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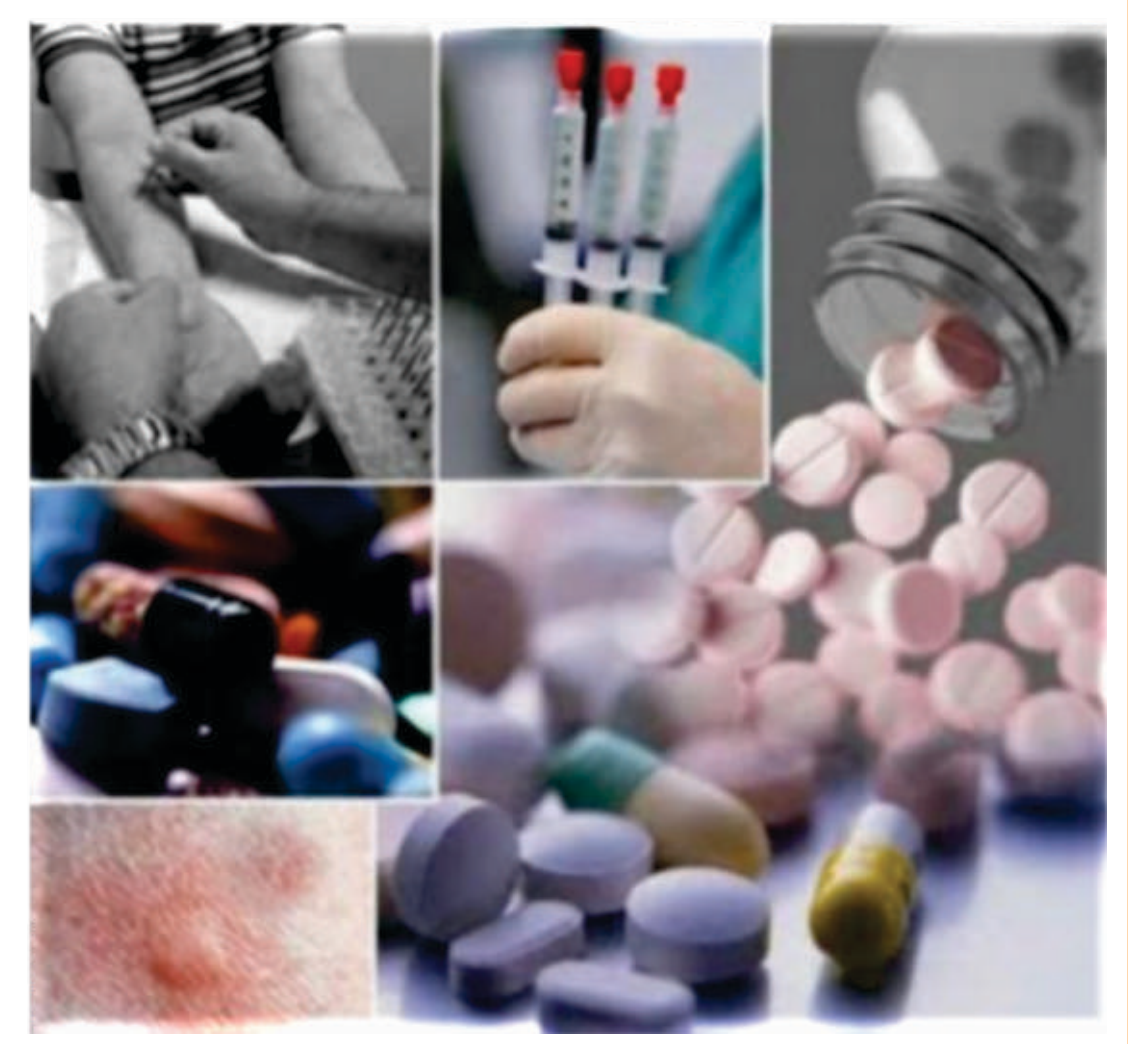
BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL



DEPARTMENT OF PHARMACOLOGY,

LTMMC & LTMGH, Sion, Mumbai – 22.

Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk . . . . ✍

Dear friends and colleagues,

It's indeed great to present the last issue of this year's Bulletin on Adverse Drug Reactions. It takes humongous investment in terms of time and finance to launch any new drug molecule. This new drug stands the test of time in its post marketing surveillance, when it is exposed to varied population, causing increased chances of detection of adverse effects not discovered in clinical trial phase. The first article deals with the journey of such drugs which were banned in the last decade due to serious adverse drug reactions.

Adverse drug reactions due to drug interactions are the ones which form a major share of preventable reactions. So the second article in this issue elaborates these common drug interactions, mechanisms and preventive approaches for it. The understanding of these will help us to optimise our patient care and enhance patient safety.

With increasing use of Tolvaptan like drugs, many cases regarding its troublesome aquaretic actions are being noticed. Here, we also report a case of tolvaptan induced polyuria. We have also summarised the ADRs from our institute to provide a glimpse of Pharmacovigilance activity at our institute. The puzzle and crossword will surely make it more interesting and entertaining.

