.^[12]

Risk Factors

Peripheral nerve is protected by a blood-nerve barrier and would seem to be at lesser risk than other organs for toxicity. However, a number of factors viz. blood flow to peripheral nerve is not auto

regulated and is vulnerable to sudden microenvironment changes; dorsal root ganglia (DRG) lack an efficient vascular barrier; endothelial cells in the epineurium are fenestrated and allow escape of some blood proteins in the extracellular space; blood-nerve barrier is less efficient than the blood brain barrier; absence of lymphatic system to remove toxins and absence of sink action of CSF enhance peripheral nerve vulnerability to toxic effects when compared to the central nervous system.^[6]

Possible risk factors for Peripheral Neuropathy are tabulated in table 2.

Table 2: Risk factors^[4,9,13,14,15]

General factors
<ul style="list-style-type: none"> • Pre existing genetic neuropathy • Acquired neuropathy-past history of peripheral nerve dysfunction due to HIV, diabetes or chemotherapy • Co-existing conditions such as diabetes , alcohol abuse ,chronic renal failure, malnutrition and nutritional deficiencies such as low serum hydroxycobalamin levels • Concurrent use of neurotoxic drugs
Specific factors
<ul style="list-style-type: none"> • For CIPN: • Single dose intensity, duration of infusion, cumulative dose, prior or concurrent treatment with cisplatin • For Antiretrovirals: • Low CD4 cell count & high viral load • Risk of PN is almost doubled when stavudine is used alone or in combination with didanosine.

Along with the above mentioned factors pharmacogenetic variations in absorption, distribution, metabolism, elimination and DNA repair mechanisms have been postulated to explain differences in the observed neurotoxicity of various molecules. For instance, polymorphisms of the gene encoding ABCB1/P-glycoprotein, one of the transporters involved in the elimination of numerous xenobiotic substances have been suggested to partially explain the variability of taxane-induced drug induced peripheral neuropathy (DIPN).^[16,17]

Pathogenetic mechanisms

Peripheral neuropathy may be divided into the following 3 groups based on the presumed site of cellular involvement:^[18]

- Neuropathy affecting the cell body, especially those of the dorsal root ganglion
- Myelinopathy or schwannopathy with primary segmental demyelination
- Distal axonopathy causing dying back axonal degeneration

As the most frequently encountered neuropathic mechanisms target neurons or their axons, toxic, DIPNs and CIPNs are most often characterized by the development of a subacute or chronic, length-dependent, distal, symmetrical polyneuropathy with a predominant sensory involvement, with or without associated dysautonomia. This corresponds to the so-called ‘dying back axonal degeneration’ affecting distal segments of the peripheral nerves.^[19] More rarely, a nonlength-dependent or multifocal neuropathy may be encountered; either resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or Lewis Sumner syndrome in DIPN associated with underlying inflammatory or dysimmune mechanisms, associated with infliximab therapy in patients of rheumatic arthritis.^[20,21] A nonlength-dependent small-fibre neuropathy may also be observed, such as in nitrofurantoin toxicity.^[22]

The drug likely accumulates over time and the phenomenon of ‘coasting’, when a neuropathy continues to progress for a time after the drug is stopped can be seen. Usually this effect persists only for 2-3 weeks, but longer intervals have been described.^[23] All patients treated with high-dose ddC reported progression of symptoms (coasting) for 2 to 3 weeks following discontinuation of therapy.^[24]

Other putative mechanisms of neurotoxicity for few drugs are summarised in table 3.

Table 3: Mechanisms of Drug Neurotoxicity^[25]

Drug Class	Mechanism
Nucleoside reverse	Depletion of mitochondrial DNA in neurons transcriptase inhibitors
Taxanes & vinca alkaloids	Disruption of neuronal axonal transport
Platinum compounds	Cross linkage of DNA strands to impair cell division, demyelination and axonal swelling in dorsal root ganglia
Oxaliplatin (acute toxicity)	Interaction with ion channels in dorsal root ganglia to enhance Na ⁺ transmission, chelation of Ca ⁺⁺ ions, overall shift to more negative membrane potential
Thalidomide, Bortezomib	Down regulation of the production of tumour necrosis factor α and inhibition of nuclear factor kappa B leading to reduced nerve growth factor mediated neuron survival
Isoniazid	Inhibition of phosphorylation of pyridoxine which leads to neuronal cellular dysfunction
Linezolid	May disrupt neuronal mitochondrial protein synthesis
Statins	Inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase leading to reduced cholesterol synthesis, which is necessary to maintain cell-membrane integrity in neurons

Anti-cancer agents activate plasma membrane localized ion channels on dorsal root ganglia and dorsal horn neurons including sodium, calcium, potassium and glutamate activated NMDA receptors to alter cytosolic ionic milieu particularly intracellular calcium that trigger secondary changes to induce neuropathic pain. These may include opening of mitochondrial permeability transition pore (mPTP) to induce intracellular calcium release; activation of protein kinase C; phosphorylation of transient receptor potential vanilloid (TRPV); activation of calpases/calpains; generation of nitric oxide and free radicals to induce cytotoxicity to axons and neuronal cell bodies. Furthermore, the inflammatory process initiated in glial cells and macrophages also trigger changes in the sensory neurons to alter nociceptive processing.^[4]

Diagnosis

In some conditions (malignancy and HIV), an inherent neuropathy can be difficult to distinguish from treatment-induced neuropathy.^[26] Differentiating drug induced neuropathy from underlying disease is of utmost importance.

✓ **Clinical presentation**

Patients with neuropathy typically present with symptoms of pain, tingling or numbness in their feet, consistent with dysfunction affecting the longest and largest fibres of the peripheral nervous system (PNS). Other manifestation of neurologic dysfunction that may be present includes hypohidrosis or hyperhidrosis, bladder and bowel disturbances, gastroparesis, sicca syndrome and other autonomic dysfunction. Clinical findings are summarised in table 4.

Table 4: Clinical findings^[2]

Physical examination	<ul style="list-style-type: none"> • Sensory loss in a stocking-glove distribution • Distal to proximal progression: Consistent with the commencement of axonal degeneration • Early loss of symmetrical ankle jerk • Motor dysfunction (eg, abnormal gait and foot drop): in severe cases
CNS examination	<ul style="list-style-type: none"> • Corticospinal tract disease: Hyperreflexia, Babinski responses and stiff-leg ataxic gait • Dorsal column degeneration: Diffusely decreased proprioceptive and vibratory sensations and gait ataxia

Drugs predominately causing sensory or motor neuropathy are distinguished in table 5.

Table 5: Drugs and clinical spectrum of neuropathy^[27]

Motor > Sensory Toxic Neuropathy	Sensory > Motor Toxic Neuropathy
<ul style="list-style-type: none"> • Dapsone • Disulfiram • Nitrofurantoin • Organophosphates • Vincristine 	<ul style="list-style-type: none"> • Cisplatin • Pyridoxine • Thalidomide • Thallium

WHO recommendations for grading of acute and subacute toxic effects of peripheral neuropathy are illustrated in table 6.

