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BULLETIN ON ADVERSE DRUG REACTIONS

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Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk

Dear friends and colleagues,

Here we bring to you this year's second issue of Bulletin on Adverse Drug Reactions.

The Pharmacovigilance cell in our institution right from its commencement till date is constantly reporting cases pertaining adverse reactions due to antiretroviral therapy in adult as well as paediatric age group. So, our first article attempts to throw light on these antiretroviral drug related toxicities. It gives a comprehensive overview of the incidence, mechanism and preventive aspects related to these adverse drug reactions.

The second article reviews the impact of substandard drugs on everyone involved in the healthcare system and various strategies to ensure as well as improve the quality of drugs all around the globe.

This issue also includes an interesting case report on azithromycin induced myaesthenic crisis. Also, we have brief analysis of ADRs from our institute and brain storming crosswords too.

I hope the readers find this issue of bulletin as an interesting knowledge feast.

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

Thank you.

Dr. Sudhir Pawar

ADVERSE EFFECTS OF ANTI RETROVIRAL AGENTS

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Introduction

Over past 35 years, HIV (Human immunodeficiency virus) infection has emerged as a major global health problem. WHO estimates in 2009, showed that 33.3 million people worldwide are living with HIV. In India currently ~5 lac patients are taking antiretroviral therapy (ART) and new infections have declined by > 50% during the last decade, which is due to effective use of combination ART. [1]

The rapid development of antiretroviral drugs has allowed considerable reduction in mortality and morbidity in HIV-infected patients.[2,3] Combination antiretroviral therapy prolongs life and prevents progression of disease caused by HIV.[4] Strict adherence to antiretroviral therapy (ART) is required to sustain HIV suppression, reduce risk of drug resistance, improve overall health, quality of life and survival. Adverse effects have been reported with the use of all antiretroviral (ARV) drugs and are among the most common reasons cited for switching or discontinuing therapy and for medication non-adherence. Interventions to reduce adverse effects may improve adherence to antiretroviral therapy.

The therapeutic goals of ART include achieving and maintaining viral suppression and improving immune function, but an overarching goal of treatment should be to select a regimen that is not only effective but also safe. To accomplish this goal, the clinician must consider the toxicity potential of an ART regimen, as well as the individual patient's underlying conditions, concomitant medications and prior history of drug intolerances. In addition, it should be appreciated that in general, the overall benefits of ART outweigh its risks. Presence of some conditions should be evaluated (e.g. anaemia, cardiovascular disease and renal impairment) which might be likely to worsen the scenario even in the absence of ART. There is need to highlight the importance of adverse events in overall patient management.[5] This article reviews the adverse effects of antiretroviral agents and their possible management.

Classification of antiretroviral drugs [1,4,5,6]

- ***Nucleoside reverse transcriptase inhibitors (NRTIs):*** *Zidovudine(AZT), Didanosine(ddI), stavudine (d4T), Lamivudine, Abacavir, Emtrcitabine, Tenofovir (nucleotide)*
- ***Non-nucleoside reverse transcriptase inhibitors (NNRTIs):*** *Nevirapine(NVP), Efavirenz(EFV), Delavirdine, Etravirine, Rilpivirine*
- ***Protease inhibitors (PIs):*** *Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir, Fosamprenavir, Lopinavir, Ataztnavir, Darunavir, Tipranavir.*

- ***Entry (fusion) inhibitors:*** *Enfuvirtide*
- ***CCR-5 inhibitors:*** *Maraviroc, Aplaviroc, Vicirivirоc*
- ***Integrase inhibitors:*** *Raltegravir, Elvitegravir, Dolutegravir*

One of the drug classes used in highly active antiretroviral therapy (HAART) is the nucleoside reverse transcriptase inhibitors (NRTIs), which commonly forms the "backbone" of the antiretroviral cocktail. Two NRTIs are often combined with 1 medication from either of the 2 remaining classes i.e. the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).[7]

Factors that predispose individual to adverse effects of ART[5]

Several factors may predispose individuals to adverse effects of ART medications. For example, compared with men, women (especially ART-naive women with CD4 counts >250 cells/mm3) seem to have a higher propensity to develop Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP) and also have higher rates of lactic acidosis due to NRTIs.

Other factors may also contribute to the development of adverse events:

- Concomitant use of medications with overlapping and additive toxicities (e.g. antitubercular drugs (ATT))
- Co-morbid conditions that may increase the risk of or exacerbate adverse effects (e.g. alcoholism or coinfection with viral hepatitis may increase the risk of hepatotoxicity)
- Drug-drug interactions that may lead to an increase in drug toxicities (e.g. interactions that result from concomitant use of statins with protease inhibitors)
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction.

Adverse effects of antiretroviral drugs[5,7]

All antiretroviral drugs can have a wide range of adverse effects on the human body including short-term and long-term adverse events. Each antiretroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Similarly, class specific adverse effects may occur. Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal (GI) effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy. Other common nuisance adverse effects are fatigue and headache caused by AZT and nightmares associated with EFV. Several uncommon but more serious adverse effects associated with antiretroviral therapy, includes AZT-associated anaemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity and NNRTI-associated hypersensitivity reactions. The details of these are discussed below.

Adverse effects of NRTIs

Class specific adverse effects [4, 8]

The selective toxicity of these drugs depends on their ability to inhibit the HIV reverse transcriptase without inhibiting host cell DNA polymerases. Although the intracellular triphosphates for all these drugs have low affinity for human DNA polymerase-α and -ß, some are capable of inhibiting human DNA polymerase-γ, which is the mitochondrial enzyme. As a result, the important toxicities common to this class of drugs result in part from the inhibition of mitochondrial DNA synthesis. These toxicities include anaemia, granulocytopenia, myopathy, peripheral neuropathy and pancreatitis. Lactic acidosis with or without hepatomegaly and hepatic steatosis is a rare but potentially fatal complication seen with stavudine, zidovudine, and didanosine. Incidence of NRTI associated lactic acidosis was 1.3 per 1000 person year. It is probably not associated independently with the other drugs. Phosphorylated emtricitabine, lamivudine and tenofovir have low affinity for DNA polymerase γ and are largely devoid of mitochondrial toxicity.

Table 1: Drug specific adverse effects [4,5,6,7,8,9,10,11]

Drug	Most common adverse effects	Comments
Zidovudine (AZT)	Nausea, headache, rash, anaemia, leukopenia, elevation of liver enzyme levels, elevation of lactic acid level, elevation of CPK level	Should not be combined with d4T. Anaemia is reversible and substitute/pause/lower dose of (AZT). Erythropoetin can be used to treat anaemia.
Lamivudine (3TC)	Neutropenia (rare)	One of the least toxic antiretroviral drugs. Caution is warranted in using this drug in patients co-infected with Hepatitis B Virus or in HBV - endemic areas.
Didanosine (ddi)	GI intolerance, pancreatitis, gout, reversible peripheral neuropathy	Should not be combined with ddi. Should be taken separately from food. Full daily dose can be given once daily.
Zalcitabine (ddC)	Reversible peripheral neuropathy, mouth ulcers, pancreatitis	Should not be combined with d4T or ddI. Relatively weak risk-benefit ratio limits usefulness
Stavudine (d4T)	Reversible peripheral neuropathy, lactic acid elevation (rarely fatal), lipoatropy, lipodystrophy	Should not be combined with AZT. Discontinue d4T in case of lactic acidosis and substitute TDF or ABC.
Tenofovir (TDF)	GI upset, Fanconi syndrome, renal tubular disorder	Phosphate wasting due to TDF nephrotoxicity. ABC can be used as a substitute to TDF.
Abacavir (ABC)	Hypersensitivity reaction, which may be characterized by fever, rash, myalgias, arthralgias, malaise	Reaction may be fatal if medication is continued or patient is rechallenged. Patients, regardless of HLA-B*5701 status, should not be re-challenged with ABC if Hypersensitivity is suspected.