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

DRUGS BANNED IN THE LAST DECADE

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Introduction

A drug, broadly speaking, is any substance that, when absorbed into the body of a living organism, alters normal bodily function. Drugs undergo rigorous testing before they are introduced into the market. The efficacy as well as safety profiles of the drug are tested. In spite of this, some adverse effects of drugs appear only after the drug is used in the general population. These adverse effects are detected though a process of regular monitoring after the drug is released called pharmacovigilance.[1]

Why is a Drug Banned?[1,2]

Adverse drug reaction or ADR is a response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. In case a drug is found to have harmful side-effects, the Food and Drug Administration (FDA) or Drug Controller General of India (DCGI) can issue a ban order on the particular drug and all manufacturers and wholesalers are asked not to stock the particular medicine.

Drugs can also be voluntarily withdrawn by the manufacturing pharmaceutical company when the adverse events pose a risk greater than the benefit provided by the drug. When drugs are used in combination with other drug(s) and if they cause adverse events, then the drug(s) combination and not the individual drug are banned. Many drugs used as single dosage or in combination with other drugs are discontinued from being produced and provided in the Indian market.

Drugs Banned in the Last Decade[2,3]

A number of single drugs as well as fixed dose combinations have been banned from manufacturing, marketing and distribution in India. An important issue about the availability of banned drugs over the counter in India is that sufficient adverse drug reactions data about these drugs have not been reported. The most common categories of drugs withdrawn in the last decade were nonsteroidal anti-inflammatory drugs (28%), antidiabetics (14.28%), antiobesity (14.28%), antihistamines (14.28%), gastroprokinetic drugs (7.14%), breast cancer and infertility drugs (7.14%), irritable bowel syndrome and constipation drugs (7.14%) and antibiotics (7.14%). Drug withdrawals from market were made mainly due to safety issues involving cardiovascular events (57.14%) and liver damage (14.28%).

Drugs banned in the last decade in India are given in Table 1.

Table 1. Drugs banned in the last decade[4-7]

Drug	Use	Year of Ban (India)	Cause
Diclofenac and its formulations (for animal use)	Analgesic	2008	Liver toxicity in vultures therefore banned for animal use in India
Rimonabant	Antiobesity	2009	Serious suicidal tendencies led the European drug regulator to recall the drug in 2009
Rosiglitazone	Antidiabetic	2011	Increased risk of heart attacks by 43% and subsequent deaths led to US FDA alert in 2007 with suspension by EMA in 2010 and withdrawal by India and New Zealand in 2011
Cisapride	Antiemetic	2011	Rare but fatal QT-prolongation led to issue of warning by US FDA and withdrawal in 2000 and in 2011 in India
Nimesulide for use in children below 12 years of age	Analgesic	2011	Liver toxicity and increased reports of ADRs in children led to withdrawal in India in 2011
Phenylpropanolamine*	Decongestant and in weight loss product	2011	Withdrawn by US FDA in 2000 due to risk of hemorrhagic stroke, or bleeding into the brain
Sibutramine	Antiobesity	2011	Increased heart attacks, strokes and cardiac arrests led to withdrawal from Indian market
Gatifloxacin for systemic use	Antibacterial	2011	Diabetic risk reported led to FDA black box warning in 2006 and withdrawn from India in 2011
Tegaserod	Gastric motility stimulant	2011	Banned globally in 2007 due to 10 fold increase in heart attacks and stroke but withdrawn in India in 2011
Letrozole for induction of ovulation in anovulatory infertility	Antineoplastic	2011	Severe genetic abnormalities in babies born to infertile women using this drug for ovulation led the Indian union health ministry to withdraw the drug in 2011
Dextropropoxyphene **	Analgesic	2013	It was withdrawn across the European Union in 2009 and recommendations against its use were issued by the US FDA, New Zealand, and Canada in the

			year 2010 due to its implication in overdose related deaths and its impact on cardiovascular electrophysiology even within therapeutic dose range
Fixed dose combination of Flupenthixol + Melitracen	Antidepressant	2013-2014	India's ministry of health and family welfare has banned the psychiatric combination flupenthixol with melitracen with immediate effect, because it said that their use was "likely to involve risk to human beings"
Metamizole (Analgin)	Analgesic	Initial Suspension of 18.6.2013 was revoked allowing the use of drug with certain condition on 13.2.2014	Agranulocytosis
Pioglitazone	Antidiabetic	Initial suspension of 18-6-2013 was revoked allowing the use of drug with certain condition on 31-7-2013	Increased risk of urinary bladder cancer

** Presently stayed by the Hon'ble High Court of Madras, **Prohibition was revoked with following conditions vide G.S.R. No. 367 (E) dated 13.04.2017:*

(a) The manufacturer shall indicate in a conspicuous manner on the package-inserts and promotional literature of the dextropropoxyphene and its formulations - "Use of drug for cancer pain only", and "Daily administered dose shall not exceed 300mg. per day".

(b) The container of the medicine containing dextropropoxyphene shall be labelled with the following words: - "Use of drug for cancer pain only", and "Daily administered dose shall not exceed 300mg. per day".

(c) The manufacturer shall advise the registered medical practitioners to administer or prescribe the said drug and its formulations for use in patients with cancer pain only.

