

BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL



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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.

You are aware that in the event of adverse drug reactions, the first decision taken is discontinuation of the offending drug, followed by replacement with an alternative agent and other management. However in some special situations the same drugs has to be reintroduced, however, with extreme precautions and in most methodological manner. The first article gives an overview of the strategies which can be utilized for safe reintroduction of the same drugs which had caused some ADRs.

Reporting an ADR has now become relatively a simple task, however one of the reasons for under reporting of ADRs is the lack of information of who, what and where to report the ADRs. The second article attempts to make this easy for us. It answers most of these questions and also gives a link to all the forms for the same. We are sure this article will help us all in removing atleast few of the obstacles in ADR reporting.

Other features in this issue include analysis of the ADRs from our institute for your quick review, interesting case series of Tenofovir induced Nephropathy 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

STRATEGIES FOR REINTRODUCTION OF A DRUG AFTER AN ADVERSE DRUG REACTION

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Introduction:

Adverse drug reactions are a common source of morbidity and mortality in patients.^[1] Drug hypersensitivity reactions amount to 5-10% of all adverse drug reactions reported. Discontinuation of therapy with the offending drug is one of the first decisions taken during management of an adverse drug reaction resulting from drug hypersensitivity (Type B ADRs)^[2] as such adverse reactions are not dose related and do not respond to reduction in dosage of the culprit drug. Further treatment of patients experiencing hypersensitivity to a drug specially a serious one is more precarious. This situation poses itself as a double challenge in the form of management of the original disease despite withdrawal of the offending drug along with management of the adverse drug reaction. Most commonly sought method to deal with such a crisis is to replace the culprit drug by an alternative (if one exists), followed by management of adverse reaction. However, it has been observed that alternatives are not always available and when a replacement is undertaken by a second line drug, patients are exposed to risk of poor efficacy coupled with adverse effects and possibly increased cost of therapy. Considering the above scenario, there are times when reintroduction of drug to which the patient is hypersensitive becomes necessary. Procedures to be followed for this have to be strategic anticipating a high risk of precipitating a hypersensitivity reaction. This short article provides a bird's eye view of the strategies for reintroduction of a drug after a hypersensitivity reaction when such an act is deemed necessary.

The following strategies, alone or in combination could be utilized for safe reintroduction of a drug after a hypersensitivity reaction:

1. Slowing infusion rates and pre-treatment with medications (antihistaminics and corticosteroids)
2. Graded challenge
3. Induction of tolerance

Slowing infusion rates and pre-treatment with medications:

Drugs like vancomycin, opioids exhibit an anaphylactoid reaction due to release of histamine from mast cells by a non- IgE mediated direct method. Reaction symptoms are similar to anaphylaxis and comprise urticaria, bronchospasm flushing and shock (Red man syndrome) but unlike a true anaphylactic

reaction, previous sensitization by the same drug is not required to elicit an anaphylactoid reaction. Commonly employed strategy to reintroduce vancomycin in such patients exhibiting an anaphylactoid reaction for which alternatives are not available, would be to lower the infusion rates coupled with premedication by drugs like antihistaminics. Reduction in infusion rates would reduce the incidence of non-immunological (anaphylactoid) reactions but not of true anaphylactic reaction of immunological origin.^[3]

Graded challenge:

Graded challenge refers to slow and cautious administration of multiple incremental doses of a drug starting from a low dose till the full therapeutic dose is achieved so as to prevent any serious adverse reaction. Patients are started with 1/10 to 1/100 of the therapeutic dose and dose is increased in 3 to 5 steps to reach the therapeutic dose. Since the main aim of graded dose challenge is just to ensure safe drug administration in a patient of unknown hypersensitivity status, if a reaction is encountered, further doses are abandoned and reaction management is initiated.

It is commonly employed in patients giving a history of hypersensitivity reaction in the past to penicillin for which cephalosporin administration is presently indicated. It is a well-known fact that a small proportion of patients allergic to penicillin also cross-react with cephalosporin. Cephalosporin antigens may crosslink IgE antibodies against penicillin in previously penicillin sensitized patients to increase release of mast cell histamine and precipitate an IgE mediated anaphylactic reaction. Although many such patients can safely tolerate cephalosporin therapy, fear of precipitation of hypersensitivity by beta-lactam ring always prevails. Under such conditions, patients can be subjected to penicillin skin testing as skin tests for cephalosporins are unreliable. If patient is negative to skin test with penicillin, cephalosporins can be administered, but in case of positive skin test or lack of skin testing facility leads towards adoption of a graded challenge technique.^[3]

Induction of drug tolerance:

Induction of drug tolerance refers to deliberately inducing a state of immunological unresponsiveness to a drug in a patient previously known to be hypersensitive to it. Under such a condition, patient who is allergic to a drug tolerates it without an adverse reaction.

Procedure of inducing drug tolerance involves starting with a very low dose of a drug (as low as 1/10000 to 1/100000 the therapeutic dose) and increasing the dose every 15 minutes to 4 hours and achieving a full therapeutic dose in 10-12 steps. Any of these steps may be interrupted by a hypersensitivity reaction in which case the protocol is temporarily stopped and reaction managed followed by resumption of protocol repeating the dose twice or thrice before the next dose is administered. It may require hours to days to achieve tolerance. Tolerance once achieved is not

permanent and patient can tolerate the drug only as long as the administration is continued. Hypersensitivity reactions to IgE dependant and immunological reactions due to activation of cell mediated immune mechanisms can be averted by induction of tolerance.

Paradigms of induction of drug tolerance include patients of HIV-AIDS with *P. jirovecii* pneumonia unable to tolerate cotrimoxazole due to cutaneous reactions, pregnant patients of syphilis allergic to penicillin, ovarian tumour patients unable to tolerate paclitaxel, patients of cardiovascular diseases who need aspirin therapy but have acute exacerbation of respiratory disease on aspirin administration.^[3]

How induction of tolerance differs from graded dose challenge:

Although both tolerance induction protocols and graded challenge protocols involve administration of incremental doses, the basic difference between the two is that graded dose is only a cautious form of drug administration to prevent any adverse drug reaction while induction of tolerance is aimed at modifying the immune system to such a state where the patient who was previously known to be reactive to the drug fails to do so. Further, graded challenge is undertaken in patients with doubtful reactivity to a drug while tolerance is induced in patients of known hypersensitivity.^[3]

Prerequisites for induction of drug tolerance:

Induction of tolerance is done only when there are no alternatives to the drug causing hypersensitivity or, alternatives available have poor efficacy for the said condition as compared to the standard drug inducing hypersensitivity (e.g. Cotrimoxazole in patients of *P. jirovecii* pneumonia)

A risk -benefit analysis of reintroduction of the drug is to be performed before initiating the procedure and it is undertaken only if benefits to the individual patient outweighs the risks of serious hypersensitivity associated with the procedure.

Patient has to be clinically stable before performing a tolerance induction. Patients with serious medical disorders like uncontrolled asthma, decompensated heart failure cannot undergo such a procedure. Also tolerance induction cannot be undertaken in patients with history of serious hypersensitivity reaction like Steven Johnson's syndrome, toxic epidermal necrolysis, nephritis, vasculitis and hepatitis.