Non-Nucleoside Reverse Transcriptase Inhibitors

Class specific adverse effects [4]

Rashes occur frequently with all NNRTIs, usually during the first 4 weeks of therapy. These generally are mild and self-limited, although rare cases of potentially fatal Stevens-Johnson syndrome have been reported with nevirapine, efavirenz and etravirine. Fat accumulation can be seen after long-term use of NNRTIs and fatal hepatitis has been associated with nevirapine use.

Drug specific adverse effects [4,,5,7]

- **Nevirapine:** Hypersensitivity rash occurred in 16%-20% of patients in studies in developed country. Other adverse effect associated with use of NVP is hepatotoxicity and its incidence is <1% to 7% in India. Initiating patients on a lower lead-in dosage of nevirapine of 200 mg once daily, followed by escalation to the full 200mg twice daily dosage after 2 weeks, helps to prevent severe rashes and Stevens-Johnson syndrome. When serious rash develops with use of NVP, a switch to EFV or an agent from another ART drug class is recommended.
- **Efavirenz:** Neuropsychiatric disorders are the most concerning adverse effects associated with efavirenz therapy with regard to tolerability and adherence. These are dizziness, suicidal ideation, depression, sleep disturbances, abnormal dreams, hangover and rash can be seen with use of EFV. In most patients, EFV-related CNS effects subside within 4 weeks after initiation of the drug. Persistent or intolerable effects should prompt substitution of EFV with an alternate ART agent e.g. other NNRTI or Integrase inhibitor.

HIV Protease Inhibitors

Class specific adverse effects [4]

A potential concern that applies to all protease inhibitors is clinically significant pharmacokinetic drug interactions. All agents in this drug class can act as inhibitors and/or inducers of hepatic CYPs and other drug metabolizing enzymes as well as drug transport proteins. Prescribing practices should be guided by up-to-date knowledge of these potential effects. Besides these drug interactions, GI side effects including nausea, vomiting and diarrhoea are common, although symptoms generally resolve within 4 weeks of starting the treatment.

Drug specific adverse effects [4,5,7]

- **Saquinavir:** Most side effects of saquinavir are mild and short lived, although long-term use is associated with lipodystrophy.
- **Ritonavir:** Most common use at present is as a PI booster at low doses (e.g. 100- 400 mg/d). The major side effect of ritonavir is GI toxicity and it may be reduced if the drug is taken with

meals. Peripheral and perioral paresthesias can occur at the therapeutic dose of 600 mg twice daily. These side effects generally abate within a few weeks of starting therapy. Ritonavir also causes dose-dependent elevations in serum total cholesterol and triglycerides, other signs of lipodystrophy and also can increase the long-term risk of atherosclerosis in some patients.

- **Indinavir:** A unique and common adverse effect of indinavir is crystalluria and nephrolithiasis. Patients must drink sufficient fluids to maintain dilute urine and prevent renal complications. Risk of nephrolithiasis is related to higher plasma drug concentrations, which presumably produces higher urine concentrations, regardless of whether or not the drug is combined with ritonavir. Other side effects are unconjugated hyperbilirubinemia, lipodystrophy syndrome, hyperglycemia, hair loss, dry skin, dry and cracked lips and ingrown toenails.

- **Lopinavir:** The most common adverse events reported with the lopinavir/ritonavir co-formulation are loose stools, diarrhea, nausea and vomiting. These are less frequent and less severe than those reported with the 600 mg twice-daily standard dose of ritonavir but more common compared to those of boosted atazanavir and darunavir regimes. The most common laboratory abnormalities include elevated total cholesterol and triglycerides. Because the same adverse effects occur with ritonavir, it is unclear whether these side effects are due to ritonavir, lopinavir, or both.

- **Atazanavir:** Like indinavir, atazanavir frequently causes unconjugated hyperbilirubinemia, although this is mainly a cosmetic side effect and not associated with hepatotoxicity.

- **Darunavir:** Because darunavir must be combined with a low dose of ritonavir, drug administration can be accompanied by all the side effects caused by ritonavir, including GI complaints in up to 20% of patients. Darunavir like fosamprenavir contains a sulfa moiety, thus rash has been reported in up to 10% of recipients.

- **Nelfinavir:** The most important side effect of nelfinavir is diarrhea or loose stools, which resolves in most patients within the first 4 weeks of therapy. Up to 20% of patients report chronic occasional diarrhea lasting >3 months, although <2% of patients discontinue the drug because of diarrhea. Nelfinavir augments intestinal calcium-dependent chloride channel secretory responses and electrolyte analysis of stool is most consistent with a secretory diarrhea. Otherwise, nelfinavir is generally well tolerated but has been associated with glucose intolerance, elevated cholesterol levels and elevated triglycerides, like other drugs in this class.

- **Fosamprenavir:** Hyperglycemia, fatigue, paresthesias and headache also have been reported. Fosamprenavir can produce skin eruptions; moderate to severe rash is reported in up to 8% of recipients and onset is usually within 2 weeks of starting therapy. Fosamprenavir has fewer effects on plasma lipid profiles than lopinavir-based regimens.

- **Tipranavir:** Tipranavir use has been associated with rare fatal hepatotoxicity. Through 48 weeks of treatment, grade 3 or 4 elevation of hepatic transaminases occurred in 20% of treatment-naive and 10% of treatment-experienced patients. Tipranavir use has been associated with rare intracranial hemorrhage (including fatalities) and bleeding episodes in patients with hemophilia.

Fusion Inhibitors [4, 12]

- **Enfuvirtide:** The most prominent adverse effects of enfuvirtide are injection-site reactions. About 98% of patients develop local side effects including pain, erythema and induration at the site of injection; 80% of patients develop nodules or cysts. Use of enfuvirtide has been associated with a higher incidence of lymphadenopathy and pneumonia in at least one study.

Entry Inhibitors [4]

- **Maraviroc:** Maraviroc is generally well tolerated, with little significant toxicity. One case of serious hepatotoxicity with allergic features has been reported, but in controlled trials significant hepatotoxicity was no more frequent with maraviroc than with placebo.

Integrase Inhibitors [4]

- **Raltegravir:** is generally well tolerated, with remarkably little clinical toxicity. In clinical trials, the most common complaints occurring at a frequency higher than in placebo recipients were headache, nausea, asthenia and fatigue. Creatine kinase elevations, myopathy and rhabdomyolysis have been reported, although a causal relationship to drug exposure is unproven. Exacerbation of depression has also been reported.

Overlapping toxicities of ART and ATT [5,13]

ARV agents and TB drugs, particularly INH, rifampicin and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should be used for treatment of active TB disease, even with co-administration of other potentially hepatotoxic drugs or when baseline liver disease is present. Patients receiving potentially hepatotoxic drugs should be monitored frequently for clinical symptoms and signs of hepatitis and should also have laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with administration of INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV infection. All patients receiving INH also should receive supplemental pyridoxine to reduce peripheral neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternative ARVs to ddI or d4 T. The table 2 give details of the overlapping toxicities of both the group of drugs.