Table 6: WHO scale for grading peripheral neuropathy^[7]

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Paresthesia and / or decreased tendon reflexes	Severe paraesthesia and / or mild weakness	Intolerable paresthesia and /or marked motor loss	Paralysis

- **Diagnostic Modalities:** Measurement of sensory and motor nerve conduction velocity (NCV), sensory nerve action potential (SNAP), and compound muscle action potential (CMAP) together with needle electromyography (EMG) are standard neurophysiological tests used while invasive sural or other whole nerve biopsies are rarely indicated. The role of skin biopsy in CIPN is evolving.^[28]

Management

Firstly, it is advisable to avoid the causative drug or occupational or environmental toxin implicated in causing neurotoxicity. Symptoms of neuropathy are usually reversible after discontinuation of these drugs and some patients are able to tolerate reintroduction of these agents after the resolution of neuropathy.^[9]

Management of toxic neuropathy includes the following:

- Non pharmacologic measures: Cool soaks, heat, massage, elevation or lowering of the limbs, and/or exercise
- The use of drugs like anticonvulsants, antidepressants, in severe cases opioids, and recently also topical local anaesthetics directed against neuropathic pain can be an option.^[29,30] Few of these drugs are given below with their dosages.

Amitriptyline: Start at 10mg nocte up to 75/80mg

Duloxetine: Start at 20mg nocte up to 120mg

Pregabalin: 75mg bd up to 600mg bd

Gabapentin: 100mg tds up to 1800mg tds

- Topically lignocaine patches, capsaicin cream and menthol (TRPM8 agonist) are used to alleviate pain while NMDA antagonist like ketamine is also been tried.

Prevention

Drug induced peripheral neuropathy can be prevented by following approaches:^[25]

- ◆ Limit or monitor for potential predisposing factors
 - Use lowest dose possible to achieve desired effect
 - Monitor blood urea nitrogen and serum creatinine in patients taking renally excreted drugs. Adjust dose appropriately if kidney disease occurs.
 - Monitor liver function in patients taking hepatically metabolised drugs.
- ◆ Monitor for signs and symptoms of peripheral neuropathy
 - Educate patient of symptoms of neuropathy
 - Routine neurological assessment
 - Electrophysiological testing
- ◆ Drugs
 - Supplementary drugs can be used to prevent PN e.g. pyridoxine in case of isoniazid induced PN.

Preventive strategies have been explicitly studied in CIPN. Several neuroprotective strategies, including Ca/Mg infusion, amifostine, glutathione, glutamine, acetyl-L-carnitine and erythropoietin as most promising, have been investigated. Drugs with potential preventive efficacy are given in table 7. Data for the efficacy of these drugs is sparse. Consequently, no explicit recommendations on neuroprotective strategies can be given yet except for the importance of identifying high-risk patients before starting chemotherapy.

Table 7: Potential drugs for prevention of peripheral neuropathy^[31]

Neurotoxicity mechanism	Drugs	Reported potential molecules for management
DRG cytotoxic inflammatory changes	Cisplatin, NRTIs	N-acetylcysteine, melatonin, amifostine, glutathione, vitamin E, pregabalin, and gabapentin, etanercept
Mitotoxicity and oxidative stress	Paclitaxel, Bortezomib, Platinum compounds	Glutamine, vitamin E, ibudilast, erythropoietin, olesoxime and acetyl-N-carnitine, minocycline, melatonin, Acetyl-L-carnitine, silibinin, olesoxime, acetyl-L-carnitine
Microtubular function Disruption	Vinca alkaloids	NSAIDs, propentofylline
Voltage-gated ion channel dysfunction 1. Sodium channels 2. Potassium channels 3. Calcium channels	1. Oxaliplatin 2. Cisplatin, Oxaliplatin 3. Cisplatin, Paclitaxel	1. Lidocaine, pregabalin and gabapentin, glutathione, glutamine and oxcarbazepine, calcium or magnesium salts 2. Retigabine 3. Nimodipine and calmodulin inhibitors, calcium or magnesium salts
Dysfunction of TRP family of ion channels 1. Ankyrin 1 (TRPA1) 2. Vanilloid 1 (TRPV1) 3. Vanilloid 4 (TRPV4)	1. Paclitaxel, Oxaliplatin 2. Cisplatin 3. Paclitaxel	1. HC0300031 2. Capsazepine and SB366791 3. RN1734
Demyelination 1. Decreased myelin sheath methylation 2. Immune-based demyelination	1. Nitrous oxide 2. Etanercept, infliximab, adalimumab, Oxaliplatin	1. Vitamin B12 2. IVIG

Conclusion

In recent years other than anti-cancer therapies many other drugs have been identified to have neurotoxic potential. Thus appropriate drug selection with proper regimen followed by vigilant approach and regular monitoring for early signs of neuropathy is essential to curb the morbidity due to it. With newer

insight in the pathogenetic mechanisms of neuropathies many different chemo-protective strategies are in pipeline. The success of these preventive approaches needs to be ascertained with well controlled clinical studies.

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DRUG INDUCED SALIVARY DISORDERS

Dr Bhakti Soman*, Dr Sunanda Bhatnagar**

*Lecturer, **Reader

*Department of Oral Medicine and Radiology,
YMT Dental College & Hospital, Kharghar, Navi Mumbai.*

Introduction

Salivary function provides host protection, assists in the initiation of food and fluid intake, and enables communication through speech. Without adequate salivary output, oral and pharyngeal health declines which in turn affects person's quality of life. The complaint of a dry mouth (xerostomia) and the objective finding of salivary dysfunction are common occurrences in older individuals which produces either transient or permanent oral and systemic problems. Salivary dysfunction, however, is not a normal consequence of aging but is due to systemic diseases, medications, and head and neck radiotherapy.^[1,2]

The most common cause of salivary disorders is the use of prescription and non-prescription medications. A study conducted by Sreebny and Schwartz reported that 80 percent of the most commonly prescribed medications cause xerostomia, while more than 400 medications are associated with salivary gland dysfunction as an adverse drug reaction (ADR).^[3] Dry mouth is a common complaint in patients treated for hypertensive, psychiatric, or urinary problems and in the elderly, mainly as a consequence of the large number of drugs used.^[4] Pajukoski et al found that 63% of hospitalized patients and 57% of outpatients complained of dry mouth, and in all patients, the use of psychiatric drugs was the main cause.^[5] In a study conducted in geriatric population Sproule et al found that in elderly population 75% of them using non-prescription products like dimenhydrinate, acetaminophen (paracetamol), diphenhydramine, alcohol and herbal products report dry mouth as a common adverse effect.^[6]

Even though dry mouth is the most commonly observed ADR, there are other iatrogenic salivary disorders like hypersalivation, salivary gland enlargement and salivary discoloration also. This review intends to throw light on the arena of salivary gland dysfunctions associated with drug use.

Physiology

Saliva consists of two components that are secreted by independent mechanisms. First a fluid component which includes ions, produced mainly by parasympathetic stimulation and secondly a protein component released mainly in response to sympathetic stimulation. Salivary gland secretion is mainly under autonomic nervous control, although various hormones may also modulate salivary composition.

Secretion appears to be dependent on several modulatory influences which act via either a cyclic AMP or calcium dependent pathway. Parasympathetic stimulation produces copious saliva of low protein concentration while sympathetic stimulation produces little saliva but of high protein concentration and may thus give a sensation of dryness.^[7] Drugs modulate either of these autonomic influences in most of the cases causing ADRs.