Pioglitazone Controversy in India[7]

Pioglitazone is widely prescribed oral hypoglycemic thiazolidinedione that selectively stimulates the nuclear peroxisome proliferator-activated receptor gamma (PPAR-gamma) and to a lesser extent PPAR-gamma. It is effective as monotherapy and in combination with both oral antidiabetics and insulin with action on both fasting and post prandial blood glucose. Bridge between bladder cancer and pioglitazone first appeared in preclinical studies in US in 1999 but initial experimental studies suggested that this might be a rat-specific phenomenon, but this urinary bladder cancer has now been reported in human clinical studies also.

This led to the withdrawal of pioglitazone on 9th June 2011 by the French Agency for the Safety of Health Products. Subsequently on June 15, 2011 the U.S. FDA announced that pioglitazone use for more than one year may be associated with an increased risk of bladder cancer, and that the information about this risk will be added to the Warnings and Precautions section of the label for pioglitazone-containing medicines. The ministry of health and family welfare of India had suspended the manufacture and sale of pioglitazone with immediate effect on June 18, 2013. The suspension caught physicians, patients and pharmaceutical companies by surprise, following which there were protests.

This ban was revoked on July 31, 2013 because, even though pioglitazone produces urinary bladder cancer in diabetic patients, numerous beneficial characteristics of the drug support its need and continuous use in India for diabetic patients. In patients using pioglitazone, urinary bladder cancer was seen after long treatment duration only and this adverse effect could be due to other drugs used in combination or genetic variation. Also, dose dependent cumulative cancer by pioglitazone is considered unlikely in Indian patients. This may be attributed to the use of a lower dose, i.e., 30 mg/day in comparison with other countries that prescribe 40 mg/day as a single dose. Further, cardiovascular complications produced by diabetic mellitus are more lethal than pioglitazone induced cancer.

Fixed Dose Drug Combinations (FDCs): Debacle in India[8]

Although FDCs are available in almost all therapeutic categories, many of them are bizarre combinations. FDCs formulated without due diligence can pose problems namely pharmacodynamics mismatch between the two components, pharmacokinetic mismatch, chemical noncompatibility, drug interactions because of the common metabolizing pathways and limitations of finer dosing titration of individual ingredients.

The Indian medicine market has become the world leader of FDCs and the estimated number of FDCs in India is over 6000 due to exploitation of the liberal licensing system. The strong marketing pressure, inadequate time and attitude of critical analysis, influence the prescribing habit towards these FDCs. In September 16, 2014, Ministry of Health and Family Welfare (MOH and FW) constituted a committee for examining the applications for rationality, safety, and efficacy of these FDCs. The committee submitted its report to the MOH and FW on April 16, 2015. Based on findings of the expert panel, on March 10, 2016, 344 FDCs were prohibited under Section 26A of Drugs and Cosmetics Act, 1940.

The industry moved the Hon'ble Delhi High Court seeking a stay on the ban notification. The Government defended saying that the step of prohibition of the irrational FDCs was taken considering the public interest and the delay in administrative procedures in revoking the license. A notification was issued by DCGI on June 17, 2016, wherein, CDSCO requested the concerned pharmaceutical manufacturers to furnish the Phase IV clinical trial protocol for the FDCs. Some examples of bad FDCs are dual nonsteroidal anti-inflammatory drugs (NSAIDs), NSAIDs with muscle relaxants and NSAIDs with H2 blockers, cough syrups with two or more antihistamines + decongestant +

bronchodilator + cough suppressant + expectorant and antifungal + antibiotic + steroid + topical local anesthetic.

Availability of banned drugs in India[9]

A very important issue which is faced in India is that majority of drugs which have been banned in other developed countries are still available for sale in India. As soon as the drugs are banned by regulatory bodies (e.g. FDA in USA), in developed countries it is notified immediately to all pharmacies and physicians. Despite this, some of the banned drugs are still available in India. There are various reasons for availability of these banned drugs in India, these are:

- Lengthy legal procedures in India that tend to delay ban on any drug, allowing manufacturers to continue manufacturing these banned drugs for longer durations of time.
- Lack of enforcement power of regulatory bodies in India.
- Easily saleable drugs at low costs, majority of the population being under poverty line in India.
- Unawareness among many private practitioners and physicians about the ban.
- Lack of up to date knowledge regarding existing and new drugs, resulting in irrational prescribing.
- An existing communication gap between the DCGI and state drug controllers.
- Disproportionately fewer drug inspectors in India in comparison with far greater number of pharmacists/wholesalers, makes it a seemingly impossible task to reach out and inspect each and every individual.

To prevent this, it is very important to implement strict laws on manufacturers by the Government of India. Awareness should be created amongst physicians, health professionals and general public about the ADR of these drugs.

Sub-Committee to Monitor Banned Drugs in India[2]

Each country has its own organization that monitors its individual circulation of banned drugs. In India, prior to drug marketing, its safety and efficacy is ascertained in accordance with the Schedule Y of Drugs and Cosmetics Act. Even after market approval, the safety and efficacy of the drug is continuously examined on the basis of information gathered via Pharmacovigilance, Post-Marketing Surveillance and information reported from other countries. In order to examine such information, the Drugs Technical Advisory Board (DTAB) under Drugs and Cosmetics Act has constituted a sub-committee, consisting of experts on the subject who examine the information received from the sources mentioned above and take a final view as to whether to prohibit the manufacture, sale and distribution of drugs or to restrict its use and accordingly recommend the Government to make suitable amendments under Section 26 A of the Drugs and Cosmetics Act which empowers the Central Government to prohibit the manufacture, sale or distribution of such drug or cosmetics.