Table 2: Overlapping toxicities associated with antiretroviral and antituberculosis drugs [13]

Toxicity	Antiretroviral drugs	Antitubercular drugs
Hepatitis	Nevirapine, protease inhibitors	Rifampicin, isoniazid, pyrazinamide, ethionamide
Rash	Nevirapine, efavirenz, abacavir	Rifampicin, isoniazid, quinolones
Anemia, neutropenia	Zidovudine	Rifampicin, isoniazid
Nausea, vomiting	Zidovudine, ritonavir, indinavir	Rifampicin, pyrazinamide, quinolones, ethionamide
Peripheral neuropathy	Stavudine, didanosine, zalcitabine	Isoniazid, ethambutol, cycloserine
CNS symptoms	Efavirenz	Streptomycin, quinolones, cycloserine

Switching antiretroviral therapy because of adverse effects [5]

Switching from an effective ART regimen to a new regimen must be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment. It is critical that providers review the following before implementing any treatment switch: the patient's medical and complete ART history including prior virologic responses to ART; resistance test results; viral tropism (when maraviroc [MVC] is being considered); HLA B*5701 status (when ABC is being considered); co-morbidities; adherence history; prior intolerances to any medications; and concomitant medications and supplements and their potential for drug interactions with ARTs. In some cases, medication costs may also be a factor to consider before switching treatment. Signs and symptoms of ART-associated adverse events may mimic those of co morbidities, adverse effects of other concomitant medications, or HIV infection itself. Therefore, concurrent with ascribing a particular clinical event to ART, alternative causes for the event should be investigated. In the case of a severe adverse event, it may be necessary to discontinue or switching ARTs pending the outcome of such an investigation. For the first few months after a switch in ART is made, the patient should be closely monitored for any new adverse events and viral load should be monitored to assure continued viral suppression.

- Acute life-threatening events (e.g. acute hypersensitivity reaction due to ABC, lactic acidosis due to stavudine [d4T] and didanosine [ddI], liver and/or severe cutaneous toxicities due to NVP) usually require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity.
- Non-life threatening toxicities (e.g. urolithiasis with atazanavir [ATV], renal tubulopathy with

tenofovir [TDF]) can usually be handled by substituting another ART agent for the presumed causative agent without interruption of ART.

- Other more chronic, non-life threatening adverse events (e.g. dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the adverse event with additional pharmacological or non- pharmacological interventions.
- Management strategies must be individualized for each patient.

Conclusion

Adverse effects have been reported with the use of all antiretroviral drugs. Early recognition of these adverse events and their management is important in overall patient management. Modification in ART should be done carefully and only when the potential benefits of the change outweigh the potential complications of altering treatment.

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SUBSTANDARD DRUGS

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Problem statement

Substandard drugs are made by licensed manufacturers operating within the framework of national pharmaceutical regulatory standards. They are referred to as "out of specification" (OOS) products, these include medicines sold past their expiration date, medicines that have been compromised in shipping or storage and medicines that are missing active ingredients or contain the wrong ratio of active ingredients.[1] They are products whose composition and ingredients do not meet the correct scientific specifications and consequently ineffective and dangerous to the patient.[2] They may result from both inadvertent and deliberate actions by a legitimate manufacture.[3] Counterfeit medicines differ from substandards as they are, "deliberately and fraudulently mislabeled with respect to identity and/or source". Counterfeit medicines are produced by illegitimate manufacturers.[3]

Substandard medicines are those that for unintentional reasons do not meet the legally required quality specifications of a country's regulators or a specialized medicine regulatory authority.[4] Similar to substandard medicines, the falsified medicines are unlawful in violating the regulator's quality specifications, but what truly defines and distinguishes them is criminal intent.[5] In 2011, the World Health Organization (WHO) member states chose to include counterfeit and substandard medicines under the new term 'substandard/spurious/falsely-labelled/falsified/counterfeit medical products' (SSFFC).[5] However, placing all illegitimate medicines under the SSFFC umbrella gives the misleading, mistaken impression that they are all deficient in the same way, when actually there are many possible deficiencies, each requiring different solutions.[1] Substandard medicines, for example, can be controlled through effective regulation and enforcement, because manufacturers are known and licensed. Counterfeits, however, can be produced in homes, small industries and backyards and are harder to regulate.[6]

The World Health Organization (WHO) in 2003 estimated that up to 25 percent of medicines consumed in developing countries are substandard.[3] The median prevalence of substandard drugs was 28.5% (range 11-48%).[5] In India the problem of substandard medicines is much more than the counterfeit drugs.[4] This review will reason the causes and consequences of increasing quantum of substandard drugs and will also throw light on different steps that could tackle the current scenario.

Scenario in India and challenges

Low and erratic drug doses and poor quality drugs have contributed to the rise of drug-resistant tuberculosis and drug resistant staphylococcus infections in India, Latin America and sub-Saharan Africa.[7] In India the incidence of substandard has risen from 0.04% in 2009 to 2.3 % in 2012 as per Drug Controller General of India. Various state drug controllers between 2003 and 2008 concluded that 6 to 7.5% of the drug samples tested failed quality standard tests annually.[8] The list of substandard drugs along with its details in India are available from 2002 to 2014.[9] Additionally there is a long list of substandard drugs found in Jammu and Kashmir is available from home page of Drugs and Food control organization, Jammu and Kashmir.[10] Though these medicines were found by authorities, it is not known if these drugs were consumed and had led to any harmful effect. Further it is also not known if these have invited any action from the FDA.

India does not use the same definitions as the WHO in distinguishing between substandard and counterfeits. Rather, it identifies "spurious medicines," which include fake and adulterated medicines and "grossly substandard" medicines, defined by percentage of active ingredient present. India does not discriminate based on the manufacturer. Counterfeit and substandard medicines reflect very different weaknesses in regulation, weaknesses that can be addressed based on manufacturer. By blurring the line between legitimate and illegitimate manufacturers, India is trying to fight two problems with a single solution, which may explain why efforts to reduce the proliferation of substandard medicines have been largely ineffective.[3]

The actions taken are directed more towards counterfeits than substandard drugs. For example, the government passed legislation requiring medicine manufacturers to put 2-D barcodes on all packages to facilitate tracking and verification of authenticity of medication.[11] These efforts may prove effective against counterfeiting but will be less effective against substandards as they cannot indicate the point in the supply chain where medicines began to lose effectiveness.[3]

Causes of Substandard drugs

Medicines are post-experience goods, meaning that consumers may not be able to perceive the quality of the product even after consuming it. Consumers have difficulty isolating the effects of the product because they cannot compare the observed outcome to the counterfactual, namely the outcomes using different treatments on an identical patient, under identical circumstances. Thus when consumers cannot perceive product quality, low-quality goods sell equally well as high quality, so producers respond to the incentive to cut costs and maximize profits. This is termed as market failure. This market failure and inadequate reforming regulations are the key factors in production of substandard drugs.[3]

There are ten categories of substandard drugs mentioned by Caudron et al which includes overconcentration of active ingredient, under-concentration of active ingredient, irregular filling of

vials, contamination, mislabelling (not counterfeit), problems with active ingredient, problems with excipients (inactive ingredients used as carriers for active ingredients in medicines), poor stability, packing problems and unsatisfactory dissolution profiles.[12]