Drug induced xerostomia

Dry mouth or xerostomia has a variety of possible causes. Common habits such as tobacco smoking, alcohol use (including in mouthwashes), and the consumption of beverages containing caffeine (coffee, some soft drinks) can cause some oral dryness. Furthermore, the cause for which the drug is being taken may also be important. For example, patients with anxiety or depressive conditions may complain of dry mouth even in the absence of drug therapy or evidence of reduced salivary flow. It is thus important to recognize that some patients complaining of a drug-related dry mouth have no evidence of a reduced salivary flow or a salivary disorder, and there may then be a psychogenic reason for the complaint.^[8]

A number of different mechanisms account for drug related dry mouth, but an anticholinergic action underlies many. The M3-muscarinic receptors (M3R) mediate parasympathetic cholinergic neurotransmission to salivary (and lacrimal) glands. Many types of other receptors viz adrenergic (alpha 1A, beta 1), histaminergic (H2) and neurokinin (NK-1) for endogenous substances exist in the salivary glands, suggesting that salivary glands may contain target systems for many drugs. Whereas gamma amino butyric acid (GABA) and benzodiazepines are shown to decrease fluid secretion and amylase release elicited by secretagogues.^[8]

The drugs most commonly implicated are discussed in table1.^[4,8,9,10]

Table 1: Salient features of drugs commonly causing xerostomia

Drug class implicated	Drugs	Comments
Antidepressants	Tricyclic antidepressant (TCA) Selective serotonin re-uptake inhibitors (SSRIs) and multiple-receptor antidepressants (such as venlafaxine, mirtazapine, bupropion, trazodone, and nefazodone)	-causes dry mouth due to blockage histaminic, cholinergic, and alpha1-adrenergic receptor sites -do not activate unwanted sites such as histamine and acetylcholine. The SSRI produce no significant changes in salivation, but dry mouth may still be seen (e.g., fluoxetine).

Antihistamines	First generation antihistaminics like chlorpheniramine Non-sedating antihistamines-most of which are histamine H1 receptor antagonists, such as acrivastine, astemizole, cetirizine, ebastine, fexofenadine, loratadine, mizolastine, and terfenadine	-produce xerostomia due their anticholinergic action. -they are not entirely free from ADRs, though there may be less complaints of dry mouth with these drugs.
Antihypertensive agents and diuretics	Ganglion blockers, beta-blockers (beta adrenoceptor antagonists) and angiotensin converting enzyme (ACE) inhibitors	Proposed mechanisms are activation of CNS and salivary gland alpha 2-adrenergic receptors and antihypertensives and diuretics may cause decreased fluid volume and loss of electrolytes secondary to increased urination and dehydration.
Antipsychotics	Phenothiazines such as fluphenazine Newer antipsychotic drugs	-cause xerostomia due to blocking muscarinic receptors -they are dopamine D(2) receptor selective but still olanzapine is seen to produce dry mouth.

Other drugs also causing dry mouth are antimigraine agents i.e. Rizatriptan; benzodiazepines, hypnotics, opioids, and drugs of abuse; bronchodilators (tiotropium); cytokines (IL-2/IFN); cytotoxics; histamine H2 antagonists and proton pump inhibitors; opiates; protease inhibitors; radioiodine; retinoids; and skeletal muscle relaxants.^[8]

Radiation therapy (RT) is a common component of treatment for head and neck cancers. Head and neck RT has serious and detrimental side-effects to the oral cavity including the loss of salivary gland function and a persistent complaint of a dry mouth. In addition, patients often experience the spectrum of oral-pharyngeal problems as a result of permanent salivary gland destruction.^[1]

Drug induced sialorrhoea:

Salivary secretion is increased by drugs that have a cholinergic action either by acting directly on parasympathomimetic receptors or by acting as anticholinesterases. Although generally a benign side effect, hypersalivation can be distressing to the patient. Intense sialorrhoea may disturb sleep; some patients may describe a choking sensation and may even aspirate excess saliva at night.^[11]

Anticholinesterases are the main cause of hypersalivation. Clozapine, an atypical antipsychotic drug claimed to have superior efficacy and to cause fewer motor adverse effects than typical antipsychotics

for people with treatment-resistant schizophrenic patients, can cause hypersalivation.^[12] It has been suggested that stimulation of both M3 and M4 muscarinic receptors present in salivary glands lead to saliva production. Clozapine is known to exert a full-agonist effect at M4 receptors; whereas, its affinity for M3 receptors is lower. Therefore, it is possible that the effects of M4 receptor stimulation would exceed those of M3 receptor blockade, resulting in hypersalivation. Clozapine-induced sialorrhoea may also be explained through its blocking actions at α 2 receptors. Another study also suggested that clozapine interferes with normal deglutition by blocking target receptors located in the pharynx or by disrupting vagal control of esophageal peristalsis.^[11]

Other drugs associated with sialorrhoea are mentioned in table 2 below.^[13]

Table 2: Drugs causing sialorrhoea

Alprazolam	Haloperidol	Remoxipidine
Amiodarone	Kanamycin	Risperidone
Buprenorphine	Ketamine	Rivastigmine
Buspirone	Lamotrigine	Tacrine
Clonazepam	l-dopa	Tobramycin
Diazoxide	Mefenamic acid	Triptorelin
Ethionamide	Nicardipine	Venlafaxine
Gentamicin	Niridazole	Zaleplon
Guanethidine	Pentoxifylline	

Drug induced salivary gland enlargement:

Several drugs have been reported to cause salivary gland enlargement which may resemble mumps. The salivary gland enlargement associated with drugs could be painful or painless in certain cases. Painless, usually bilateral, salivary gland enlargement (resembling sialosis) may be an occasional side-effect of phenylbutazone, oxyphenbutazone, or chlorhexidine. Clozapine may cause transient salivary gland swelling along with sialorrhoea. Antihypertensives, anti-thyroid agents, cytotoxics, ganglion-blocking agents, iodides, phenothiazines, and sulphonamides may cause salivary gland enlargement and pain, as may drugs causing dry mouth.^[14]

The mechanism of drug-induced sialadenitis remains unclear in most cases. Either oedema or spasm of smooth muscle in the salivary gland or a hypersensitivity reaction could be responsible.^[13] The salivary gland enlargement caused by intravenous radiological contrast media is probably allergic in origin.^[14]

Drug induced sialolithiasis:

Drug therapy is a relatively unknown cause of stones in the salivary glands. A solitary case report describes the occurrence of salivary gland stone following atomoxetine therapy which was removed by massaging the gland digitally is documented.^[15]

Drug induced salivary discoloration:

Discoloration of saliva (red or orange saliva) as well as other body fluids may be seen in patients treated with clofazimine, levodopa, rifampicin, and rifabutin therapy.^[16]

Management:

While treating iatrogenic salivary disorders careful history and scrutiny of drugs that patient is receiving is of paramount importance. Discontinuation of culprit drug if symptoms are distressing is mandatory. Drug substitutions may help reduce the adverse side effects of medications that produce xerostomia if similar drugs are available that have fewer xerostomia side effects. For example, replacement of selective serotonin reuptake inhibitors causes less dry mouth than do tricyclic antidepressants.