Conclusion

Banned and drugs which could be banned in future are an ever-increasing concern. Use of banned drugs causes long-term implications to our physical health. As more and more drugs are being synthesized and marketed with better efficacy and improved safety, it raises doubts about earlier drugs of doubtful efficacy or harmful safety profile and need for their replacement. Drug authorities should be prompt enough to withdraw the sale of drugs which are harmful, useless or of little benefit to mankind. Officials needs to lay down stringent laws against drug manufacturers who produce banned drugs. It should take strict measures towards pharmaceutical companies reluctant to take voluntary recall of already banned drugs or drugs with documented adverse effect profile. This will ensure marketing of nothing other than safe medicines and aid better patient care. Awareness programs should be conducted in Government hospitals as well as for private medical practitioners to make them aware of the current status of drugs in market. Medical students should be taught about drugs banned from use and side effects associated with these drugs, so that they can refrain from using the same for patient care. Physicians should begin reporting ADRs to the nearest pharmacovigilance centre to help generate ADR database. All the healthcare professionals should be encouraged to participate in ADRs and pharmacovigilance planning. ADR reporting should be made mandatory as they are in developed countries.

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ADVERSE DRUG REACTIONS DUE TO DRUG INTERACTIONS

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Introduction

The WHO defines an adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function."[1] ADRs represent a significant public health problem but they are sometimes preventable. Much attention has been given to identifying the patient populations most at risk, the drugs most commonly responsible and the potential causes of ADRs. Around 5% of all hospital admissions are the result of an ADR and around 10%- 20% of inpatients will have at least one ADR during their hospital stay.[2-4]

Drug-Drug interaction (DDI) is one of the important cause of ADRs which are considered preventable medication-related problems. In clinical practice, DDIs are often responsible for ADRs and may lead to an increased risk of hospitalization and higher health care costs.[5-9] A drug interaction occurs when the effects of one drug is altered by another substance which includes drugs (drug-drug interactions), food (food-drug interactions), herbal (herbal-drug interactions), and other substances.[5] Some drugs have been withdrawn from the market because of serious adverse reactions associated with DDIs.[10] In literature, little is known about the actual number of patients with adverse reactions resulting from DDIs and most of the studies available are related to the hospital setting. Up to 15% of hospitalized geriatric patients experience mild to moderate ADRs related to DDIs.[11] A study by Becker et al. found that 0.054% of emergency department visits, 0.57% of hospital admissions and 0.12% of re-hospitalizations are caused by DDIs. Although the percentages are modest the number of ADRs due to DDIs is substantial because of the large numbers of emergency department visits and re-hospitalizations.[12]

The term drug-drug interaction (DDI) can be defined as 'the pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone.[13] As described by Tatro, the effect of a DDI may be one of (a) Antagonism: for example, a loss of blood pressure control by clonidine when tricyclic antidepressants are added to a regimen (b) Synergism: an example of which is the increased anticoagulant effect resulting from co-administering salicylates and warfarin or (c) Idiosyncrasy: such as the possible though rare severe effects like hyperpyrexia and hypertension that have been associated with patients concurrently receiving pethidine and a monoamine oxidase inhibitor.[13]

Types of DDIs

DDIs can be classified into two main types:

1. Actual DDIs- The actual drug interactions are defined on the basis of clinical evidence, i.e., these are confirmed by laboratory tests or by symptoms.

2. Potential DDIs- Potential drug interactions can be defined as documented interactions which may either enhance or antagonize the pharmacological activity of the drugs, resulting in potential adverse effects.

Thus Potential drug-drug interactions are defined on the basis of retrospective chart reviews and actual drug-drug interactions are defined on the basis of clinical evidence.[14]

By definition, a potential DDI can be categorized as follows:

a) Contraindicated category: This is a combination of drugs that should never be used because of potentially high risk of dangerous interactions.

b) Serious (Use alternative) category: indicates that there is potential for serious interaction and regular monitoring by the treating physician is required or alternate medication may be needed.

c) Significant (Monitor closely) category: refers to the possibility of significant interaction and monitoring by treating physician is likely required.

d) Minor categorization means that interaction is unlikely, minor, or non-significant.

A fundamental understanding of the clinical pharmacology of drug interactions and a framework for avoiding preventable drug interactions remains critically important. Thus, we need to overlay solutions on a base that is strong in basic principles of clinical pharmacology and drug interactions.

Mechanisms of Drug Interactions

A. Drug interactions that occur even before drugs enter the body

Eg.1. Phenytoin when added to solutions of dextrose, forms an insoluble salt which precipitates at the bottom of the IV bag. Thus, it is no longer available for control of seizures.

Eg.2. Amphotericin B is used for urinary bladder perfusion in aggressive fungal infections. When administered in saline, the drug tends to precipitate. This can erode through the bladder wall if not removed. The clinical presentation of such cases is an acute abdomen due to perforation of the bladder.

Eg.3. Aminoglycosides should not be co-mixed in IV fluids with beta-lactam antibiotics. This can cause chemical antagonism

B. Due to formulation incompatibility, or during the process of absorption, distribution, metabolism, and elimination.

Eg.1. Cytochrome P450 enzymes, flavin monooxygenases and reductase are more frequently rate limiting. These are the target of clinically significant drug interactions, such as the inhibition of cyclosporine metabolism by erythromycin.