The procedure should be performed by a qualified person, skilled and experienced in dealing with the procedure. First few sessions may need inpatient or intensive care setup to manage any untoward event.^[4]

Choosing the right strategy:

There is no rule of Thumb to choose one amongst the strategies enlisted above in a particular case of drug withdrawal. Rather, it depends on assessment of the patient in terms of patient factors and the

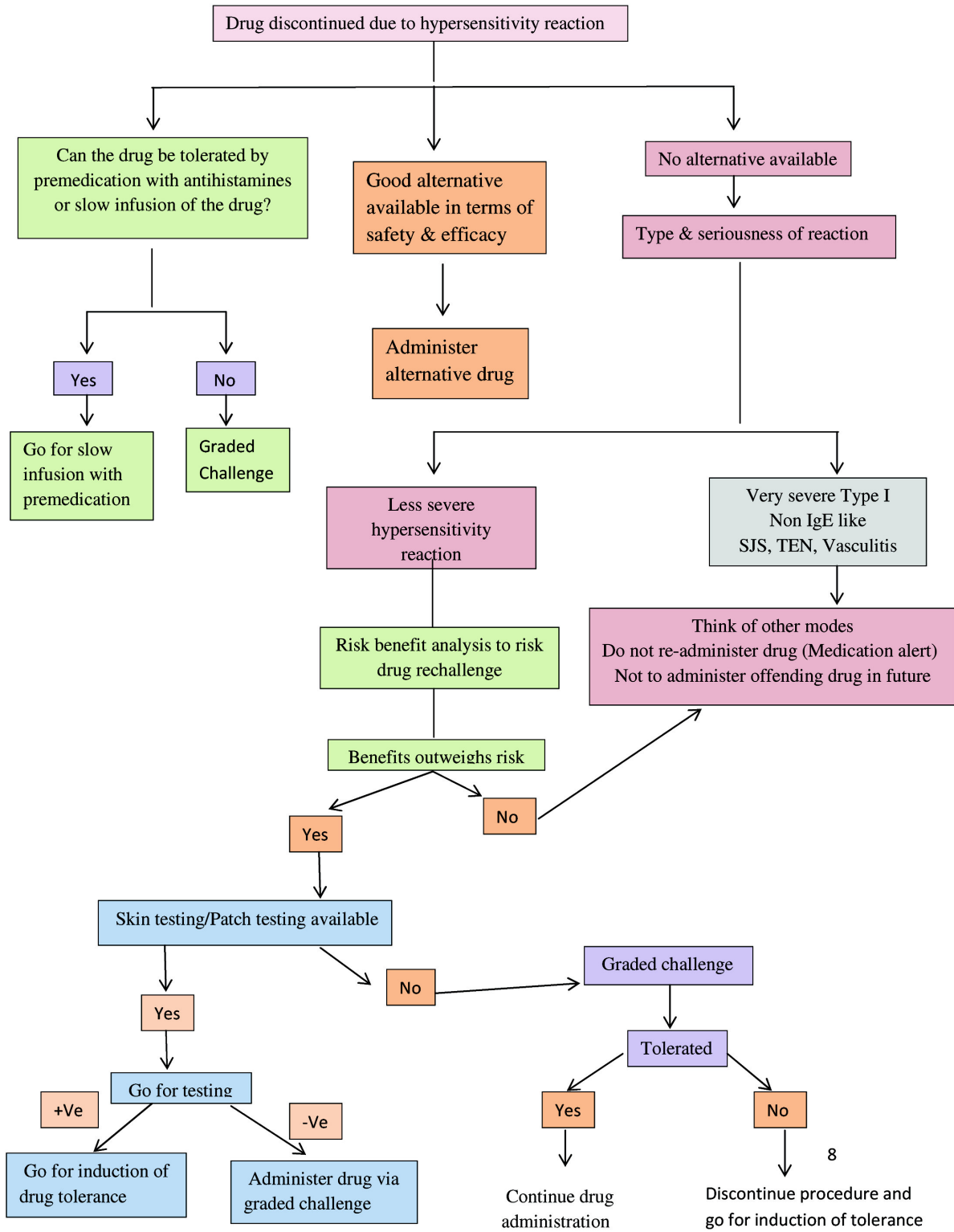
drug factors. Patient factors that influence adoption of a particular strategy for reintroduction include - previous history of exposure to the offending drug, history of a hypersensitivity reaction to the same drug, severity and type of hypersensitivity reaction (anaphylactic shock or rashes), time duration between previous and present experience of hypersensitivity (days or years) and results of tests for determination of hypersensitivity (e.g. skin tests with penicillin, patch tests for drugs inducing contact dermatitis, etc.) The drug factors depend on the route of administration or type of hypersensitivity reaction the drug is known to cause (IgE mediated anaphylaxis, non IgE mediated anaphylactoid reaction, antigen antibody mediated reactions or delayed hypersensitivity reaction due to activation of cell mediated immunity). Thus, a patient with recent history of anaphylaxis to penicillin needs to undergo a tolerance induction protocol for reintroduction of penicillin in the same patient while a patient with history of mild rash to sulphonamides 10 years ago may need a graded challenge to prevent any untoward reaction. However, if such a reaction occurs, a complete tolerance induction protocol may be initiated.

Previous history of severe reactions like Steven Johnson's syndrome, toxic epidermal necrolysis, interstitial nephritis, severe hepatitis and vasculitis are contraindications to all the above strategies of drug re-challenge. One of the few exceptions to this is use of infliximab for colon cancer where even risk of such a severe reaction is less compared to the survival benefit conferred by the drug.^[4] General principle for choosing a reintroduction strategy in a patient is outlined in the algorithm below (Fig. 1.)

Summary:

Drug hypersensitivity reactions frequently lead to discontinuation of drug therapy. Carefully selected, individualized strategies may allow reintroduction of a drug post discontinuation if the benefits of therapy outweigh risk. Strategies like infusion rate reduction and premedication with antihistaminics as well as graded dose challenge and induction of tolerance may be truly useful in optimizing drug therapy in such patients. Currently, lack of availability of skin tests, standard tolerance induction protocols and skilled personnel trained in tolerance induction protocols limit the utility of these strategies in clinical practice.

Figure 1. Algorithm showing the general principles for choosing a drug reintroduction strategy



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PHARMACOVIGILANCE: ADVERSE EVENT REPORTING

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Introduction

The impact of adverse events (AEs) and adverse drug reactions (ADRs) on public health with the use of medicinal products is huge and continues to remain so even with the great advances in medical knowledge. It continues to be an important cause of morbidity and mortality in various countries including India^[1,2]. Thus, safety monitoring of medicines is of paramount importance and is the responsibility of all stake holders in the healthcare system.

Indian scenario

In India, the Ministry of Health and Family Welfare (MoHFW), Government of India launched the nationwide Pharmacovigilance Programme of India (PvPI) in 2010 to inspire confidence and trust among patients and healthcare professionals with respect to safety of medicines. Since April 2011, Indian Pharmacopoeia Commission (IPC) under the MoHFW has been functioning as the National Coordination Centre (NCC) for PvPI. Pharmacovigilance Programme of India has identified various regional resource centres to provide training and technical support to various adverse event monitoring centres (AMCs) which are basically hospitals and institutions spread out in various parts of India.^[3] It has reported around 2.3 lakh adverse drug reactions (ADRs) through its 210 ADR monitoring centres (AMCs) and around 25% of these reports were contributed from market authorisation holders (MAHs). However, rest of 75% came from integration of PvPI with national health programmes and consumers.^[4]

Reporting of adverse events

Spontaneous reporting of AEs is considered to be basis of post marketing surveillance of drug safety which would help in early detection, assessment and prevention or minimization of these adverse events. Many countries have an appropriate functional pharmacovigilance systems in place but underreporting of AEs is still a challenge.^[5] One of the main reasons for under-reporting is due to lack of awareness and training among healthcare professionals on reporting of AEs to health authorities (HAs) or marketing authorization holders (MAHs).^[6] The current article gives an overview of various aspects of adverse event reporting and attempts to create awareness on pharmacovigilance.

i. Spontaneous reporting^[3]

- Monitoring of adverse drug reactions is carried through active surveillance (organized follow-up of patients treated with specific drug) or passive surveillance (spontaneous or voluntary reporting).
- A spontaneous report is an unsolicited communication by a healthcare professional or consumer to health authority or marketing authorization holder/company of one or more adverse drug reaction in a patient receiving medicinal product and that does not come from a study or any organized data collection scheme.
- This information on adverse reaction relating to drug should be captured in a "Suspected Adverse Drug reaction reporting form" available on the official website of IPC (www.ipc.gov.in) or CDSCO (www.cdsc.nic.in). Specific forms are available to record adverse reactions associated with transfusion of blood & blood related products, and adverse event following immunization (AEFI).

ii. Who can report?^[3]

- Any healthcare professionals (HCPs including physicians, dentists, pharmacists, nurses, etc.)
- Non-healthcare professionals including consumers can report suspected ADRs to either HAs or MAHs.

iii. Why to report?^[3]

- As a healthcare professional, it is our ethical and moral responsibility to report adverse reactions associated with the use of medicinal products and safeguard the health of public.
- Safety information available regarding a medicinal product during its pre-clinical and clinical studies is limited and thus post marketing reporting helps MAHs and HAs in making better safety related decisions.
- Helps in decreasing/preventing burden of adverse drug reactions and enhances patient safety.
- Helps in decreasing ADR related morbidity and mortality along with its healthcare costs.
- Promote rational use of medicines and adherence.

iv. What to report?^[3]

- Report all types of suspected adverse reactions irrespective of whether they are known or unknown, serious or non-serious, frequent or rare, and regardless of causal relationship with the use of medicinal products, biologics, vaccines, traditional medicines (herbal

remedies), medical devices, contrast media and other pharmaceuticals.