If an older patient can take anticholinergic medications during the daytime, nocturnal xerostomia can be diminished, because salivary output is lowest at night. Patient can divide his or her drug dosages; he or she may be able to avoid the side effects caused by a large single dose. A dentist's scrutiny of drug side effects can assist in diminishing the xerostomia potential of many pharmaceuticals used by elderly patients.^[2]

General measures

For patients with remaining viable salivary gland tissue, stimulation techniques are helpful. Sugar-free chewing gum, candies, and mints can stimulate remaining salivary secretions, as well as enhance secretion of salivary secretory IgA. If the prognosis for restoration of normal salivation is poor, such as with head and neck radiotherapy for oral cancers, then use of artificial saliva and lubricants may ameliorate some xerostomia symptoms. These products tend to diminish the sensation of oral dryness and improve oral functioning. Preference of products depends on effect, duration, lubrication, taste, delivery system, and cost; many patients nevertheless primarily use water.^[1]

Patients, particularly older adults, must be reminded to maintain hydration (water is the drink of choice) to assist with xerostomia. Several habits, such as smoking, mouth breathing, and consumption of caffeine-containing beverages, have been shown to increase the risk of xerostomia. Limiting or stopping these practices should lessen the severity of dry mouth symptoms.

Medications

The U.S. Food and Drug Administration has approved two secretagogues, pilocarpine^[17, 18] and cevimeline^[19, 20] for the treatment of xerostomia and salivary hypofunction. These drugs are effective in

increasing secretions and diminishing xerostomia complaints in patients with sufficient exocrine tissue. Treating xerostomia with medications that enhance salivation is another therapeutic option particularly in the relatively healthy person for whom polypharmacy may not be a critical concern.

Pilocarpine:

Secretagogues such as pilocarpine can increase secretions and diminish xerostomia complaints in patients with sufficiently remaining exocrine tissue. Pilocarpine is typically given in a dosage of 5 mg orally three times a day and before bedtime.

Cevimeline

It is approved for the treatment of dry mouth in Sjogren Syndrome in a dosage of 30 mg orally three times daily. Like pilocarpine, it is a muscarinic agonist that increases production of saliva. Pilocarpine is a non-selective muscarinic agonist, whereas cevimeline reportedly has a higher affinity for M1 and M3 muscarinic receptor subtypes thus minimizing adverse effects on pulmonary and cardiac function.

Bethanechol: another cholinergic agonist, has been used (25 mg tid) to stimulate saliva in post head and neck radiotherapy patients, with few reported significant side-effects.

Tackling complications

Table 3 mentions the management of complications due to xerostomia.^[2]

Xerostomia associated problems	Management strategy
Dental caries	Daily use of fluorinated dentifrice(0.05% sodium fluoride) Use of fluoride gel and varnish to teeth Dental examination at least every 6 months and intra-oral radiograph every 12 month
Oral candidiasis	Antifungal (Nystatin)- oral suspension, ointments, lozenges
Bacterial infections	Systemic antibiotic for 10 days- Amoxicillin clavulanate, clindamycin, cephalexin Increase hydration and salivary stimulation
Poor fitting prostheses	Soft and hard tissue relines by dentist Denture adhesives

Conclusion:

Oral Adverse drug effects are often less attended and can affect overall patient's quality of life. Though, benign but distressing adverse effects of drugs on salivary gland do occur. A combined approach of physician and dentist will help in tackling such problems specially in cases of radiotherapy induced xerostomia. It is incumbent upon the practitioner to try to stay abreast of this ever evolving field of drugs and their ADRs to provide holistic health.

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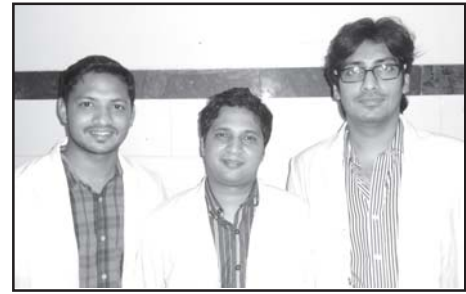
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**ANALYSIS OF ADVERSE DRUG REACTION
REPORTED**

(January 2014 - March 2014)

**Presented by Dr Shivkumar Shete*, Harshda Dipnaik
, Dr Jaisen Lokhande *, Dr Neha Kadhe****,
Dr Swati Patil***** Dr Sudhir Pawar*****.**



**-Technical Associate - Pharmacovigilance. ** Pharmacovigilance Trainee
-Assistant Professor, * Associate Professor, *****-Professor and Head,
Department of Pharmacology, LTMMC & GH, Sion Mumbai*

Total Case Reports: 68

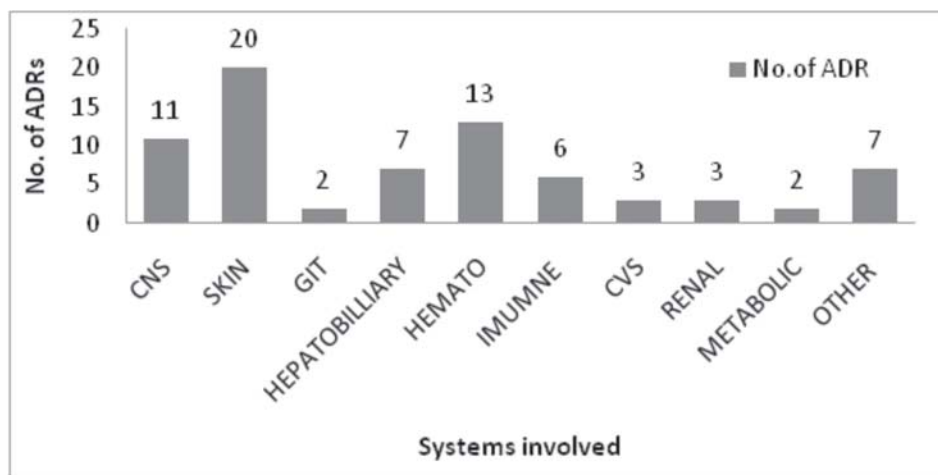
I. Age and Gender distribution:

Age groups	Number of patient	Males	Females
<3yrs	11	7	4
3-17yrs	15	11	4
18-44yrs	24	12	12
45-60yrs	9	4	5
>60yrs	9	2	7
total	68	36	32

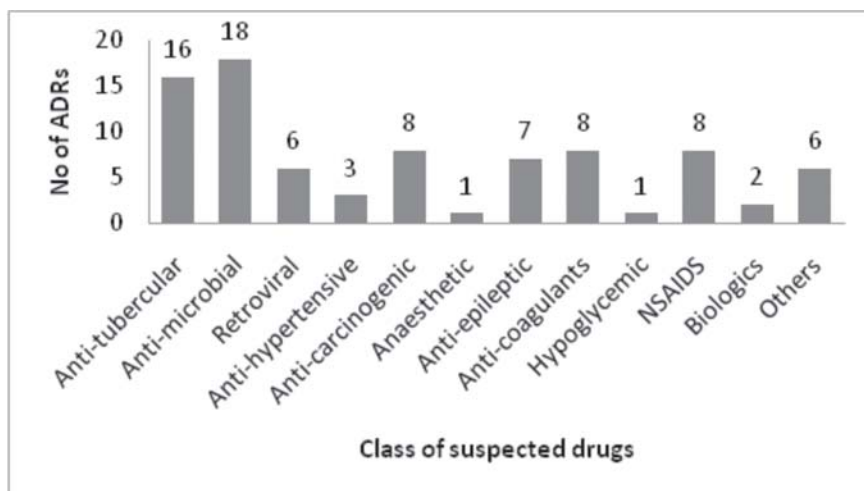
II. Seriousness of reactions reported:

Seriousness of reactions reported	Number of cases
Yes	63
No	05

III. System of distribution of the adverse drug reaction:

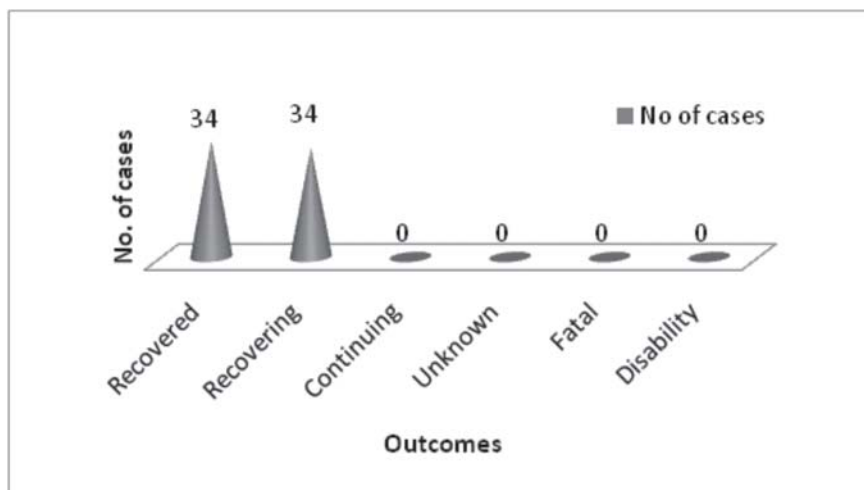


IV. Class of Suspected Drugs:

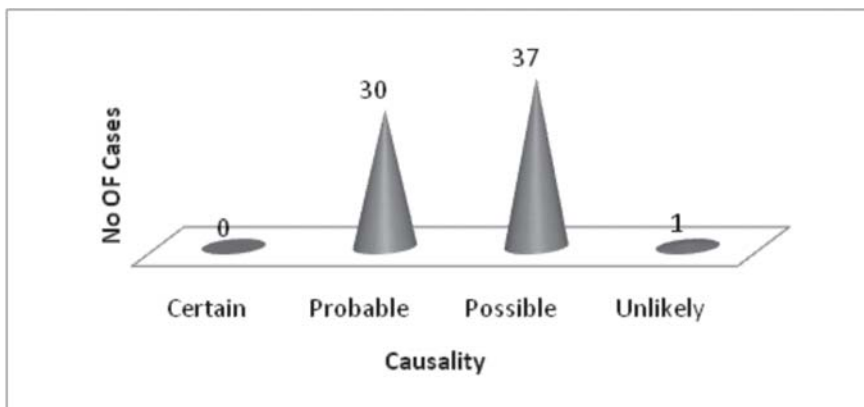


Others include steroids, histamines, electrolytes, anti-leprosy, anti-cholinergic.

V. Outcome of the reaction:



VI. Causality assessment (WHO causality assessment scale):



EVALUATION OF A CASE

VINCRISTINE INDUCED PERIPHERAL NEUROPATHY IN A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Dr Nitin Shinde*, **Dr Sujata Sharma[#]**, **Dr Jaisen Lokhande****, **Dr Sharmada Nerlekar*****, **Dr Abhilasha Rashmi****, **Dr Mamta Manglani^{##}**, **Dr Sudhir Pawar******

* - First year Resident, ** - Assistant Professor, ***- Associate Professor, **** - Professor and Head - Department of Pharmacology, LTMMC & GH

[#]- Assistant Professor, ^{##} - Professor and Head - Department of Pediatrics, LTMMC & GH

Introduction:

Vincristine is a vinca alkaloid derived from the *Catharanthus roseus*, formerly known as *Vinca rosea* from which it gets its name. Vincristine is one of the important chemotherapeutic agents used in various types of cancers including Acute Lymphoblastic Leukemia (ALL). One of the commonly encountered adverse effects of Vincristine is peripheral neuropathy which can manifest as pain, altered sensation in the limbs and weakness of limbs. The peripheral neuropathy induced by chemotherapy can be progressive and often irreversible condition^[1] and can be severe enough to avoid, reduce, or stop the use of Vincristine.

We report here a case of Vincristine induced peripheral neuropathy in a pediatric patient with B cell acute lymphoblastic leukemia.

Case history:

A 5 year old female child (11.8 kg with B.S.A of 0.56 m²), diagnosed as a case of B cell Acute Lymphoblastic Leukemia (ALL) in March 2013 and was started on chemotherapy with MCP - 841 protocol which consists of Inj L-Asparaginase, Inj Vincristine, intrathecal Methotrexate, Inj Daunomycin, Inj Cytarabine and Tab. Prednisolone. Patient completed induction cycle along with cranial radiation without any significant adverse reactions. She had received total 10 doses of Vincristine (cumulative dose of 7.5mg).

However after starting the consolidation cycle, she presented on 17-09-2013 in the paediatric ward with chief complaints of pain and weakness of lower limbs with repeated accidental falls since 5 to 7 days and bilateral ptosis. She was afebrile with normal vital parameters. Neurological examination revealed normal sensorium. Except for bilateral ptosis, cranial nerves were normal. She had hypotonia in both lower limbs with power of 2/5 and normal upper limb tone and power. There was no ascending

or descending pattern of weakness noticed. Bilateral knee and ankle jerks were not elicitable and plantars were absent. Sensory examination was normal, except for increased pain in both lower limbs and thighs. She had no signs of raised intracranial tension. The cerebrospinal fluid examination was normal. Her stool culture did not grow polio virus. She was not on any drugs that could potentiate neurotoxicity of Vincristine. Serum electrolytes and calcium levels were normal. MRI Brain & spine were normal. Electromyogram (EMG) was normal. Nerve conduction studies revealed decreased conduction velocity in both lower limb with increased latency and markedly decreased amplitude suggestive of mixed (axonopathic and demyelinating) sensorimotor neuropathy. A diagnosis of Vincristine induced neuropathy was therefore made.

In view of this, the dose of Vincristine was reduced by 50% of the total dose in rest of the chemotherapy. She was also given physiotherapy. Patient showed signs of improved over a period of 1 month and is presently able to walk without support.

Discussion:

Chemotherapy-induced peripheral neuropathies (CIPNs) are common neuropathic and pain syndrome in adult and paediatric cancer patients and survivors.^[2] The chemotherapeutic agents most often associated with CIPNs are the platinum-based compounds such as taxanes, vinca alkaloids (eg. Vincristine), thalidomide, and newer agents, such as bortezomib.^[2]

Vincristine is one of the mainstay drugs in paediatric oncology used for treatment of a variety of malignancies, including paediatric acute lymphoblastic leukemia (ALL). In the United States, over half of children with cancer who receive chemotherapy are given a treatment regimen that includes Vincristine.