Eg.2. The ability of aluminium containing medicines such as sucralfate and antacids to reduce the absorption of antibiotics like ciprofloxacin and azithromycin.

Eg.3. Drugs such as ketoconazole and delavirdine require an acidic environment to be in the noncharged form that is preferentially absorbed. Solubility is drastically reduced in the presence of neutral or basic medications such as omeprazole and lansoprazole.

Although prescription of more drugs for one patient is common and a necessary practice, it was shown that the incidence of potential DDIs (pDDIs) is close to 40% in patients taking 5 drugs, and it exceeds 80%, in patients taking 7 or more medications.[15] The estimated proportion of patients receiving interacting drugs with potential for an ADR or changes in therapeutic effect varies between 0.63 and 56%[16-19] depending on the study. DDI and ADR are frequently the end result of polypharmacy as shown by an integrative review.[20] These are associated with others predictors shown in the following Table 1.

Table 1: Predictors of polypharmacy resulting into DDI and ADR -

Sex differences
Alcohol consumption and smoking habits
Increased age
Diagnoses of diseases and multiple comorbidities
Use the specific types drugs, such as patients using clopidogrel with proton pump inhibitors, tamoxifen, co-prescription of macrolide antibiotics and calcium-channel blockers, trimethoprim/ sulfamethoxazole, antidepressants, warfarin, benzodiazepines
Cognitive impairment and various functional problems that affect practical drug management capacity, living situation, access to health care

ADRs due to DDIs in Geriatric patients

The age-related physiological changes and altered pharmacokinetic and pharmacodynamics in elderly patients (aged ≥ 65 years) place them at high risk for DDI-related adverse events.[21-22] In geriatric outpatient cohort, the percentage is as high as 21.31% of patients experiencing at least one ADR as a consequence of a DDI.[16, 19] As per an Indian study by Romana et al found that DDIs due insulin, salbutamol, amlodipine and digoxin commonly resulted in an ADR.[23]

Non-adherence to treatment is a common problem in older adults. DDIs and ADRs during hospitalization have been reported to be associated with non-adherence. Different interventions to optimize prescribing

appropriateness in older adults, for example, the Beers' criteria, most often used in the United States.[24] The validated 'Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) and Screening Tool to Alert doctors to the Right, i.e. appropriate, indicated Treatment (START) criteria[25] in the Ireland and United Kingdom and the instrument Medication Appropriateness Index (MAI)[26] have been explored in studies. These interventions may help in decreasing the ADRs due to DDIs.

ADRs due to DDIs in Paediatric patients

Children can be more vulnerable to the occurrence of potential DDIs than adults because: a) hospitalized children can be administered more than 25 drugs during their stay[27], b) they can react differently to drug administration than adults, which is explained by changes in absorption, distribution, metabolism and excretion[28], and c) unlicensed and off label prescription of drugs.[29]

In the paediatric population, the prevalence of potential DDIs ranges from 3.8% to 75%[30].With regard to risk factors associated with potential DDIs, the risk in hospitalized children was found to increase with patient age, average number of prescriptions per visit, number of visits per year, some diagnoses (epilepsy, leukemia, rheumatoid arthritis) and groups of drugs (antiepileptic, anti-neoplastic, systemic antifungal and immunosuppressant drugs, as well as those used for respiratory tract obstructive conditions).[31]

ADRs arising from DDIs with over-the-counter (OTC) drugs

NSAIDs such as ibuprofen are generally safe and effective for individuals seeking an OTC analgesic/ antipyretic. Reports of ADRs arising from DDIs with NSAIDs and common medications occurred primarily in studies of prescription-strength NSAIDs.[32] Some trials found increased risk of DDIs when prescription-strength NSAIDs and anti-hypertensive were co-administered over a period of multiple weeks.[33] It may be prudent to advise such patients to avoid use of even short-term OTC NSAIDs unless they are under close medical supervision.

Ways to prevent DDIs

It is impossible to remember all of the drug interactions that can occur. It is therefore important to develop a stepwise approach to preventing adverse reactions due to drug interactions.

- First, taking a good medication history is essential. "AVOID Mistakes" mnemonic can help to develop good practice habits and offers a useful way of remembering the components of a good drug history.

  A - Allergies?

V - Vitamins or herbs?

O - Old drugs/OTC as well as current

I - Interactions

D - Dependence?

M - Mendel History (family history) of any drug problem

- Second, it is essential that physicians develop an understanding of which patients are at risk for drug interactions. Of course any patient taking 2 medications is at some risk.
- Third, any time a patient is taking multiple drugs, the first step is to check a readily available pocket reference, recognizing that the interaction may not be listed and a more complete search may be required.
- Fourth, consult other members of the health care team.
- Fifth, use one of the computerized databases available.