There are various actors that serve as important mediators in the chain of making quality medicines. The seven key actors along the supply chain of importance are manufacturers, national governments, international organizations, wholesalers, transporters, retailers, consumers and each has a significant role to play.[13,14]

The raw material available for manufacturing drugs are not of good quality and also good quality material is costly, hence to reduce the cost; manufacturers are lured to use substandard material. Government tries to curb the market failure by enforcing regulations to provide missing information directly (by requiring that drug companies provide information about potential side effects and contraindications, for example) or indirectly (by granting and withholding approval of a medicine, signalling to consumers whether the medicine meets a basic safety standard). Ideally, these services simplify consumer choices and give consumers the information they need to adjust consumption levels to the optimal amount. In practice, national regulatory agencies often do not have the funding, expertise and processes in place needed to fulfil this role.[12]

Additionally, many countries do not have processes in place to monitor and regulate the supply chain. As supply chains cross borders, effective regulation requires coordination among national regulatory authorities, police, customs services and national judiciaries. The market for medicines is thoroughly internationalized and no government has proven capable of perfectly regulating the medicines produced or sold within its borders. Addressing these problems requires international cooperation among national governments and international organizations.[2]

International organizations are among the main funders of medicines as humanitarian aid. They help to oversee medicine delivery in emergency situations and collaborate with other organizations to obtain donations of medicines. In addition to purchasing and providing essential medicines, international organizations propose solutions, analyze problems within the medicine supply chain and develop methods of collaboration among different actors. International organizations are limited in their ability to regulate the spread of substandard drugs because most regulation and enforcement is done at the national level.[3]

Wholesalers influence the chain in two important ways: by improving price and accessibility and by influencing the behaviour of other market participants. Regarding the first point, the non-governmental organizations, which often serve as wholesalers, have a relatively low monetary incentive to reduce quality and increase the price, because there are no shareholders demanding increased payouts.[3]

Transport allows medicines to reach recipient countries and consumers along the medical supply chain. Transportation conditions, therefore, must be regulated and monitored.[3] While retail availability,

prices and quality are partly dependent on suppliers further up the chain, the last link, medicine retailers (which include pharmacies, drug shops, grocery stores, market stalls and itinerant hawkers) provide essential information regarding medicine intake to customers. Problems at the retail supply level include: retailer lack of knowledge about the medicines they handle, stocking of unregistered medicines and expiration of medicines.[14]

To summarize many factors complicate the problem at each stage of the supply chain: limited economic resources to procure medicines, let alone implement a national medicines policy; high burden of illness; limited pharmaceutical manufacturing capacity; diverse pharmaceutical supply chains; parallel counterfeit supply chains; logistical difficulties in safe storage, transport and distribution; insufficiently trained personnel; uninformed distributors and consumer[15] and lack of economic resources and accessible channels of recourse for consumers.[6,7]

Effects of substandard drugs

It is clear that regardless of where along the supply chain substandard medicines are compromised, they pose serious public health risks.[3] Use of substandard drugs not only increases mortality and morbidity but may result in harmful side effects or allergies or endanger drug-resistant pathogens that limit the therapeutic effectiveness of legitimate medicines.[17,18,19,20] They also contribute to the spread of infectious diseases[20] and, if contaminated with pathogens (fungi, bacteria, viruses, or parasites) or other toxic elements, can cause further illness or poisoning.[21] At worst, substandard drugs result in death.[3,12,22] The use of these drugs is associated with social and economic effects, as they reduce patient's confidence in their doctors, pharmacists and even in modern medicines as a whole. They erode citizen's trust in their government's ability to maintain and enforce regulatory standards. Their spread also undermines government's credibility with respect to providing quality health care.[18,23] Thus overall effects of these medications are not only harmful to the individual but also for a nation and thus has tremendous impact on healthcare system.

Measures to curb substandard

The measures that could help in tackling the problem of substandard drugs are:

- Bringing national governments' and manufacturers' incentives in line with those of procurers and consumers
- Outline ways in which manufacturers, procurers and distributors can better monitor medicine supply chains.
- Measures by governments, international organizations and researchers to clarify the differences between substandards and counterfeits and increase their emphasis on substandards.[3]

Governments along with international organizations need to take assertive steps so that the manufacturers develop and enforce supply chain monitoring and safe practices. National governments can make specific and stringent registration requirements and pass orders to hold manufacturers accountable for substandard medicines.[3] The state-level agencies are the ones that license and monitor drug manufacturing establishments, drug testing laboratories, regulate medicine quality and approve drug formulations for manufacture. So, while GMP-based regulatory frameworks are set at the national level, enforcement and monitoring falls on state governments.[23] To create incentives for nations to tackle substandard medicines, the WHO should make the information available in public domain like information pertaining poor manufacturing and regulatory performance by manufacturers and governments.[3]

The WHO committee recommends strengthening regulatory systems; adding inspectors to police wholesalers, distributors and manufacturers; enforcing quality standards; and licensing only those manufacturers that meet international standards.[24] In 2008, Prequalification of Medicines (PQP) updated the procedure for prequalification to increase transparency and accountability. The WHO has also initiated a study that highlights the benefits to manufacturers of registering products under PQP. To improve the quality of medicines, the WHO should constantly adjust and enhance PQP to meet new demands.[3,24,25]

Medicine procurers (international organizations, retailers, wholesalers) could then patronize countries and manufacturers with the cleanest manufacturing records (i.e., those that produce the fewest substandard medicines). To encourage medicine manufacturers to uphold high production standards, procurers should patronize manufacturers based on their ability to consistently produce high quality medicines. Procures must use tools as much as possible to determine the range of options available to them to ensure they buy and distribute high-quality medicines. By doing so, they will create incentives for manufacturers to self-regulate. Finally, to create economic incentives for manufacturers in developing countries to improve their practices, procurers could approach manufacturers in developed countries to see if they can match prices for medicines made in developing countries.[3]

According to Agwunobi and London mass retailers in non-health industries have reduced costs and improved quality by eliminating middlemen, purchasing in bulk and embracing price competition. Adopting similar efficiency improvements would increase the quality, reach and affordability of medicines.[26] Thus ensuring high quality, establishing trustworthy transport, surprise checks at various levels of supply chain and increasing transparency in the monitoring procedures and policy will assure a robust management of this problem. Increasing consumer awareness in these areas as well as active involvement of consumer at various levels might help to decrease the quantum of substandard drugs.[3]

The drug testing technologies like semi-quantitative thin-layer chromatography (TLC) (GPHF-Minilab) and disintegration tests, Raman spectrometry and near-infrared (NIR) spectrometry can be used to

assure the quality of medications. A study done by Roger et al found that NIR and Raman spectrometry compared favorably to TLC in most respects except cost. However the indirect costs of TLC- including requirements for a climate controlled location and trained laboratory staff-are considered, the cost advantage of TLC may disappear in developing countries.[27]

Conclusion

The problem of substandard medicines is just a tip of iceberg as there is a scarcity of data to measure the prevalence of problem related to substandard quality of medicines. International organizations, governments and researchers must clarify the differences between substandard and counterfeit medicines and other alternative terminologies used which create confusion. High demand, erratic supply, lack of awareness and weak regulatory systems encourage manufacturing of substandard medicines. Bold steps should be taken to control these. It will be very important to bring national governments and manufacturer's incentives in line with those of procurers and consumers to create awareness and formulate standard guidelines to make uniform quality drugs throughout the country and world. A robust generic market will prevent shortage and price hike which lead to sale of poor quality drugs. Finally, the manufacturers, procurers and distributors can better monitor medicine supply chains for which special training and quality control measures should be undertaken. The strict implementation of the rules at international and national level can easily prevent the menace of substandard medicines.