The dose limiting toxicity of Vincristine consists of a peripheral neuropathy characterized by progressive motor, sensory, and autonomic involvement in varying combinations.^[3] Recently a study was conducted by paediatric neurology division of AIIMS, Delhi to investigate the incidence of CIPN in paediatric population. The study included 80 consecutive ALL Survivors to whom Inj. Vincristine was given (1.4 mg/m²) and their detailed electrophysiological nerve conduction study proved that 33.75% had neuropathy electro-physiologically, with symmetric motor axonal polyneuropathy was the most common pattern seen.

Vincristine-induced neuropathy is usually mild; and severe complications including partial or total paralysis are reported in rare cases. Symptoms usually appear 2 to 19 weeks after the commencement of Vincristine.^[4] Depression of the Achilles reflex is the earliest indication of peripheral neuropathy.^[2] After 3 or more weekly doses, loss of other deep tendon reflexes occur and are accompanied by peripheral paresthesias, pain and tingling. If therapy is prolonged or high doses are administered, wrist and foot drop, ataxia, a slapping gait and difficulty in walking may occur. Young children may refuse to walk due to extreme pain.

Vincristine neurotoxicity may be aggravated by the following: a higher dosage regimen (>30-50 mg); hypersensitivity to the drug, pre-existing liver dysfunction; hereditary neuropathy; and concomitant use of other drugs, such as allopurinol, erythromycin, isoniazid, mitomycin C, phenytoin, and itraconazole. Administration of multiple neurotoxic agents is not uncommon in cancer patients and can result in a higher grade of overall neurotoxicity.^[5]

In the present case, the patient did not have any such risk factors however the patient showed improvement on stopping Vincristine whereas other drugs were continued. Moreover there is enough evidence published in literature about Vincristine being one of the common drugs to cause neuropathy.

Based on the above and according to WHO scale of Causality assessment, the association of Vincristine with the ADR can be considered to be “**Probable**” because of temporal relation with Vincristine, having a “dechallenge response” positive and the ADR is unlikely to be caused by other drugs or the underlying disease.

Early diagnosis, preventive strategies and management of symptoms have shown to increase favourable outcomes in paediatric cancers. Assessment of nerve conduction velocity, nerve biopsy study and regular clinical evaluation are necessary not only for early diagnosis but also for dosage modification, as given below for Vincristine.

Areflexia only	Continue Vincristine at 100% dose.
Abnormal buttoning, writing	Reduce dose to 67%
Moderate motor neuropathy(±cranial)	Hold until recovery and reduce by 50%
Severe motor neuropathy	Omit Vincristine

Various chemoprotective agents can also be employed to reduce the incidence of neuropathic ADR although the evidence is limited to few small investigational studies.

For example Vitamin E at a dose of 600 mg daily protect against cellular oxidative damage^[6], infusion of calcium and magnesium when given at a dose of 1gm each as Calcium gluconate or Magnesium sulphate^[7] have shown mainly to protect against platinum compounds by binding to platinum agents whereas Glutamine orally 10 gms thrice a day for 4 days have prevented neuropathy in patients on chemotherapy.^[8] Similarly other drugs like Glutathione, Amifostin and Physostigmine have also shown to improve recovery from neuropathy related symptoms but very less information is available about their exact dosage formulation and mechanism for prevention of peripheral neuropathy.

Other known management given includes use of steroids, opioid and non-opioid analgesics, oral Acetyl L-Carnitine (ALC) -1500 mg twice daily and use of tricyclic antidepressants like Amitriptyline, Nortriptyline anticonvulsants like Gabapentin and Pregabalin. Some non pharmacological measures like Acupuncture & TENS (Trans Cutaneous Nerve Stimulation) are also being tried in certain cases.^[9]

Finally, various pharmacogenomic studies have determined that children with acute lymphoblastic leukemia and associated with low CYP3A5 expression genotype has an increased risk of Vincristine neurotoxicity. Screening for this genotype may help in selected patients may help in the prevention of this ADR.^[10]

Conclusion: Chemotherapy induced peripheral neuropathy (CIPN) is a common, debilitating and dose-limiting side effect of many chemotherapeutic agents. The standard of care for CIPN still remains early diagnosis and dose reduction and/or discontinuation of the offending chemotherapy treatment. Although many therapies have been investigated for the prevention and/or treatment of CIPN, currently no agent has shown satisfactory beneficial evidence to be recommended for the treatment or prophylaxis of CIPN.

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PUBLISHED CASE REPORTS ON VINCRISTINE INDUCED NEUROPATHY

Compiled by Dr Jaisen Lokhande

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

Severe neurotoxicities in a case of Charcot-Marie-Tooth disease type 2 caused by vincristine for acutelymphoblastic leukemia.

J Pediatr Hematol Oncol. 2008 Jul;30(7):519-21.

Nishikawa T, Kawakami K, Kumamoto T, Tonooka S, Abe A, Hayasaka K, et al.

We report a 13-year-old male patient with Charcot-Marie-Tooth disease (CMT) type 2 who developed severe neuropathy because of vincristine (VCR) for his acute lymphoblastic leukemia. A clumsy gait, muscle weakness in his fingers, and inverted champagne bottle-like muscle in the lower limbs were noticed after remission induction treatment for acute lymphoblastic leukemia, which included VCR at a total dose of 8 mg/m. An electrophysiologic study showed an almost normal median motor nerve conduction velocity (approximately 50 m/s), markedly reduced M-wave amplitude and sensory disturbance. He was diagnosed as CMT type 2 based on his symptoms and electrophysiologic findings. His symptoms gradually worsened, and even after VCR was discontinued, he could not walk alone for 7 months. VCR has previously been considered to be relatively safe in CMT type 2, however, some patients with CMT type 2 might show severe neurologic toxicities, as seen in patients with CMT type 1.

Low dose vincristine-induced severe polyneuropathy in a Hodgkin lymphoma patient: a case report (vincristine-induced severe polyneuropathy).

J Pediatr Hematol Oncol. 2009 Oct;31(10):787-9.

Cil T, Altintas A, Tamam Y, Battalolu E, Isikdogan A.

Chemotherapeutic drugs are the most common toxic agents for peripheral nerves. Vincristine is a vinca alkaloid drug that is used for the treatment of several malignancies in combination with other chemotherapeutic agents. Treatment with intravenous (IV) vincristine at doses above 5 mg leads to a dose-dependent neuropathy with sensory symptoms but higher cumulative doses at around 30 to 50 mg are needed for the development of motor symptoms. The standard maximum adult IV vincristine dose is 2 mg IV per dose given at weekly intervals. However, administration of a single 2-mg dose IV vincristine may rarely result in the development of peripheral neuropathy. Few case reports have been presented on vincristine-associated severe paralysis in patients with preexisting hereditary neuropathy like Charcot-Marie Tooth (CMT) disease, who received doses even lower than 2 mg. Herein, we reported a Hodgkin lymphoma patient who developed severe polyneuropathy after receiving 2 mg vincristine treatment and was subsequently found to carry the CMT1A duplication responsible for CMT disease.