Resources for detecting DDIs

Frequent launches of new drugs and approval of new indications for marketed medicines make recognition of occurrence of DDIs more difficult for the health care professionals. To cope with this, several DDI screening programs or databases have been developed and implemented as clinical decision support tools.[34, 35]

Spontaneous reporting systems can represent a valuable source of ADRs. These give an insight into prevalence of DDIs which are associated with ADRs. The major limitations of the locally developed databases and spontaneous reporting systems are limited availability and under-reporting of ADRs, the presence of reports with missing information such as concomitant drugs and lack of information about the user population and drug exposure patterns[36, 37]. To overcome these issues, web-based commercially available electronic databases were developed and are most commonly used in clinical practice. The major disadvantage of electronic databases is that they report a large number of DDIs of low clinical relevance, with numerous alerts of low clinical relevance which can mask DDI's of true importance.[38]

Web-based commercially available electronic databases to help health care providers to anticipate and prevent drug interactions are Micromedex ® Healthcare Series (Drug-Reax), Drug Interaction Facts, Lexi-Interact® software, Pharmavista, Epocrates Rx, MediQ®, Drug interaction checker (www.drugs.com), Drug Digest®, Drugs®, Medscape etc.

Micromedex ® Healthcare Series (Drug-Reax) gives information about clinical consequences of DDIs, classifies underlying mechanism and onset of the adverse outcome (either rapid or delayed) as well as severity (such as minor, moderate or major) and provides the level of evidence which supports this

information. It is updated every 3 months. Drug Interaction Facts® software is mostly used in cancer patients. The software includes similar features such as severity of DDI and level of evidence. It captures the majority of potential DDIs but it does not incorporate doses of the drugs into evaluation. Lexi-Interact® is also a commercially available non-oncology-specific software. This software too, does not consider dosing of the drugs in the assessment of potential DDIs. Online version Lexi-Interact® software is updated daily. Pharmavista®, electronic database is available in French and German language. This is updated monthly. The Stockley's drug interaction is a textbook which is considered as one of the most reliable sources to evaluate potential DDI, its online software is also available. Thus, there are several softwares for detection of DDIs, but there are deficiencies of clinical relevance in the detected DDIs. Such deficiencies should be focused in upcoming research so that more relevant information to the prescribers can be provided.

Conclusion

The onus of minimizing the occurrence of ADRs, lies in the hands of health care practitioners. Prevention of ADRs can be made possible through knowledge gained by the reporting of ADRs to national and global reporting agencies, to drug manufacturers and in published primary literature. In addition to this, awareness regarding the most commonly occurring DDIs should be raised by the utilization of drug-drug interaction guides and drug interaction computerized softwares, in order to help prescribers detect DDIs and take action for preventing their negative clinical outcomes.

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ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(July 2018 to October 2018)

Compiled by Dr. Monika Bhanushali, Dr. Neha Shende, Dr. Harshad Katyarmal

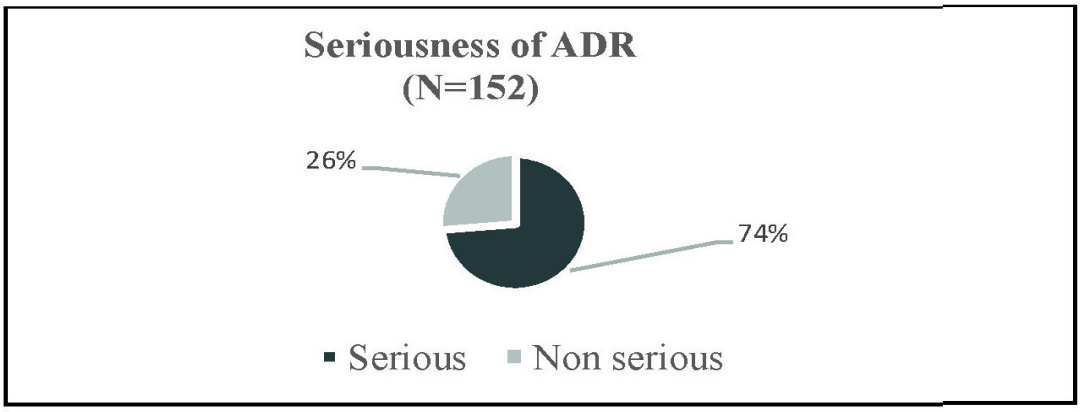
2nd year residents, Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Total No. of cases : N = 152

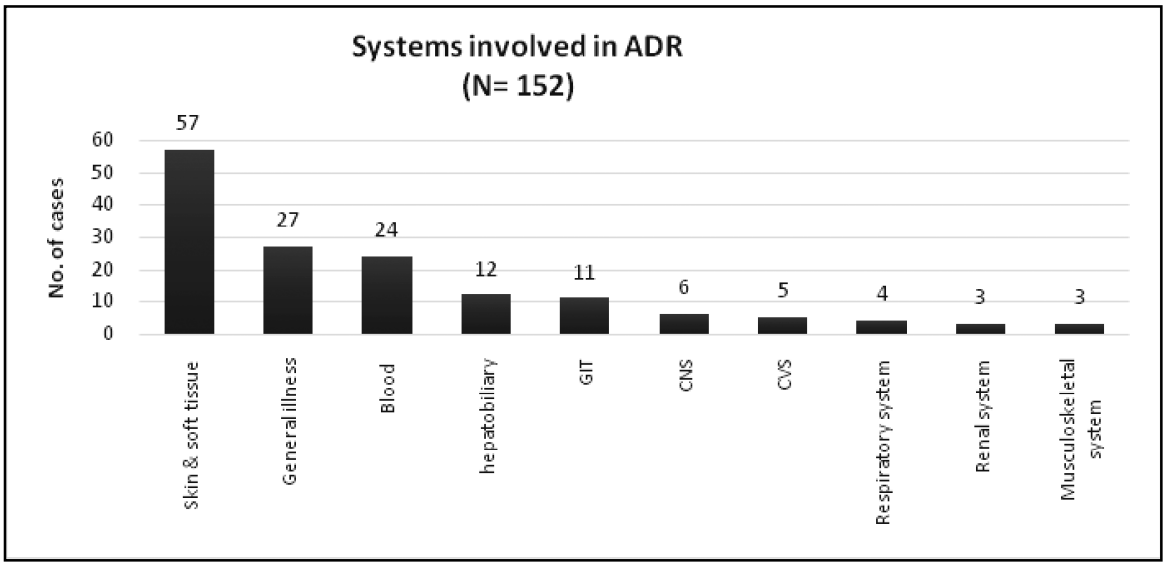
1. Age and Gender distribution :