- Specific fields of interest are outcomes associated with the use of drugs in special population such as pregnancy, lactation, paediatric, and geriatric.
- Recommended to report ADRs due to lack of efficacy, overdose, resistance, and suspected pharmaceutical defects such as spurious and adulterated drugs.
- Also report ADRs due to product abuse, off-label use, misuse, and occupational exposure.

v. How to report?^[3]

- To capture adverse reactions, HCPs can use "Suspected adverse drug reaction reporting form" for drugs, "transfusion reaction reporting form" (TRRF) for blood and blood products and "adverse events following immunization (AEFI) reporting form" for vaccines or immunological products.

The forms can be downloaded from the following sites:

1. Suspected adverse drug reaction reporting form -
<http://www.ipc.gov.in/PvPI/adr/ADR%20Reporting%20Form.pdf>
2. Transfusion reaction reporting form -
http://www.nib.gov.in/Haemovigilance/TRRF_Form.pdf
3. Adverse events following immunization (AEFI) reporting form -
<http://www.ipc.gov.in/PvPI/adr/Serious%20AEFI%20Case%20notification%20form.pdf>

- Alternatively, consumers can use "Medicines side effect reporting form" to report adverse reactions with the use of drugs which is available in various languages including Assamese, Bengali, Gujarati, Hindi, Kannada, Malayalam, Marathi, Oriya, Tamil, Telugu. These forms can be made available from the following site - <http://www.ipc.gov.in/PvPI/adr.html>
- Collect most of the information and fill reporting forms with patient information such as patient initials (to ensure confidentiality), age at the time of event or date of birth, sex, and weight; suspected adverse reaction information such as description & date of reaction, seriousness, outcome and recovery date (if applicable); suspected medication details such as brand or generic name, manufacturer, batch or lot number, expiry date, dosage details, therapy start and stop dates, indication, dechallenge/rechallenge details, concomitant or treatment drugs, relevant tests, and other relevant history; reporter details such as reporter name, address, causality, and date of report.
- In case complete information is not available, provide mandatory information such as patient initials, age at onset of reaction(s), gender, reaction term(s), date of onset of reaction, suspected drug name, dose, start date of therapy, indication, seriousness, outcome, dechallenge/rechallenge details, reporter's name, address, causality and date of

report in order to consider the report as valid. In case further information is available at a later stage, provide the same as follow-up information.

vi. Whom to Report?[3]

- All the filled and completed forms need to be submitted to the coordinator or technical associate to the nearest AMC or directly to NCC. The following website gives the complete list of AMCs in India and can be used to locate the AMC nearby. <http://www.ipc.gov.in/PvPI/adr/List%20of%20ADR%20Monitoring%20Centres%20under%20Pharmacovigilance%20Programme%20of%20India%20%20.pdf>
- A reporter can also mail the filled in form to pvpi.ipcindia@gmail.com
- A reporter can also call or dial toll free number 1800-180-3024 from any mobile to report adverse reactions associated with the use of medicinal products from 9.00am to 5.30pm in weekdays.
- Alternatively, HCPs can download android application (ADR reporting) from Google Play store developed by PvPI to support instantaneous ADR reporting from anywhere and anytime. This application acts as a one touch access tool to report ADRs in India (Figure 01).

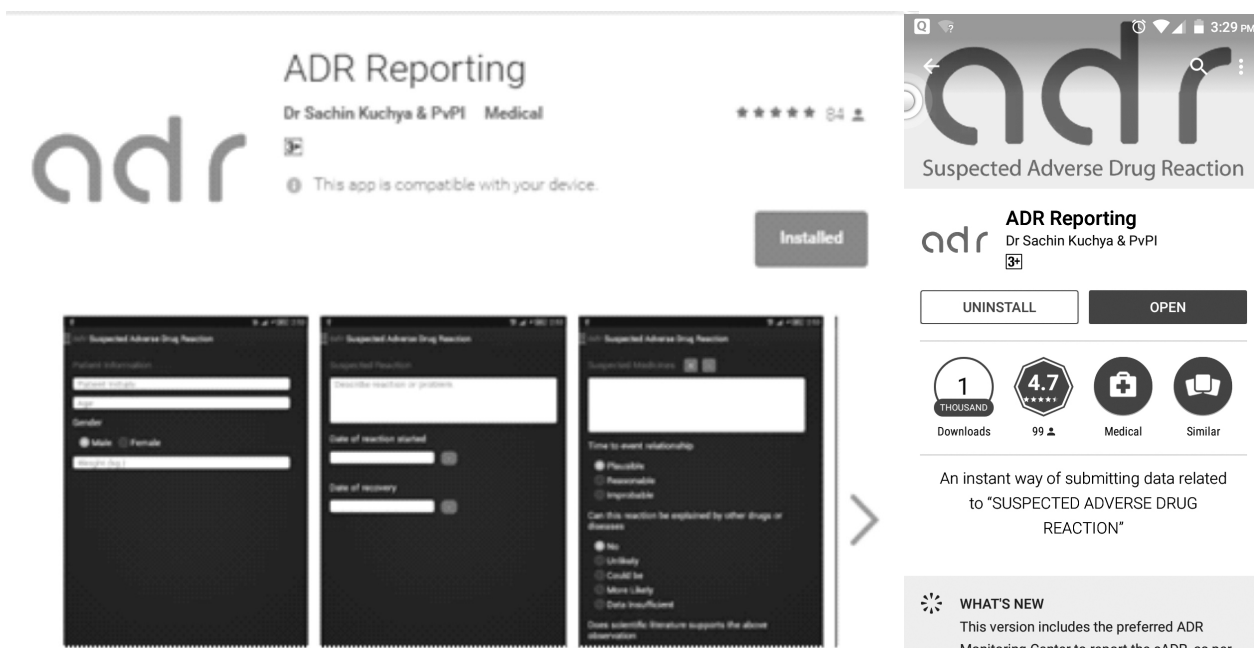


Figure 01: Screenshot of ADR reporting application

Knowledge and skill development

In order to build and strengthen pharmacovigilance skills of healthcare professionals and to promote patient safety, PvPI has come up with a year-long training calendar for 2017 with specific slots for

each state or union territory. The details of this skill development programme on "Basics and regulatory aspects of pharmacovigilance" could be found at the below link: <http://ipc.nic.in/index1.asp?EncHid=&lang=1&linkid=86&lid=640>

In addition to these regular trainings and workshops, PvPI is also posting its latest updates online on a regular basis, publishing monthly "PvPI newsletter" to discuss various updates related to pharmacovigilance in India and "drug safety alert" to discuss safety signals from various drugs. Below are the links for these: PvPI updates:

<http://ipc.nic.in/index1.asp?EncHid=&lang=1&linkid=75&lid=254>

PvPI newsletter: <http://ipc.nic.in/index2.asp?slid=540&sublinkid=448&lang=1&EncHid=>

Drug safety alerts: <http://ipc.nic.in/index2.asp?EncHid=&slid=541&sublinkid=449&lang=1>

Conclusion

There has been a significant progress in adverse reaction reporting with collaborative efforts from PvPI and industry. Planned steps in establishing pharmacovigilance systems, building knowledge, skill set and creating awareness among healthcare professionals is achieving positive results and gaining further momentum. This is the need of the hour for consumers and healthcare professionals to make use of these trainings and established systems to support adverse event reporting and safety monitoring of medicinal products in order to improve patient safety.