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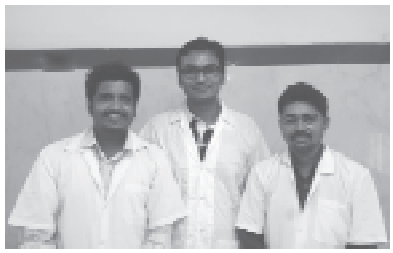
ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(April 2014 - July 2014)



Dr Shivkumar Shete*, Harshda Dipnaik**

**Technical Associate - Pharmacovigilance.*

*** Pharmacovigilance Trainee*

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

Total Case Reports: 82

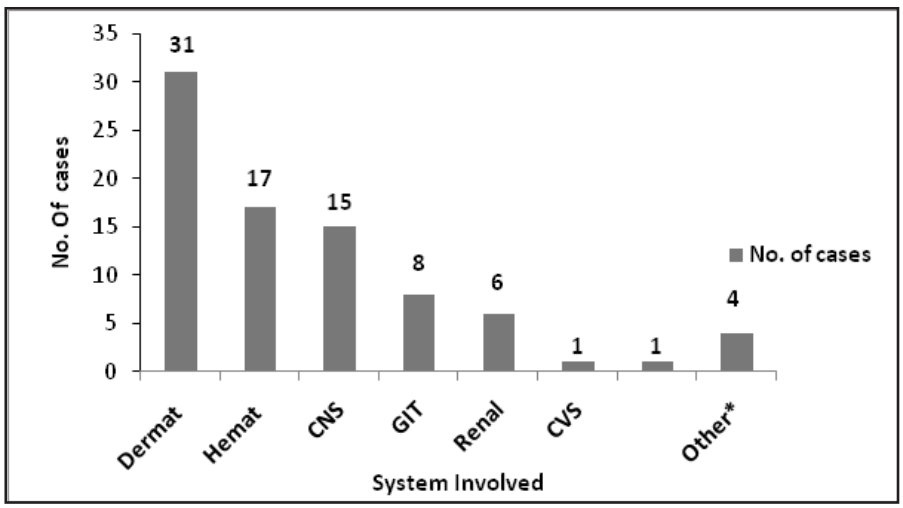
I. Age and Gender Distribution

Age groups	Number of patient	Males	Females
<3yrs	7	5	2
3-17yrs	29	16	13
18-44yrs	25	13	12
45-60yrs	13	8	5
>60yrs	8	2	6
total	82	44	38

II. Seriousness of the Reaction

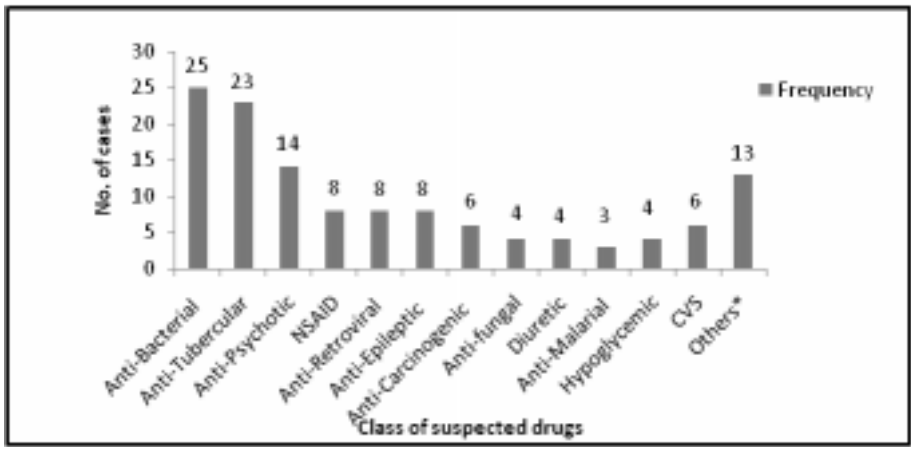
Seriousness of the reaction	Number of cases
Yes	73
No	9

III. System of distribution of the adverse drug reaction (N=82)



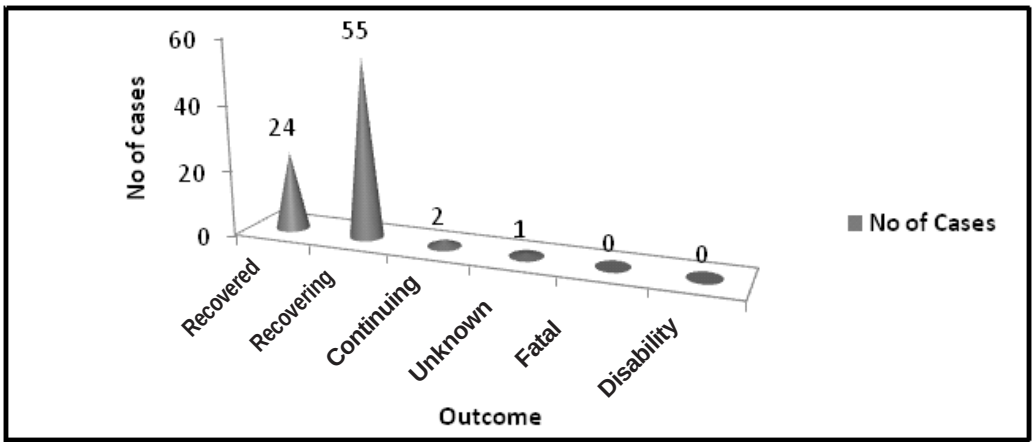
* Others include cases of involving immunological, muscular, ophthalmic and dental system.

IV. Class of Suspected Drugs (N=82)

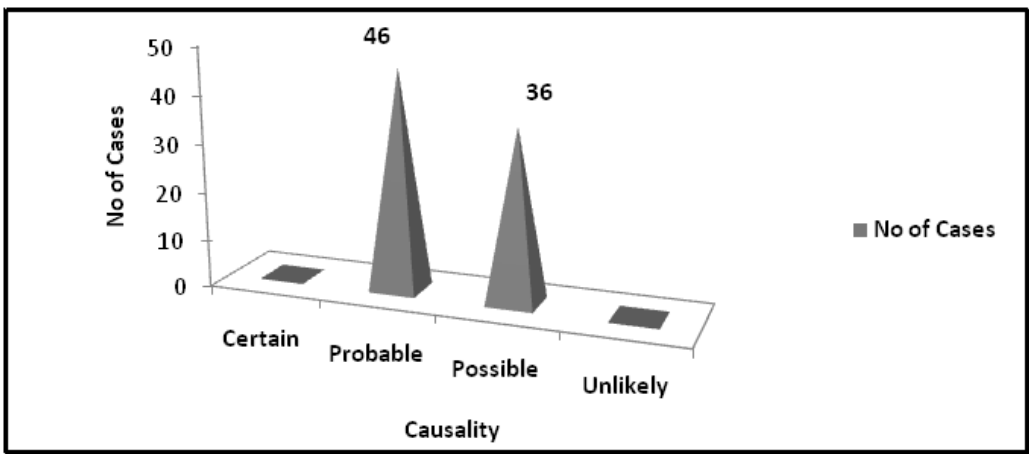


*Others include corticosteroid, antiasthmatic, anti-leprosy, antiviral, anti-gout, anti-arthritis, biological, anti-spasmodic, anti-emetic and immunosuppressant.