Age group (years)	No. of patients	Males	Females	Transgender
<3	13	8	5	
3 to 17	23	10	13	
18-44	58	24	32	2
45-60	31	18	13	
>60	27	15	12	
Total	152	75	75	2

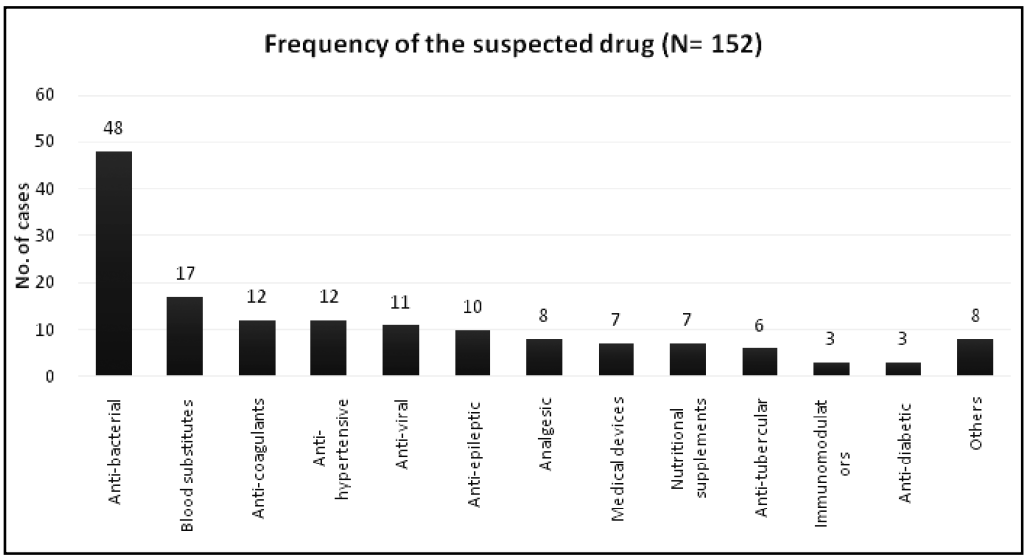
2. Seriousness of the ADR :