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ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED IN LTMMC AND GH

(November 2016 to February 2017)

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Total Case Reports: 121

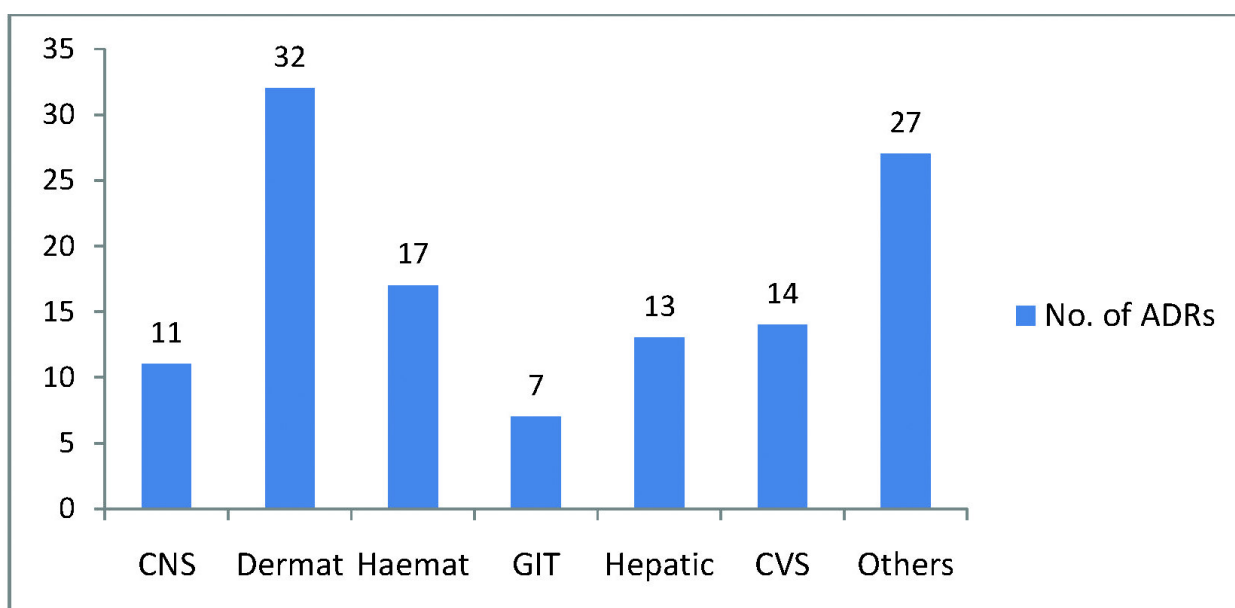
I. Age and Gender distribution:

Age groups	Number of patients	Males	Female
<3 years	14	8	6
3-17 years	35	20	15
18-44 years	40	17	23
45-60 years	15	9	6
>60 years	17	9	8
Total	121	63	58

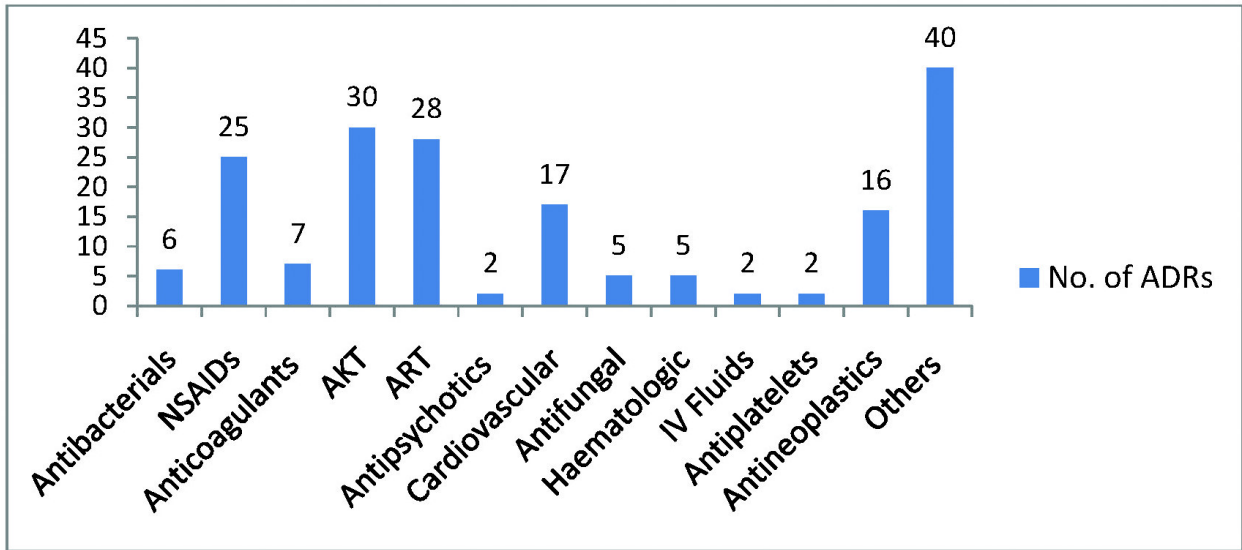
II. Seriousness of the reaction:

Seriousness of the ADR	No. of cases (N=121)
Yes	104
No	17

III. System involved in the ADR: N=121



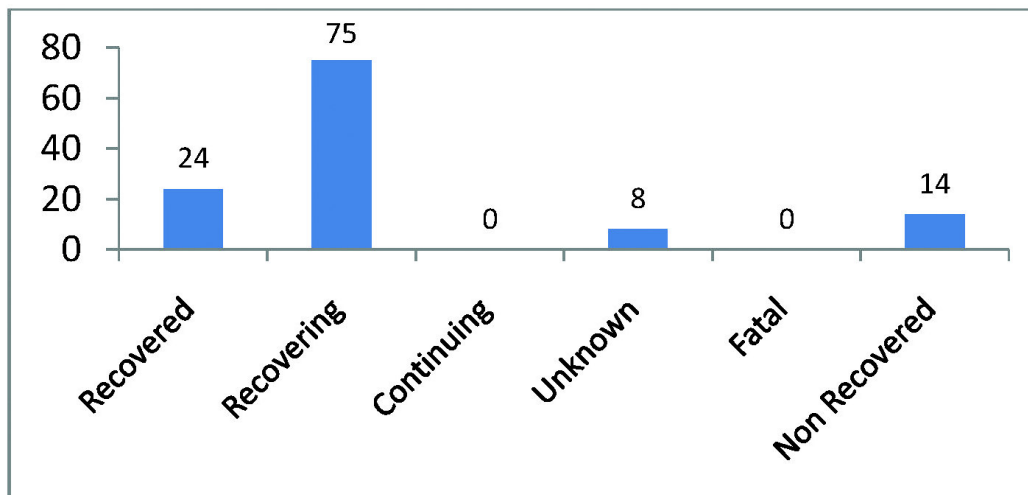
IV. Class of the Suspected drug: N=185



* Other drugs include cardiovascular drugs, antivirals, anticancer, anthelmintic, antihistaminic, antipsychotic, antitoxin, vaccines and antispasmodics.