V. Outcome of the reaction (N=82)



VI. Causality assessment (WHO causality assessment scale (N=82)



EVALUATION OF CASE
AZITHROMYCIN INDUCED MYASTHENIC CRISIS

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**Associate Professor, **Professor,*
****Professor and Head. Department of Medicine, LTMMC & GH, Sion, Mumbai*

Introduction

Azithromycin is a macrolide antibiotic used to treat community-acquired pneumonia, pharyngitis, non gonococcal urethritis caused by C. Trachomatis and Legionnaires' pneumonia. Though well tolerated, azithromycin can produce mild gastric upset, abdominal pain, headache & dizziness. Rarely, neuromuscular adverse effects have been reported including new onset of myasthenic syndrome and exacerbation of symptoms of myasthenia gravis (MG).[1] Such an adverse effect can pose a clinical challenge to differentiate whether exacerbation is due to infection or because of drugs.

Here we report a case of myasthenic crisis precipitated by azithromycin, which required withdrawal of suspected drug and prompt medical management with intensive care.

Case History

27 years old female was a known case of myasthenia gravis with thymoma since7 years and was started on treatment with Tab. Pyridostigmine (60 mg) four times a day and Tab. Prednisolone (55mg) once daily.

Patient came to our hospital with chief complaints of fever, cold and cough with expectoration since 5 days. On examination, patient was febrile. She had bilateral crepitations in lungs. Patient was diagnosed as a case of lower respiratory tract infection and was admitted to the hospital. She was prescribed Inj. Azithromycin 500mg, Inj. Ceftriaxone 1gm, Inj. Pantoprazole 40mg, intravenously and Tab. Paracetamol 500mg per oral.

Patient first received Inj. Azithromycin after which within 3-4 minutes she started feeling generalized weakness. Symptoms got worsened dramatically and progressed to extreme muscle weakness, difficulty in speaking, swallowing and ptosis. Patient was cyanosed and gasping. On examination, patient was atonic with grade zero power in limbs and reflexes were absent. She was intubated and shifted to intensive care unit.

Diagnosis of azithromycin induced myasthenic crisis was made. Inj. Azithromycin was stopped. Patient was then treated with Inj. Methylprednisolone (500mg) in normal saline over 1 hour and Tab. Pyridostigmine (60 mg) was continued, to which patient responded over a course of time.

On the next day, the treatment for lower respiratory tract infection was resumed with Inj. Ceftriaxone (1gm), and supportive treatment with Metronidazole, Pantoprazole and Paracetamol was instituted.

On 3rd day, patient was extubated without any respiratory compromise. At that time, power was regained to Grade 4, reflexes and other examinations were within normal limits, i.e. she recovered completely.

Discussion

In the present case, patient developed myasthenic crisis soon after administration of intravenous azithromycin. The suspected drug was discontinued and patient was managed under intensive care unit with respiratory support. Treatment for respiratory infection was provided with ceftriaxone which is less likely to cause such an adverse reaction. Patient responded well to treatment and recovered completely.

According to WHO scale of Causality assessment, the association of azithromycin with the ADR can be considered to be "Probable" because of strong temporal relation with azithromycin and having a "dechallenge response" positive as the reaction improved after discontinuing the suspected drug, irrespective of the infective condition.

Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular transmission, leading to generalized or localized weakness characterized by fatigability.[2] It is the most common disorder of the neuromuscular junction, with an annual incidence of 0.25-2 patients per 100 000.[3]

Myasthenic crisis is a complication of MG characterized by worsening muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation.[2] A more comprehensive definition of myasthenic crisis also includes post-surgical patients, in whom exacerbation of muscle weakness from MG causes a delay in extubation.[4] Exact incidence of drug induced myasthenic crisis is not known, but 15 to 20% of myasthenic patients are affected by myasthenic crisis at least once in their lives which could be precipitated by drug or other precipitants.[2]

The median time for first myasthenic crisis from onset of MG ranges from 8-12 months. However, myasthenic crisis may be the initial presentation of MG in one-fifth of patients. Overall, women are twice as likely as men to be affected. A bimodal distribution of myasthenic crisis is seen. An early peak prior to age 55 affects women four times more as compared to men, whereas after age 55 women and

men are equally affected. The average age of admission with myasthenic crisis is almost 59 years. 18% percent of patients admitted with myasthenic crisis will require discharge to a rehabilitation centre.[5] The most common precipitant is infection, most commonly, bacterial pneumonia followed by a bacterial or viral upper respiratory infection. Other precipitants include aspiration pneumonitis, surgery, pregnancy, perimenstrual state, certain drugs and tapering of immune-modulators. Approximately one-third to one-half of patients may have no obvious cause for their myasthenic crisis.[6,7]

Commonly used drugs which may worsen myasthenia gravis are ketolides (telithromycin); aminoglycosides (amikacin, gentamicin, streptomycin); vancomycin; clindamycin; macrolides (doxycycline, erythromycin, minocycline, oxytetracycline, tetracycline, azithromycin), quinolones (ciprofloxacin, ofloxacin, norfloxacin), antimalarials (chloroquine, hydroxychloroquine, quinine) and urinary antiseptic (nalidixic acid). Apart from these antibiotics, some anticonvulsants (phenytoin, carbamazepine), antipsychotics (neuroleptics), cardiovascular agents (beta blockers, calcium channel blockers, class I anti-arrhythmic drugs) and some neuromuscular-blocking agents, local anesthetics, and muscle relaxants can also increase the risk.[7]

Four possible mechanisms for drug induced myasthenic crisis have been explained:-

- Inhibition of neuronal transmission at the presynaptic terminal
- Lack of acetylcholine release (possibly related to inhibition of calcium influx into the presynaptic terminal)
- Blockade of the postsynaptic acetylcholine receptors (AChRs)
- Prevention of action potential transmission past the postsynaptic terminal secondary to changes in postsynaptic ion permeability.[9,10]

Various case reports have reported variety of clinical presentations ranging from ocular muscle weakness to severe respiratory muscle paralysis. Morbidity results from intermittent impairment of muscle strength, which may cause aspiration, increased incidence of pneumonia, falls, and even respiratory failure if not treated.[6]

Prevention and prompt treatment of myasthenic crisis is of utmost importance. A cautious clinical approach about prescribing antibiotics to myasthenic patients can be a preventive strategy. Drugs should be administered in set up of emergency trolley for intubation. In case of antibiotic induced myasthenic crisis it should be replaced by other antiobiotic having fewer propensities to cause such an adverse event. Penicillins and sulfonamides are safer alternatives in this regard.

Advancement in the critical care techniques and the introduction of immunomodulation therapy has dramatically reduced the mortality rates of myasthenic crisis. A recent study suggests that aggressive respiratory treatment (use of suction, intermittent positive pressure breathing or bronchodilator treatments and chest physiotherapy) can lower the risk for atelectasis and ventilator-associated

pneumonia.[8] Other treatment includes plasma exchange (PE) and human intravenous immunoglobulin (IVIg).[7]

Corticosteroids are used in conjunction with IVIg and PE. High-dose prednisone (60-100 mg daily or 1-1.5 mg/kg/d) may be initiated concurrently with IVIg or PE as prednisone begins to work after 2 weeks, at a point when the effects of PE and IVIg are waning. Cyclosporine may be considered after initiation of IVIg or PE in patients who cannot tolerate or who are refractory to corticosteroids. However, the onset of action of cyclosporine is 1-2 months.[5]

There is a case report of azithromycin induced myasthenic crisis which was reversed by use of intravenous calcium gluconate. Intravenous Calcium gluconate is known to potentiate the presynaptic release of Acetylcholine resulting in the reversal of drug induced presynaptic block. Empirical use of intravenous calcium gluconate before administering azithromycin can be considered.[11]

Conclusion

Myasthenic crisis are often precipitated by infections which require antibiotic administration. Nearly every antibiotic ever studied has demonstrated some deleterious effect. This poses a challenging dilemma for clinicians as infections must be adequately treated. Thus, a vigilant clinical approach is mandatory to ascertain the precipitant factor for myasthenic crisis.