Fulminant peripheral neuropathy with severe quadriparesis associated with vincristine therapy.

Ann Pharmacother 2000 Oct;34(10):1136-8

Moudgil S S, Riggs J E

To report a case of fulminant neuropathy with severe quadriparesis associated with vincristine chemotherapy. A 48-year-old white man with acute lymphoblastic leukemia was started on an induction chemotherapeutic regimen that included intravenous vincristine. He received a total of 6 mg of vincristine over two weeks during induction chemotherapy. Over the next two weeks, he developed a fulminant peripheral neuropathy with severe quadriparesis. Although commonly associated with peripheral neuropathy, vincristine neurotoxicity only rarely involves instances of fulminant peripheral neuropathy with severe quadriparesis. Guillain-Barré syndrome is also associated with leukemia and may present as a fulminant peripheral neuropathy with severe quadriparesis. Fulminant neuropathy with severe quadriparesis occurring in patients with leukemia being treated with vincristine (and who do not have coexistent Charcot-Marie-Tooth disease) is more likely due to Guillain-Barré syndrome than to vincristine neurotoxicity.

Early recognition of hereditary motor and sensory neuropathy type 1 can avoid life-threatening Vincristine neurotoxicity.

Br J Haematol. 2001 Nov;115(2):323-5.

Naumann R, Mohm J, Reuner U, Kroschinsky F, Rautenstrauss B, Ehninger G.

Hereditary motor and sensory neuropathy type 1 (HMSN-1) is an autosomal dominant disorder, which is usually not associated with neoplastic diseases. The disease predisposes to severe vincristine neurotoxicity. We report a 31-year-old woman with recurrent Hodgkin's lymphoma and unrecognized HMSN-1 who developed severe motor neuropathy 3 weeks after the first cycle of treatment including 2 mg of vincristine. HMSN is diagnosed in most cases retrospectively, usually suggested by the observation of foot abnormalities or family history. Recognizing early signs of HMSN, such as areflexia and pes cavus deformity, can prevent severe neurotoxicity of polychemotherapy by avoiding vincristine.

Vincristine-induced peripheral neuropathy in a neonate with congenital acute lymphoblastic leukemia.

J Pediatr Hematol Oncol. 2010 Apr;32(3):e114-7.

Baker SK, Lipson DM.

We report the case of a 46-day-old boy with a fulminant vincristine-induced peripheral neuropathy after treatment for congenital acute lymphoblastic leukemia. Flaccid paralysis developed at the end of the first phase of induction, requiring intubation and ventilation for 51 days. Treatment was initiated with levocarnitine, N-acetylcysteine, and pyridoxine and progressive reversal of the neuropathy occurred over the next 4 months. Potential differences in pathogenesis and presentation of vincristine neurotoxicity and Guillain-Barre syndrome in the neonate are discussed.

REGULATORY UPDATES

Compiled by Dr. Vikram Wankhade, Dr. Girish Joshi***

**-Third year Resident, **-Professor (Additional)*

Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Doripenem: Drug Safety Communication - Risk When Used to Treat Pneumonia on Ventilated Patients

The FDA has concluded that doripenem, an antibacterial drug used to treat patients who develop pneumonia while on ventilators, carries an increased risk of death and lower clinical cure rates compared to use of imipenem and cilastatin for injection. Based on an FDA analysis of data from a three-year clinical trial that was prematurely stopped in 2011 due to these safety concerns, FDA approved changes to the doripenem drug label that describe these risks. The revised label includes a new warning about this unapproved use. Doripenem is not approved to treat any type of pneumonia. Doripenem is still considered safe and effective for its FDA-approved indications - treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections, including kidney infections (pyelonephritis).

FDA Safety Alerts for Human Medical Products: Doribax (doripenem): Drug Safety Communication - Risk When Used to Treat Pneumonia on Ventilated Patient. [homepage on the Internet]. 2014. [Cited 2014 April 25]. Available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm>

Epidural Corticosteroid Injection: Drug Safety Communication - Risk of Rare But Serious Neurologic Problems

FDA is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. The effectiveness and safety of epidural administration of corticosteroids have not been established, and FDA has not approved corticosteroids for this use. FDA is requiring the addition of a Warning to the drug labels of injectable corticosteroids to describe these risks.

FDA will convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.

FDA Safety Alerts for Human Medical Products: Epidural Corticosteroid Injection: Drug Safety Communication - Risk of Rare But Serious Neurologic Problems. [homepage on the Internet]. 2014. [Cited 2014 April 25]. Available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm394530.htm>

Saxagliptin: Drug Safety Communication - FDA to Review Heart Failure Risk

FDA has requested clinical trial data from the manufacturer of saxagliptin to investigate a possible association between use of the type 2 diabetes drugs and heart failure. FDA's request resulted from a study published in the *New England Journal of Medicine (NEJM)*, which reported an increased rate of hospitalization for heart failure, when the heart does not pump blood well enough, with use of saxagliptin compared to an inactive treatment. The manufacturer is expected to submit the trial data to FDA by early March 2014, after which FDA will conduct a thorough analysis and report findings publicly. Patients should not stop taking saxagliptin and should speak with their health care professionals about any questions or concerns. Health care professionals should continue to follow the prescribing recommendations in the drug labels.

FDA Safety Alerts for Human Medical Products: Saxagliptin (marketed as Onglyza and Kombiglyze XR): Drug Safety Communication - FDA to Review Heart Failure Risk. [homepage on the Internet]. 2014. [Cited 2014 April 25]. Available from: <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm385471.htm>

Testosterone Products: Drug Safety Communication - FDA Investigating Risk of Cardiovascular Events

FDA is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. We have been monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy. FDA is providing this alert while it continues to evaluate the information from these studies and other available data. FDA will communicate final conclusions and recommendations when the evaluation is complete.

At this time, FDA has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death. Patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals. Health care professionals should consider whether the benefits of FDA-approved testosterone treatment are likely to exceed the potential risks of treatment. The prescribing information in the drug labels of FDA-approved testosterone products should be followed.

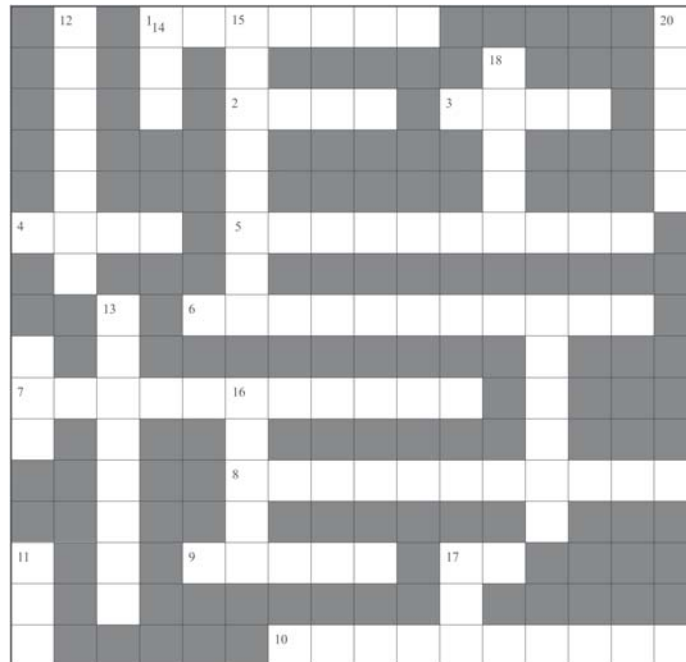
FDA Safety Alerts for Human Medical Products: Testosterone Products: Drug Safety Communication - FDA Investigating Risk of Cardiovascular Events. [homepage on the Internet]. 2014. [Cited 2014 April 25]. Available from:

http://www.fda.gov/Safety/MedWatch/SafetyInformationSafetyAlertsforHumanMedicalProducts/ucm384225.htm?utm_source=rss&utm_medium=rss&utm_campaign=testosterone-products-drug-safety-communication-fda-investigating-risk-of-cardiovascular-events