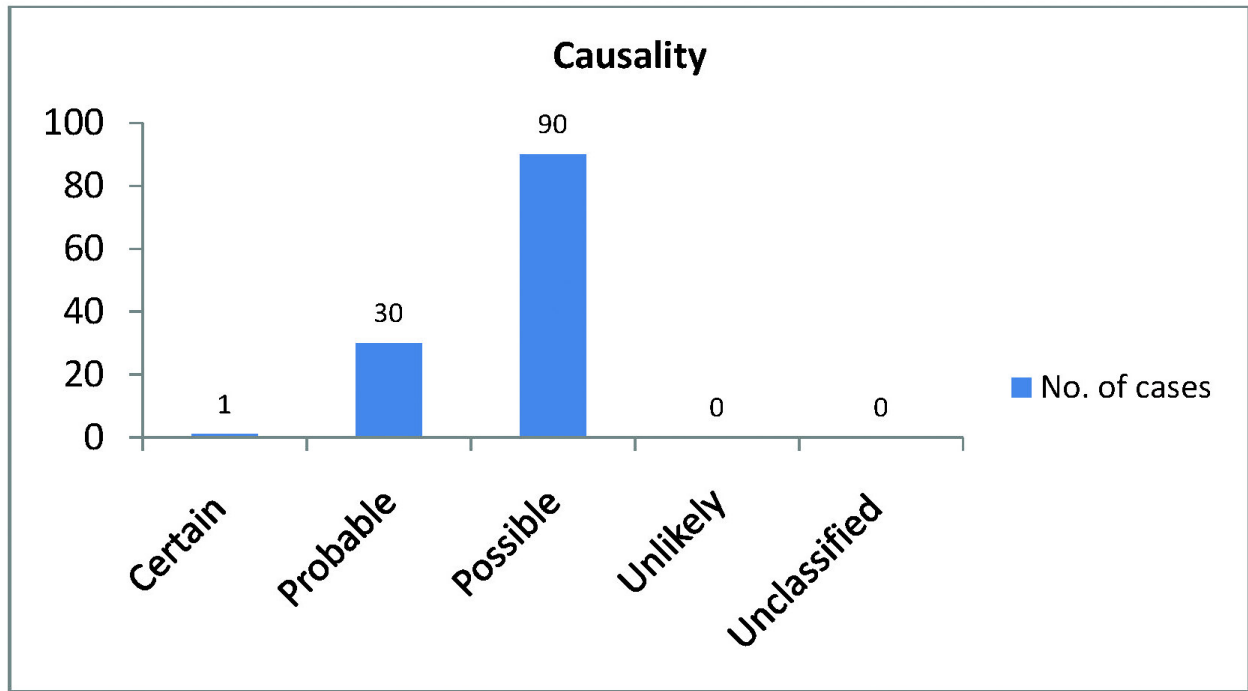
(Since one ADR was suspected to be caused by many drugs hence here N=185 whereas total number of reactions were N = 121)

V. Outcome of the reactions: N=121



The terms "recovering" and "non recovered" were in relation to the last follow-up.

VI. Causality Assessment (WHO UMC Classification): N=121



EVALUATION OF A CASE SERIES

Tenofovir induced Nephropathy - Case series

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* - 3rd year resident; ** - Assistant Professor; *** – Prof (Addl); **** – Prof and Head of Department. Department of Pharmacology, LTMMC and GH, Sion

Tenofovir is anti-retroviral nucleoside reverse transcriptase inhibitor (NRTI) and commonly prescribed drug because of convenient dosing schedule, high anti-retroviral efficacy & potency, relatively favourable side effects in comparison to other NRTIs. It is also available in hospital formulary of many developing countries hence have large usage^[1].

Although relatively favourable side effects, Tenofovir has been linked to the development of proximal tubular dysfunction, Fanconi's syndrome and acute kidney injury^[1]. According to post-marketing safety data covering 4,55,392 person-year of Tenofovir exposure, serious renal adverse events were seen in only 0.5% of patients and graded elevation in serum creatinine in 2.2% of patients^[2].

We noted three cases reported as Tenofovir induced Nephropathy within period of three months at ADR Monitoring Centre of this tertiary care hospital. Hence there was need to report and publish this case series.

Case 1.

A 46 years old male patient with immune-compromised state diagnosed since 3 months and on anti-retroviral regimen fixed dose combination (FDC) of TLE (Tenofovir 300 mg + Lamivudine 150 mg + Efavirenz 600 mg) once daily, was admitted in medicine ward and investigated for pain in epigastrium. Serum creatinine was 17.4mg/dl (Normal range- 0.6 to 1.2 mg/dl) on admission. CD4 count was 56 cells/mm³ (Normal range - 500 to 1400 cells/mm³). Drug induced nephritis was diagnosed and suspected drug Tenofovir was stopped and replaced by Zidovudine. Lamivudine & Efavirenz were continued with same dose. After 5 days of stopping the suspected drug, serum creatinine level decreased to 5.1 mg/dl

The reaction was serious as patient required hospitalization. There was a temporal association of Tenofovir with the adverse reaction and the patient showed signs of recovery both symptomatically and by laboratory parameters on stopping the suspected drug (dechallenge positive). However, considering that HIV has also been associated with nephropathy, in the present case according to WHO UMC (World Health Organization Uppsala Monitoring Centre) scale and NARANJO scale, the causality of nephropathy is POSSIBLY associated with Tenofovir.

Case 2:

A 32 years old woman with immune-compromised state since 6 months on anti-retroviral i.e. fixed dose combination (FDC) regimen of TLE (Tenofovir 300 mg + Lamivudine 150 mg + Efavirenz 600 mg) once daily, was admitted with chief complaints of pain in abdomen and vomiting with breathlessness since 2 days. On investigation her serum creatinine value was 7.8 mg/dl and CD4 count was 60 cells/mm³. Other laboratory investigations include Serum Urea - 117 mg/dl (Normal range - 7 to 20 mg/dl), pH - 7.196 (Normal range - 7.38 to 7.42), Na⁺ - 125 (Normal range - 135 to 155 mEq/L), Serum HCO₃⁻ - 5.6 mEq/L (Normal range - 19 to 25 mEq/L). The diagnosis of Fanconi's syndrome was made based on laboratory values of Na, HCO₃, etc. which were decreased.

Suspected drug Tenofovir was stopped and substituted with Zidovudine. Lamivudine and Efavirenz were continued with the same dose.

After withdrawal of suspected drug, Sr. creatinine level was decreased to 5.6.

As patient required hospitalization this reaction was categorized as serious. Outcome was fatal in this case. The cause of death was chronic kidney injury with disseminated retroviral disease.

HIV infection has been associated with nephropathy hence according to WHO UMC causality and NARANJO scale, the reaction nephropathy (chronic kidney disease) with Fanconi's syndrome was POSSIBLY associated with suspected drug (Tenofovir).

Case 3:

A 60 years old male patient of immune-compromised status since 48 months was on anti-retroviral regimen of TLE (Tenofovir 300 mg + Lamivudine 150 mg + Efavirenz 600 mg) once daily. He was admitted with chief complaints of pain in abdomen. On investigation his serum creatinine value was 8.4 mg/dl. Patient was diagnosed as drug induced nephropathy. Suspected drug Tenofovir was stopped and replaced by Zidovudine. Lamivudine and Efavirenz were continued.

After 5 days of stopping the suspected drug, serum creatinine level decreased to 5.2 mg/dl. The reaction was serious as patient required hospitalization and patient was recovering stage both symptomatically and by laboratory parameters. Since, HIV has been associated with nephropathy the reaction nephropathy is POSSIBLY related to Tenofovir by WHO UMC and Naranjo scales.

Discussion

Tenofovir disoproxil fumarate is oral prodrug of tenofovir. It is an acyclic nucleoside phosphonate (i.e., nucleotide) analog of adenosine.^[3] It is the first nucleotide analogue reverse transcriptase inhibitor to be approved for the treatment of HIV infection after Adefovir.^[3]

Tenofovir is the only NtRTI approved for management of HIV at a dose of 300 mg OD[2]. It's oral bioavailability is 25% which increases to 40% after fatty meal^[4]. Its plasma T_{1/2} is 17 hrs^[4] that allow once daily dose. On phosphorylation to active Tenofovir diphosphate competitively inhibits HIV reverse transcriptase thus causing termination of chain elongation after incorporation into viral DNA. Elimination occurs through both glomerular filtration, tubular secretion and hence dose adjustment in renal insufficiency is essential^[1].