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PUBLISHED CASES OF ANTIMICROBIAL INDUCED MYASTHENIC SYNDROME

Compiled by **Dr Jaisen Lokhande**

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

Exacerbation of pseudoparalytic myasthenia gravis following azithromycin.

Schweiz Med Wochenschr. 1996 Feb 24;126(8):308-10.

Cadisch R, Streit E, Hartmann K.

We report the case of a 25-year-old female patient with severe aggravation of myasthenia gravis due to azithromycin which was prescribed for an influenza syndrome. One hour after the intake of 500 mg azithromycin the patient developed weakness of the legs and respiratory distress due to respiratory muscle failure. She was hospitalized in a comatose state and required intubation and mechanical ventilation for six days. Acute worsening of myasthenia gravis was observed in this patient in 1986 after parenteral administration of erythromycin. Erythromycin causing aggravation ofmyasthenia gravis by interfering with neuromuscular transmission is reported in the literature. The close temporal relationship between the intake of azithromycin and severe worsening of myasthenia gravis in our patient suggests that azithromycin, a new azalid-antibiotic of the macrolid group, can exacerbate myasthenia gravis. We conclude that azithromycin should be added to the list of drugs to be used with caution in patients with myastheniagravis.

Fluoroquinolone associated myasthenia gravis exacerbation: clinical analysis of 9 cases.

Zhonghua Yi Xue Za Zhi. 2013 May 7;93(17):1283-6.

Wang SH, Xie YC, Jiang B, Zhang JY, Qu Y, Zhao Y, Li Y, Qiao SS, Xu CL.

Objective: To explore the characteristics of acute exacerbations of myasthenia gravis after fluoroquinolone exposure.

Methods: Gender, age, prior type, absolute score, concurrent disease, precipitated disease, use of antibiotic, onset/symptom/degree of exacerbation, therapeutic measures and prognosis at Month 1 were retrospectively analyzed for 9 patients after fluoroquinolone systemic exposure.

Results: Ciprofloxacin (n = 4), levofloxacin (n = 1) and moxifloxacin (n = 4) exposure resulted in myasthenia gravis exacerbation. Myasthenia gravis exacerbations developed at 15 minutes to 4 days post-exposure. And the clinical scores of quantitative myasthenia gravis (QMG) increased by an

average of 10. The main syndromes included dyspnea, diplopia, ptosis and dysphagia. All patients improved upon the withdrawal of fluoroquinolone in conjunctions with other interventions.

Conclusion: Fluoroquinolone exposure may result in myasthenia gravis exacerbations in patients with underlying diseases. Healthcare professionals should be aware of this serious drug-disease association.

Ampicillin may aggravate clinical and experimental myasthenia gravis.

Arch Neurol. 1986 Mar;43(3):255-6.

Argov Z, Brenner T, Abramsky O.

Ampicillin trihydrate aggravated the symptoms of two myasthenic patients. One patient had severe temporary weakness after an ampicillin sodium challenge. Ampicillin increased the preexisting electrical decrement in three rabbits with experimental autoimmune myasthenia gravis while the drug had no deleterious effects in less affected or normal animals. Myasthenic patients receiving ampicillin should be closely monitored for possible acute exacerbations.

Pegylated Interferon Induced Myasthenia Crisis-A Case Report.

Journal of clinical neuromuscular disease2013;14(3):123-125.

Congeni JP and Kirkpatrick RB

ABSTRACT Interferons (IFNs) have antiviral, antimitogenic, and immunostimulatory effects and are often used in the treatment of viral hepatitis and some neoplasms. Combination pegylated IFN-alpha and ribavirin therapy is currently recommended for the treatment of hepatitis C. Triple therapy, with the addition of a protease inhibitor, such as telaprevir or boceprevir, has recently become a mainstay of therapy for certain genotypes. There have also been reports outlining side effects associated with conventional IFN therapy and its immunostimulatory effects, which may cause autoimmune phenomena, including but not limited to Guillain-Barre syndrome, polymyositis, acute and chronic demyelinating polyneuropathy, and myasthenia gravis. Although a number of cases of interferon-induced myasthenia gravis have been reported, we present a case of interferon-induced myasthenia crisis that developed soon after retreatment of hepatitis C with combination interferon, ribavirin, and telaprevir.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by **Dr Jaisen Lokhande**

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

FDA Drug Safety Communication: FDA warns that cancer drug docetaxel may cause symptoms of alcohol intoxication after treatment

The U.S. Food and Drug Administration (FDA) has warned that docetaxel which is chemotherapy drug used for various cancers and given by intravenous route contains ethanol. It said that there may be a possibility that patients may experience intoxication. It is also revising the labels of all docetaxel drug products to warn about this risk. The FDA also urges that the health care professionals should consider the alcohol content of docetaxel when prescribing or administering the drug to patients, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications to prevent certain drug interactions. FDA recommends that patients should be aware of alcohol content in docetaxel and should avoid driving, operating machinery, or performing other activities that are dangerous, for one to two hours after the infusion of docetaxel.

Docetaxel is a prescription chemotherapy drug used to treat different kinds of cancer, including cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer. Several forms of docetaxel are currently marketed, including generics products. The various products contain different amounts of alcohol, which is used to dissolve the active ingredients so docetaxel can be given intravenously. Health care professionals should be aware of the differences in formulations in order to monitor and counsel patients appropriately.

Adapted from: FDA Drug Safety Communication: FDA warns that cancer drug docetaxel may cause symptoms of alcohol intoxication after treatment. [homepage on the Internet]. 2014 [cited 2014 Sep 25]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm401752.htm

FDA recommends health care professionals discontinue prescribing and dispensing prescription combination drug products with more than 325 mg of acetaminophen to protect consumers

FDA is recommending health care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 mg of acetaminophen per tablet, capsule, or other dosage unit. There are no available data to show that taking more than 325 mg of acetaminophen per dosage unit provides additional benefit that outweighs the added risks for liver injury. Further, limiting the amount of acetaminophen per dosage unit will reduce the risk of severe liver injury from inadvertent acetaminophen overdose, which can lead to liver failure, liver transplant, and death.