CROSSWORD PUZZLE

Dr Sharmada Nerlekar*, Dr Abhilasha Rashmi**, Dr Nitin Shinde***

*-Associate, **-Assistant Professor, ***- First year Resident, Department of Pharmacology,
LTMMC & GH, Sion, Mumbai

**ACROSS-**

- Q1. The risk of urinary ____ stones may be increased with mega doses of Ascorbic acid.(7)
- Q2. Asthma, severe _____ and heart block are the compelling contraindications to the use of beta blockers(4).
- Q3. Due to less toxicity _____ includes Tenofovir in its first line 3 drug regimen as an alternative when either Zidovudine or Nevirapine cannot be used due to toxicity or contraindication.(4)
- Q4. Vitamin E can interfere with _____ therapy.(4)
- Q5. _____ an organic thiophosphate is particularly used for prophylaxis of radiotherapy related xerostomia.(10)
- Q6. _____ an iron chelating agent can also be used to ameliorate anthracycline infusion site reaction due to extravasation.(11)
- Q7. _____ haematological abnormality associated with amodiaquine when used in children and HIV patients on treatment.(11)
- Q8. Major adverse reactions of thiacetazone are hepatitis, SJS, bone marrow depression and _____ dermatitis.(11)
- Q9. Neutropenia one of the adverse effect associated with high dose captopril commonly occurs in patients with _____ insufficiency.(5)
- Q10. Peripheral neuropathy is the most prominent adverse effect of this proteasome inhibitor used to treat multiple myeloma _____.(10)

BELOW-

- Q11. Some of the contraindications of using verapamil are hypotension, cardiogenic shock, marked bradycardia and ____ syndrome.(3)
- Q12. Prolonged intake of mega doses (0.2 to 2 g/day) of pyridoxine has been linked with _____ neuropathy.(7)
- Q13. Atazanavir a protease inhibitor, can cause _____ in some patients without liver damage due to inhibition of hepatic glucuronyl transferase(8)
- Q14. Paromomycin is known to produce ____ toxicity.(3)
- Q15. Isotretinoin is highly teratogenic causing craniofacial, heart and CNS abnormalities called _____ embryopathy.(8)
- Q16. NRTI drug related toxicity like lactic acidosis, severe hepatomegaly and hepatic steatosis are common in women, _____ persons and alcoholics. (5)
- Q17. The risk of haemolysis and leucopenia with primaquine is increased in patients of rheumatoid arthritis, _____ and in the acutely ill (3)
- Q18. Institution of _____ in HIV patients with latent or partially treated opportunistic infections may produce immune reconstitution syndrome characterized by marked inflammatory reaction against residual organisms & constitutional symptoms.(5)
- Q19. Vincristine can cause this syndrome _____.(5)

ALPHABET ‘E’ PUZZLE

Dr Abhilasha Rashmi*, Dr Sharmada Nerlekar, Dr Nitin Shinde*****

-Assistant, **-Associate Professor, *-First year Resident, Department of Pharmacology, LTMMC & GH, Sion, Mumbai.*

1.E									
2.	E								
3.		E							
4.			E						
5.				E					
6.					E				
7.						E			
8.							E		
9.								E	
10.									E

1. This is the only Bisphosphonate which inhibits bone mineralization and is associated with Osteomalacia.
2. The most important side effect of this HIV protease inhibitor (Antiretroviral drug) is diarrhea, which resolves in most patients within the first 4 weeks of therapy.
3. In treatment of early stage breast cancer, visual disturbances, fractures, arthralgia and diarrhea are most frequently seen with this steroidal estrogen synthesis inhibitor, as compared to Tamoxifen.
4. Symptoms of bloating and dyspepsia occurring with this Bile acid sequestrant can be substantially reduced if the drug is completely suspended in liquid several hours before ingestion.
5. Thrombocytopenia (28%), fatigue (12%), peripheral neuropathy (12%), neutropenia (11%) and anemia (8%) are the common side effects seen with this monoclonal antibody when used for treatment of Multiple Myeloma.
6. Elevation of liver enzymes is an important adverse effect seen with this aldose reductase inhibitor which is found to be effective in treatment of Diabetic Neuropathy.
7. The dose limiting toxicity in upto 35% of patients under treatment of this antineoplastic drug is diarrhea, for which intensive Loperamide therapy is given.
8. Sun exposure should be avoided after application of this drug which is the first topical retinoid approved by FDA for the treatment of Psoriasis.
9. Because of its hypocalcemia causing tendency, this calcimimetic drug should not be used in a patient if the initial serum calcium concentration is less than 8.4mg/dl.
10. Vomiting and diarrhea occurring with this synthetic Antimalarial drug may result in therapeutic failure owing to decreased drug absorption.

Answers :

1) Etidronate 2) Nelfinavir 3) Exemestane 4) Colestipol 5) Bortezomib 6) Epalrestat 7) Irinotecan
 8) Tazarotene 9) Cinacalcet 10) Atovaquone

CROSSWORD ANSWERS:

- 1) OXALATE 2) COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE) 3) NACO 4) IRON
 5) AMIFOSTINE 6) DEXRAZOXANE 7) NEUTROPENIA 8) EXFOLIATIVE 9) RENAL 10)
 BORTEZOMIB 11) WPW (syndrome) 12) SENSORY 13) JAUNDICE 14) OTO (toxicity) 15)
 ACCUTANE 16) OBESE 17) SLE 18) HAART 19) SIADH

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

Please feel free to contact us for the same.

Names	Extension No.	E-mail
Dr Sudhir Pawar	3162	dr.sudhirpawar@gmail.com
Dr Neha Kadhe	3206	nehakadhe@yahoo.com
Dr Manjari Advani	3205	manjari.advani@gmail.com
Dr Jaisen Lokhande	3164	dr_jaisen@yahoo.co.in
Dr Swati Patil	3161	drswati246@gmail.com
Dr Nitin Shinde	3204	dr.ni3.4u@gmail.com
Dr Sumeet Pradhan	3204	sgpradhan1018@gmail.com
Dr Chiranjeevi Bonda	3204	chiru138@gmail.com

Address for correspondence :

Department of Pharmacology,
College Building, LTMMC & LTMGH,
Sion, Mumbai-400022.
Tel.: 022-2406 3161/2
E-mail: ltmghbulletin@yahoo.com



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