Common side effects are nausea, diarrhoea, vomiting, and flatulence. Headache, rash, dizziness and asthenia are also seen commonly.^[4] Some rare adverse effects include acute renal failure, Fanconi's syndrome, osteomalacia and bone fracture.^[1]

Incidence of nephropathy due to Tenofovir is 0.3 to 2%^[1]. Other drugs causing nephropathy included antibiotic like aminoglycoside, beta-lactams, anti-retrovirals like acyclovir, adefovir, cidofovir, NSAID, lithium, quinolone, rifampicin, sulphonamide, vancomycin, interferon alfa which results into acute interstitial nephritis. Diphenhydramine, doxylamine, benzodiazepine, clopidogrel, statins leads to rhabdomyolysis related kidney injury whereas foscarnet, gancyclovir, indinavir, methotrexate leads to crystal nephropathy^[6].

Tenofovir nephropathy is characterized by proximal tubular cell injury which may manifest as acute kidney injury, chronic kidney disease and features of proximal tubular injury, including Fanconi's syndrome.^[1] From the past decade, many transporters are identified which are responsible for absorption and secretion of drug in the PCT of renal tubule. These transporters belong to different families, the important ones are organic anion transporters (OAT), organic cation transporters (OCT)

, P-glycoprotein (Pgp), Multidrug resistant-associated protein transporters (MRP), Peptide transporters (PEPT).^[1,2] 20 to 30% of the Tenofovir is transported actively through OAT-1 and lesser amount through OAT-3 transporter present on basolateral membrane. Any drug which competes to pass through these transporters increases the concentration of Tenofovir in blood.^[8] Normally Tenofovir in the cell of PCT is actively secreted through MRP-2 and MRP-4 transporter into lumen and finally excreted into urine. Drugs like Ritonavir, Probenecid, and Acyclovir which inhibit these transporters increase the concentration of Tenofovir inside cell. The accumulated Tenofovir diffuses into mitochondria of PCT cell and bind to mitochondrial DNA polymerase. Tenofovir destructs the mt-DNA and finally mitochondria are destroyed. Power house of cell are vanished so cell undergoes apoptotic process and all the physiological process in the PCT is disturbed. Destruction of PCT leads to hypophosphatemia, acidosis, glycosuria, aminoaciduria, hypokalaemia (Fanconi's Syndrome: case 2) & collecting duct leads to diabetes incipidus.^[1,2,3,8]

Risk factors include co-administration with drugs like Indinavir, Cidofovir & Adefovir, Lopinavir-Ritonavir which increases plasma concentration of Tenofovir by 30% due to competitively inhibiting

the same transport of Tenofovir i.e. MRP-2 in tubular epithelial membrane. Other risk factors include reduced GFR due to advanced age, low body weight, lower CD4 count due to higher viral load, hypertension, polymorphism in genes encoding proximal tubule transport, etc.^[7]

According to previous studies, the mean duration for detection of nephritis due to Tenofovir was within few weeks but in our cases it is more than that (3 months for the case 1; 6 months for case 2 and 48 months for case 3) for the detection. The late onset of the ADR is associated with increased severity as documented in the literature and as seen in our cases. The outcome of case 2 where the ADR was detected after 6 months of starting the drug was fatal.

Tenofovir induced nephritis can be prevented by initiating adequate hydration before starting medication, avoiding co-administration of nephrotoxic drug and maintaining recommended plasma concentration of the drug.^[8]

Most of the patients recover spontaneously after suspending the drug administration as this reaction is reversible at the initial stages. 33% patients require dialysis.^[9] Intravenous dopamine 1-3 ug/kg/min appears to cause selective vasodilatation of renal vessels, but prospective and meta-analysis study showed that it does not affect mortality of patients^[9]. As per the literature, the incidence of HIV induced nephropathy is about 60-70% in a study in US^[10] and 12.7% as in one study from North India^[10].

Conclusion

Tenofovir is a known cause for reversible renal failure and tubular dysfunction. Baseline parameters of kidney function are to be evaluated before starting the Tenofovir. Clinicians should carefully monitor the sensitive parameter of kidney dysfunction like urine or serum phosphate level other than serum creatinine for early detection of renal damage. Early withdrawal of Tenofovir is important to prevent irreversible damage/chronic renal impairment.

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PUBLISHED CASE REPORTS ON TENOFOVIR INDUCED RENAL DAMAGE

Compiled by Dr Smita Mali

Assistant Professor, Department of Pharmacology, LTMMC & Gh, Sion, Mumbai-22.

Tenofovir induced acute kidney injury in a patient with unilateral renal agenesis despite initially nonimpaired renal function

Eur J Med Res, (2011) 16: 564

Schleenvoigt BT, Stallmach A, Pletz MW.

We report a 37 year old late presenting HIV positive male patient. He was admitted with wasting, chronic diarrhoea and oesophageal candidiasis. Serology confirmed HIV-1 infection, viral load was 55copies/ml, CD4+ cells were 77 / μ l, and the cd4/cd8 ratio was 0.11. An agenesis of the right kidney with a contra-lateral hypertrophy was detected by abdominal ultrasound. However, normal values for creatinine (75 μ mol/l) and urea (5.6 mmol/l) did not suggest an impaired renal function. In addition, history revealed no risk factors for renal insufficiency (no diabetes mellitus, non-smoker, no hypertension). Concomitant medication did not contain drugs with known high potential for nephrotoxicity (trimethoprim 160mg three times per week, sulfamethoxazol 800mg three times per week, folic acid 5 mg twice daily, fluconazole 100mg daily, ceftriaxone 2g daily, pantoprazole 40 mg twice daily, enoxaparin 40 mg s.c. daily, mirtazapine 15 mg daily). We started with tenofovir, emtricitabin plus raltegravir to achieve fast reduction of viral load.

Two days after initiation of ART laboratory monitoring of the renal function showed steadily increasing values for urea and creatinine reaching maximal levels of 14.2 mmol/l and 172 μ mol/l, respectively on day 6 despite intravenous volume substitution. The patient developed acute kidney injury. Then NRTI backbone was switched from tenofovir plus emtricitabin to abacavir plus lamivudine. After discontinuation of tenofovir renal parameters restored within 36 hours to baseline values and remained at normal values during the further course. Since its introduction in 2001 the nucleotide analogue tenofovir is one of the most frequently used substances in HIV treatment. Our case showed that tenofovir can induce a renal damage in patients with renal agenesis despite initially non-impaired renal function.

Acute renal failure in an AIDS patient on tenofovir: a case report

Journal of Medical Case Reports 2008, 2:94

Kapitsinou PP, Ansari N

We report a patient 53-year-old woman with AIDS of 6 years duration developed progressive weakness, dyspnea on exertion and constipation. Her Antiretroviral therapy (ART) consisted of

tenofovir (300 mg/day), efavirenz (600 mg/day) and lamivudine (300 mg/day) which was continuously given for 26 months. Laboratory tests disclosed the following concentrations: metabolic acidosis (pH: 7.15) with BUN - 57 mg/dL; creatinine - 9.8 mg/dL; phosphorous - 5.7 mg/dL; CPK - 119 U/L; uric acid - 4.9 mg/dL; lactate - 0.63 mmol/L and albumin 3.8 g/dL. Urinalysis showed marked glucosuria (294 mg/dL) with normoglycemia and proteinuria (124 mg/dL) and an absence of active urinary sediment. Urine pH was 6.0. The rates of fractional excretion of phosphorus and uric acid were 58% and 37% respectively. The findings of renal ultrasound were normal, as were the findings for all serologic tests. Her CD4+ lymphocyte count was 241 and her viral load 460 HIV RNA copies/ml. Diagnosis of ARF and Fanconi syndrome during treatment with tenofovir was made. This patient's condition improved on discontinuation of tenofovir treatment without requiring renal replacement therapy. This concludes that vigilant screening of kidney function is required regularly after initiation of tenofovir due to possible appearance of renal failure.

Tenofovir-related nephrotoxicity: case report and review of the literature.

Pharmacotherapy. 2004 Mar;24(3):415-8.

James CW, Steinhaus MC, Szabo S, Dressier RM.