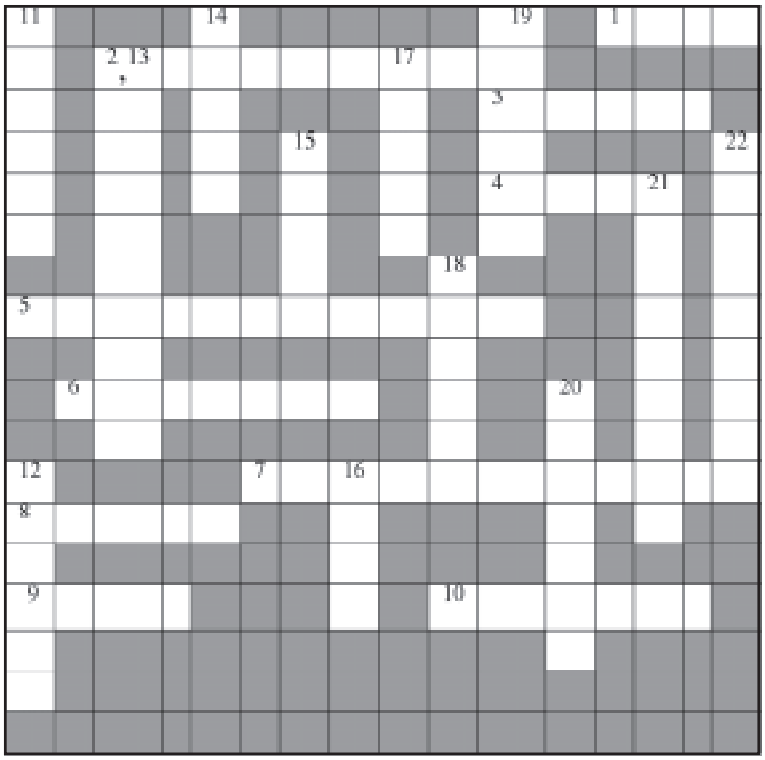
When making individual dosing determinations, health care providers should always consider the amounts of both the acetaminophen and the opioid components in the prescription combination drug product.

Adapted from: *FDA recommends health care professionals discontinue prescribing and dispensing prescription combination drug products with more than 325 mg of acetaminophen to protect consumers. [homepage on the Internet]. 2014 [cited 2014 Sep 25]. Available from:http://www.fda.gov/Drugs/DrugSafety/ucm381644*

CROSSWORD PUZZLE

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

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



ACROSS

Q1. Due to risk of Q-T prolongation, arrhythmias, phototoxicity and unpredictable hypoglycaemia, the fluroquinolone____ floxacin has been banned in India since March 2011. (4).

Q2. _____ necrosis of head of femur , humerous or knee joint is an occasional abrupt onset complication of high dose corticosteroid therapy.(9).

Q3. This cheap inhalational general anaesthetic which can be given by open drop method can cause adverse effects like eye congestion, soreness of trachea and burns on face. (5).

Q4. The adverse effect of ovarian cysts is lesser with Ulipristal, a recently approved _____ when used as an emergency coantraceptive. (4)

Q5. Osteonecrosis of the jaw and renal toxicity have been associated with the use of this parenteral highly potent third generation bisphosphonate. (11)

Q6. Phenytoin and Phenobarbitone reduce the responsiveness of target tissues to calcitriol & their prolonged use (as an antiepileptic) can cause _____ or osteomalacia. (7)

Q7. Lupus erythematosus or rheumatoid arthritis like symptoms develop on prolonged use of this antihypertensive drug in doses above100mg/day. (11)

Q8. The most prominent adverse effect of _____alkaloids is dry gangrene of hands and feet which become black as if burnt. (5)

Q9. A high incidence of bone marrow hypoplasia has been reported in _____ patients with Pneumocystis jiroveci infection when treated with high dose Cotrimoxazole. (4)

Q10. Adverse effects of Cycloserine are more in patients with a history of _____ illness or seizures. (6)

DOWN

Q11. Chronic use of Amiodarone can cause_____. (6)

Q12. Milk alkali syndrome was characterized by headache, anorexia, weakness and _____ stones due to concurrent hypercalcemia and alkalosis. (5)

Q13. _____ and acceleration of osteoporosis are prominent adverse effects seen with Anastrozole, an aromatase inhibitor used in breast cancer therapy. (10)

Q14. Few cases of sudden loss of vision due to ___ amongst users of PDE-5 inhibitors like Sildenafil have been reported. (5)

Q15. Isoflurane does not provoke the adverse effect of seizures and is particularly suitable for _____ surgery. (5)

Q16. All tetracyclines except _____ cycline are to be avoided in renal failure. (4)

Q17. Long term use of Dantrolene can cause dose dependent serious _____ toxicity in 0.1-0.5% patients. (5)

Q18. Midazolam can cause problems like blackouts and _____ in elderly. (6)

Q19. Long term use of Progesterone in HRT may increase the risk of _____ cancer. (6)

Q20. As Vancomycin has high propensity to produce kidney damage and _____ loss, its use is restricted. (7)

Q21. Reports of blood dyscrasias and liver dysfunction have restricted the use of this atypical antidepressant. (9)

Q22. Use of Pitavastatin in combination with Gemfibrozil should be avoided, as the latter decreases its _____, thereby increasing its adverse drug reactions. (9)

ALPHABET 'F' PUZZLE

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

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

1. Seizures may be precipitated in patients who had been taking benzodiazepines for long period, when this benzodiazepine antagonist is used for treatment of benzodiazepine overdose.
2. This is the most neurotoxic Nitrogen Mustard which causes altered mental status, coma, seizures and cerebellar ataxia, which can be prevented by administration of methylene blue, 50 mg, a day before and three times per day during drug infusion.
3. FDA recommends that candidates for therapy with this anti TNF-α monoclonal antibody should be tested for latent tuberculosis and those who test positive, should be prophylactically treated with Isoniazid.
4. This is a thiophosphate cytoprotective agent which is used for reduction of renal toxicity associated with repeated administration of Cisplatin and also to reduce xerostomia in patients undergoing irradiation for head and neck cancer.
5. Deficiency symptoms of this vitamin, which was originally called Lactochrome, are cheilosis, sore red tongue, skin rashes, cataract, migraine and rarely esophageal and cervical malignancy.
6. The principal dose limiting toxicities of this antiviral and immunomodulator cytokine group are myelosuppression, neurotoxicity, depression and autoimmune disorders.
7. Hot flushes, leg cramps and a threefold increase in deep vein thrombosis and pulmonary embolism are the major ADRs seen with this Selective Estrogen Receptor Modulator (SERM) which is used primarily for prevention and treatment of osteoporosis.
8. To avoid sudden fall of systolic BP more than 25 mm of mercury, a gap of at least 24 hours is needed following administration of this phosphodiesterase-5 inhibitor for safe use of nitrates in patients of angina.
9. Loss of short term memory and confabulation are the major findings seen with this syndrome associated with vitamin B1 (Thiamine) deficiency due to heavy alcohol consumption over a long period.
10. Incidences of side effects like diarrhea, vomiting, rhinitis and rashes are more commonly seen in pediatric population than adults after oral administration of this carbacephem β lactam antibiotic.

ALPHABET 'F' PUZZLE:

1. Flumazenil 2. Ifosfamide 3. Infliximab 4. Amifostine 5. Riboflavin 6. Interferon 7. Raloxifene 8. Sildenafil 9. Korsakoff's 10. Loracarbef

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CROSSWORD ANSWERS

1) GATI 2) AVASCULAR 3) ETHER 4) SPRM (Selective Progesterone Receptor Modulator) 5) ZOLEDRONATE 6) RICKETS 7) HYDRALAZINE 8) ERGOT 9) AIDS 10) MENTAL 11) GOITER 12) RENAL 13) ARTHRALGIA 14) NAION (Non Arteritic Ischaemic Optic Neuropathy) 15) NEURO 16) DOXY 17) LIVER 18) ATAXIA 19) BREAST 20) HEARING 21) MIANSERIN 22) CLEARANCE

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

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