Tenofovir is a nucleotide reverse transcriptase inhibitor for treatment of human immunodeficiency virus (HIV) infection. Several cases of renal failure associated with tenofovir therapy recently have been reported. A 54-year-old man with HIV experienced decreasing renal function and Fanconi's syndrome secondary to tenofovir therapy. His condition gradually improved after discontinuation of the drug. The available medical literature for reported cases of tenofovir-related nephrotoxicity indicates that this complication is apparently rare. However, our case report and literature review underscore the importance of monitoring renal function when treating patients with any nucleotide reverse transcriptase inhibitor.

Tenofovir-Related Nephrotoxicity in Human Immunodeficiency Virus-Infected Patients: Three Cases of Renal Failure, Fanconi Syndrome and Nephrogenic Diabetes Insipidus.

Clinical Infectious Diseases 2003; 36:1070-3

Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, Legendre C, Martinez F, Molina JM.

We report 3 cases of renal toxicity associated with use of the antiviral agent tenofovir. Renal failure, proximal tubular dysfunction, and nephrogenic diabetes insipidus were observed, and, in 2 cases, renal biopsy revealed severe tubular necrosis with characteristic nuclear changes.

All 3 affected patients had a long medical history of HIV infection (mode 15 years) had received different courses of antiretroviral therapies before they began receiving tenofovir. When tenofovir

therapy was started, the CD4 cell count was 50 cells/mm³ in these 3 patients. Tenofovir DF (300 mg per day) was given orally in combination with other antiviral agents considered to have no renal side effects (table 1). None of the patients had evidence of previous nephropathy or serious renal function impairment: they had serum creatinine levels of <1.20 mg/dL and proteinuria was not detected. No other drugs that interfere with renal function were given.

Table 1:

No	Age (years)	Antiretroviral therapy	Duration of Tenofovir treatment	Serum creatinine level, mg/dL		?pH & sr K+ present	Glucosuria present	Diabetes insipidus present
				Baseline	Peak			
1	55	Lopinavir-ritonavir, abacavir	7 months	0.91	7.8	Yes	Yes	No
2	31	Didanosine, lamivudine, ritonavir, amprenavir, T20	6 months	0.93	1.74	No	Yes	Yes
3	42	Lamivudine, abacavir, lopinavir-ritonavir	11 months	1.15	2.71	Yes	No	No

No signs of HIV-associated nephropathy were detected. Discontinuation of all antiretroviral therapy was associated with improvement of renal function and rapid (<2 weeks) normalization of proteinuria, leukocyturia, hypophosphatemia, acidosis, and hypokalemia. However, the serum creatinine level remained elevated in both patients [2.14 mg/dL] in one patient, and [1.69 mg/dL] in the other), indicating that there was partially irreversible renal damage. All antiretroviral agents other than tenofovir were reintroduced a few weeks after discontinuation of tenofovir therapy, and there were no new increases in the serum creatinine level or recurrences of tubular dysfunction.

Patients receiving tenofovir must be monitored closely for early signs of tubulopathy (glycosuria, acidosis, mild increase in the plasma creatinine level and proteinuria).

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr. Jaisen Lokhande

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

Changes suggested in Package inserts for inclusion of new adverse reactions

Furosemide - Risk of dermatitis lichenoid: The Pharmacovigilance Program of India-Indian Pharmacopoeia Commission (PvPI-IPC) has recommended that the Central Drugs Standard Control Organisation (CDSCO) revise the drug safety label of furosemide to include dermatitis lichenoid as potential adverse drug reaction. Signal Review Panel (SRP)-PvPI-IPC concluded the causal relationship between furosemide and dermatitis lichenoid based on the Individual Case Safety Reports (ICSR) received.

Itraconazole - Risk of acute generalized exanthematous pustulosis : The PvPI-IPC has recommended that the CDSCO revise the drug safety label of itraconazole to include acute generalized exanthematous pustulosis as a potential adverse drug reaction.

Lithium carbonate - Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome: The PvPI-IPC has recommended that CDSCO revise the drug safety label of lithium carbonate to include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome as a potential adverse drug reaction.

SGLT2 inhibitors - Potential risk of toe amputation: The European Medicines Agency (EMA) recommended to include warning of potential increased risk of toe amputation in prescribing information for sodium-glucose co-transporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin used for T2DM. The adverse event was noted due to increase in lower limb amputations (mostly affecting toes) after interim data analysis of two clinical trials on canagliflozin (CANagliflozin cardioVascular Assessment Study: CANVAS and CANVAS-R). The final incidence rates will depend on analysis of the final study results. The mechanism by which canagliflozin may increase the risk of amputation is still unclear. Similar increase in lower limb amputations was not seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, data available to date are limited and the risk may also apply to these other medicines.

Fluoroquinolones - Potential risk of persistent and disabling side effects: Health Canada has recommended updating the safety information for all fluoroquinolone products to include information about the risk of persistent and disabling side effects including tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders. The side effects of tendinopathy, peripheral neuropathy and central nervous system disorders are included in the current safety information. However, the possibility of persistent duration of these events was not included in the safety information for all fluoroquinolone products. There was little information in the scientific and medical literature on persistent and disabling nature of side effects reported with fluoroquinolone use.

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

MATCH THE FOLLOWING DRUG WITH ITS ADVERSE EFFECT.

Dr.Sharmada Nerlekar*, Dr.Abhilasha Rashmi*

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

- | | |
|----------------------|---|
| 1. Octreotide | a) Nephrotoxicity |
| 2. Flecainide | b) Iritis |
| 3. Quinacrine | c) Suicidal tendencies |
| 4. Etanercept | d) Methemoglobinemia |
| 5. Minocycline | e) Haemorrhagic cystitis |
| 6. Cisplatin | f) Cardiotoxicity |
| 7. Prilocaine | g) Coronary Steal Phenomenon in elderly |
| 8. Fomivirsen | h) Biliary sludge of gall |
| 9. Doxorubicin | i) Vertigo |
| 10. Aldesleukein | j) Hypoprothrombinemia |
| 11. Dipyridamole | k) Gout Precipitation |
| 12. Rimonabant | l) Discoloration of skin and eyes |
| 13. Cyclophosphamide | m) Activation of latent Tuberculosis |
| 14. Pyrazinamide | n) Capillary leak Syndrome |
| 15. Ceftriaxone | o) Severe exacerbation of arrhythmia |

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

ALPHABET 'O' PUZZLE

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

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

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

- Though very effective for bipolar disorder maintenance treatment, the use of this atypical antipsychotic drug has decreased dramatically due to concerns over adverse metabolic effects like weight gain, hyperlipidemia and hyperglycemia.
- FDA approved as initial therapy for Multiple Myeloma, toxicities of this monoclonal antibody include thrombocytopenia (28%), fatigue (12%), peripheral neuropathy (12%), and neutropenia.
- _____ is considered as a safe anesthetic to use for patients with ischemic heart disease as it is a potent coronary vasodilator, thus producing increased coronary blood flow and decreased myocardial O₂ consumption.
- Hemolytic uremic syndrome represents the most dangerous toxic manifestation of this anticancer antibiotic and is believed to result from drug-induced endothelial damage.
- The common early symptoms of Isoniazid overdose are ataxia, peripheral _____, dizziness, and slurred speech, while the most dangerous are grand mal seizures and coma.
- Approximately 25% of patients receiving this Somatostatin analog develop gallbladder sludge or even gallstones, presumably due to decreased gallbladder contraction and bile secretion.
- Approximately 30% of patients experience GI side effects with this propionic acid derivative NSAID, which are decreased if the drug is taken with food or antacids.
- Side effects like vomiting and diarrhea may decrease drug absorption, resulting in therapeutic failure, but, readministration of this antimalarial drug within an hour of vomiting may still be effective in patients with P. falciparum malaria.
- The use of this luminal amoebicide, especially at doses exceeding 2 g/day, for long periods is associated with subacute myelo-optic neuropathy.
- The practice of keeping crushed _____ leaves as a quid in the mouth between cheeks & gums is the most common cause of oral cavity cancer in India.

- | | | | |
|-----|-------------|----|-------------|
| 10. | DRY TOBACCO | 5. | NEUROPATHY |
| 9. | CLIQUNOL | 4. | MITOMYCIN C |
| 8. | ATOVAQONE | 3. | ISOFLURANE |
| 7. | KETOPROFEN | 2. | BORTEZOMIB |
| 6. | OCTREOTIDE | 1. | OLANZAPINE |

ALPHABET 'O' PUZZLE: ANSWERS :

NATIONAL CONFERENCE IN PHARMACOVIGILANCE HELD IN MARCH 2017

March 17, 2017

Department of Pharmacology

LokmanyaTilak Municipal Medical College & General Hospital, Sion

The National Conference in Pharmacovigilance held on March 17, was a remarkable day for pharmacology and pharmaceutical professionals, academicians, clinicians and students. Organised by the Department of Pharmacology, in collaboration with the Pharmacovigilance Program of India (PvPI), the conference was held at, LTMMC & GH, Sion, Mumbai with an aim to share knowledge and expertise in the field of pharmacovigilance and ensure patient's safety through collaboration and encouraging pharmacovigilance. The scientific activity was attended by over 80 delegates from varying parts of India as well as by pharmaceutical industry personnel.

Highlights of the conference

- The Chairperson of National Conference in Pharmacovigilance 2017, **Dr. Sudhir Pawar**, welcomed and addressed the delegates and gave an overview of the evolution of LTMMC & GH, Sion as an ADR monitoring cell in PvPI. He highlighted the various pharmacovigilance activities conducted in LTMMC & GH and the suggested measures to improve spontaneous reporting and signal detection at institute level.
- An eminent speaker and respectable academician, **Dr. Y. K. Gupta**, Professor and Head, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, set the tone of the conference by talking about causality assessment and compensation in clinical trials. He conversed the latest amendments and emerging issues related to compensation and taught the formula to calculate the quantum of compensation in a simplified manner. The session was truly interactive with many case studies being discussed and delegates were asked to comment on the relatedness of the adverse drug reactions (ADR) and compensation.
- **Dr. Nithya Gogtay**, Professor, Clinical Pharmacology, Seth G.S. Medical College & K.E.M. Hospital, Mumbai, speaking on 'Challenges in ADR reporting', underlined some significant examples of published ADRs, unexpected ADRs with new drugs, drug withdrawals and discussed the various reasons and contributing variables for under-reporting. She concluded stating the need for attitudinal and cultural changes for long term improvement of ADR reporting.
- **Dr. Mohammed Raza**, Director, Medical Affairs, VigiMedsafe, briefed the delegates about the various forms for ADR reporting including ADR-PvPI, Yellow card, AEFI, CIOMS, etc. The important databases and software for case processing and signaldetection such as Oracle, Extendo, etc. and for literature search such as Pubmed and Embase were detailed. He also threw some light on the dictionaries available for identifying and coding the adverse events.

- **Dr. Indu Nambiar**, Senior Manager, Pharmacovigilance, BoehringerIngelheim, provided a pharmaceutical industry perspective of pharmacovigilance and discussed measures to maintain compliance and quality of individual case safety reports (ICSR). She discussed the types of ICSR quality control done at local and global level and role of independent QC personnel, vendor performing data entry and audits to help improve and strengthen the pharmacovigilance.
- **Dr. Suparna Chatterjee**, Professor, Dept. of Pharmacology, Institute of Postgraduate Medical Education & Research, Kolkata, delivered a talk on 'Data mining and signal detection' and gave useful insights regarding the definition of signal in pharmacovigilance, sources of drug safety information, process of signal management, role of computational signal detection algorithms and explained the statistical and clinical review methods used at the WHO UMC (Uppsala Monitoring Centre) and US FDA to validate potential safety alerts.
- **Dr. Neha Kadhe**, Additional Professor, Department of Pharmacology, LTMMC & GH, Sion, Mumbai and the Organizing secretary of the National conference in Pharmacovigilance explained the fundamental role of patients in spontaneous reporting and quoted a few examples leading to FDA regulatory action such as major reviews and labeling changes. She particularized on the different methods of patient reporting globally and in India including the blue form in India. The need of patient reporting in clinical trials, especially in oncology trials and overall challenges were discussed and the presentation concluded with some suggestions to improve spontaneous reporting by patients and guidance required.
- **Dr. Shirish Sherlekar** from Tata Consultancy Services guided the young delegates regarding the career opportunities in pharmacovigilance. He discussed the increasing complexity of pharmacovigilance necessitating a multidisciplinary approach and thereby increasing the career prospects in various areas. He suggested pharmacovigilance opportunities in medical review, regulatory medical writing, medical affairs, regulatory compliance and clinical trial support providing a good insight into career perspectives.

Panel Discussions

Serious Adverse Events(SAE) Handling in India

The panel discussion on '**Serious Adverse Events(SAE) Handling in India**' was moderated by **Dr. Y. K.Gupta**, Professor and Head, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, and the **panelist** were,

Dr. Bangarurajan, Deputy Drugs Controller, (India), CDSCO, West Zone, Mumbai.

Dr. Pravin Ghadge, Head - Medical Writing & Pharmacovigilance at Reliance Life Sciences;

Dr. Renuka Munshi, Professor and Head, Department of Clinical Pharmacology, TN Medical College & BYL Nair Hospital, Mumbai and

Dr. Hemangi Karnik, Professor, Department of Anaesthesiology, LTMMC & GH, Sion.

The discussion mainly focused on the reporting of SAE in clinical trials and the emerging role of Ethics Committee (EC) in assessing causality and relatedness and its associated practical problems. The factors underlying the non-reporting of the SAE were debated with various perspectives. The moderator questioned whether even EC should be held responsible for non-reporting within the specified timelines along with the sponsor and investigator and if DCGI should take strict action against them. Considering the fact that the trial protocols are approved by the EC, it was deliberated whether it is the responsibility of the EC to monitor trials and a suggestion was put forth regarding the regular training of the EC members on the risks and compensations. The differentiating points about reporting of SAE in a clinical trial and clinical setting were conversed with regards to the method of reporting and compensation to the patient. The panel discussion concluded with various suggestions from the honoured panelist on the possible strategies to improve SAE reporting process in our country.

Clinicians' Expectations from an ADR Monitoring Centre: How to meet the Golden Centre?

The panel discussion moderated by Dr. Nithya Gogtay had mainly clinical experts from diverse disciplines from LTMMC & GH as panelist including,

Dr. Bharti Tendulkar, Professor and Head, Department of Anaesthesiology;

Dr. Nivedita Moulick, Professor and Head, Department of Medicine;

Dr. Mamta Manglani, Professor and Head, Department of Paediatrics; and

Dr. Suparna Chatterjee, Professor, Dept of Pharmacology, Institute of Postgraduate Medical Education & Research, Kolkata, as an ADR Expert.

Despite having excellent clinicians and clinical expertise, India is a very poor reporter of SAE. With this probing question, the moderator initiated the panel discussion and the clinicians from various branches stated their expectations from the ADR monitoring centres (AMC). These demands were correlated with the services provided at the AMC and certain expectations of the AMC's from the clinicians. The possible reasons for the smooth functioning of some centres and under functioning of some were deliberated upon and an attempt was made to find a common ground. The varying constraints faced by the AMC's on a day to day basis were discussed and the ADR expert put forth views regarding the situation at the several AMC's in India and similar or dissimilar experiences. The moderator and panelist proposed few suggestions for common grounds and feasibility such as linking of AMC with the drug information centres, a mobile application for faster reporting, creating awareness of ADR reporting among clinicians, routine interaction of residents with the pharmacovigilance committees, regular feedback to the clinicians regarding causality, action taken on the reports, new drug safety

alerts, and conducting teaching and training sessions on ADRs. The discussion concluded with the varying standpoints of the panelist on the impact of such measures with the purview to meet the golden centre.

The conference concluded with a vote of thanks to all the delegates and the distinguished speakers for their valuable contribution and support in making the National Conference in Pharmacovigilance a great success.

For further details, please log on to

<http://ltmgh.com/FrontView/inner.aspx?Mkey=MTEy&lKey=Mw==>

NOTES

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

Please feel free to contact us for the same.

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