3. System involved in ADR :

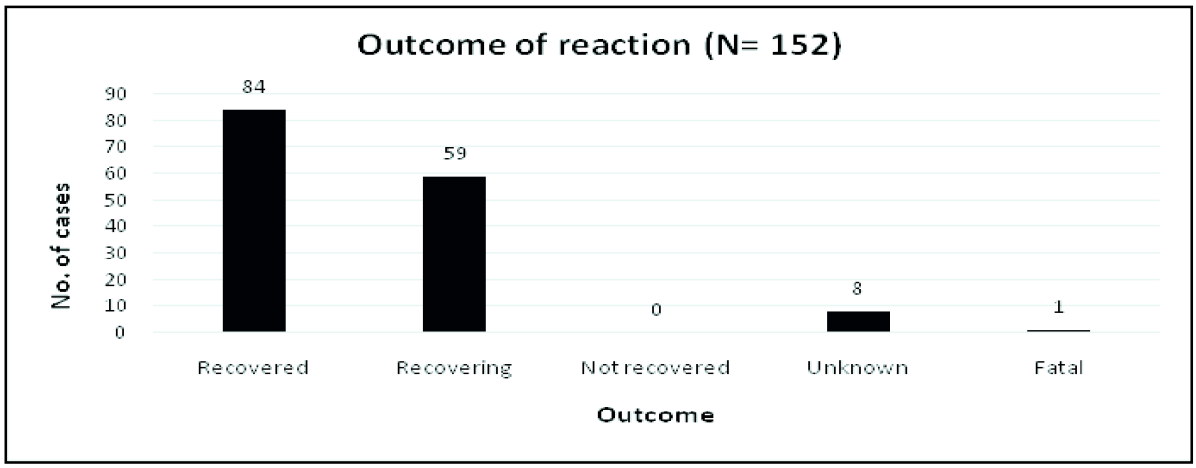


4. Class of the suspected drug:

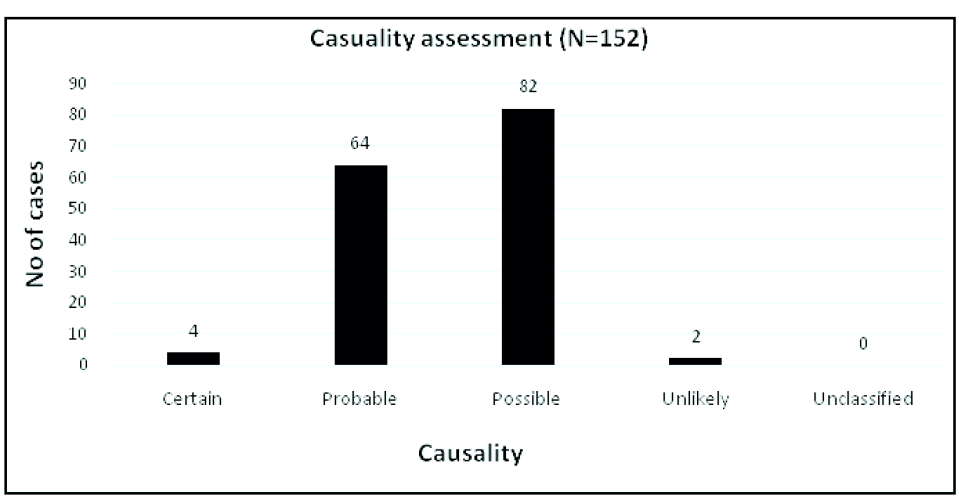


Others* class of drugs include ADRs of anti-depressant, steroids, anti-psychotics, aquaretic, chelating agents, anti-fungal, sedative, opioid agonist.

5. Outcome of the reaction:



6. Causality assessment (WHO UMC Classification) :



EVALUATION OF A CASE

TOLVAPTAN INDUCED POLYURIA

Dr. Smita Brahma[*], Dr. Neha Shende[**], Dr. Prathamesh Avhad[***], Dr Rahul Gudaghe[****]

[*]Speciality Medical Officer, [**]Second year resident, [***]First year resident, Department of Pharmacology, [****]First year resident, Department of Medicine

Introduction

Polyuria is defined as excretion of excessive amount of urine >3L/day or 40ml/kg/day. The two main mechanisms behind polyuria are excretion of non-absorbable solutes such as glucose and excretion of water. Diabetes mellitus is the most common cause of polyuria in adult and children. Apart from it diabetes insipidus, urinary tract infections including bladder, chronic renal failure and psychogenic polydipsia are other important causes. It can also be seen in some hereditary condition like sickle cell anaemia, polycystic kidney et cetera. Drugs are also an important cause of polyuria.[1,2]. These include diuretics, lithium, caffeine, ethanol, foscarnet, cidofovir, amphotericin B, vasopressin receptor antagonist such as tolvaptan, antipsychotics such as thioridazine and chlorpromazine.

Tolvaptan is commonly used to treat hyponatremia associated with SIADH (Syndrome of Inappropriate ADH Secretion), congestive cardiac failure and cirrhosis of liver. Inhibition of ADH induced water reabsorption in collecting duct results in aquaretic side effects of Tolvaptan. In this present report, we describe a case of tolvaptan induced polyuria in a post hypophysectomy patient.

Case History

A 69 years old male patient, diagnosed with pituitary adenoma, was referred from a private hospital to Lokmanya Tilak Municipal Medical College and General Hospital, Sion for treatment of the same. He was admitted in the Department of Neurosurgery for an elective surgery. The operative procedure involved resection of the adenoma which was apparently uneventful. The patient remained in the ward for 7 post-operative days. Thereafter, he was prescribed Tab. Thyroxin 25 µg once a day, Tab. Prednisolone 20 mg once a day, Tab. Amoxicillin + Clavulanate 625 mg, twice a day and Tab. Levetiracetam 500mg once a day on discharge.

One-week later, patient developed generalized weakness, headache which eventually progressed within a few days to altered consciousness, vomiting and paresis of whole body. The patient was rushed to casualty department. Following preliminary clinical evaluation and basic blood investigations, he was diagnosed with hyponatraemic encephalopathy. His serum sodium and potassium levels were found to be 110mEq/L and 3.5mEq/L respectively. He was managed with hypertonic saline (3% Normal Saline) and inj. Hydrocortisone (100mg) once a day for initial 48 hours.

After the patient was stabilised, he was started with tab. Tolvaptan 15 mg twice a day orally. Following the intake of the second dose in the evening he started complaining of frequent thirst, despite receiving 1 pint of normal saline. Regular 24 hours urine level monitoring revealed a urine output of 3320 ml, 3500 ml and 7200 ml respectively on next three days. Due to this increased urine output, tablet tolvaptan was withheld. The patient, then showed a gradual improvement of symptoms and a decrease in urine output level to 1200 ml after 2 days of stopping tab. Tolvaptan.

It is a known fact that hypophysectomy results in polyuria. However, in this case there was stronger temporal relationship between intake of tablet Tolvaptan and onset of polyuria. The condition cannot be explained by other drugs or disease. Moreover, de-challenge was positive and no re-challenge was done. So, as per WHO-UMC criteria, causality is "probable" for occurrence of polyuria as an ADR following administration of tolvaptan. Severity of reaction is of "Level 2" as per modified Hartwig and Siegel scale.

Discussion

Tolvaptan is a selective oral Vasopressin 2 (V2) receptor antagonist[3]. It has been approved by the USFDA, for its use in treatment of clinically significant hypervolemic hyponatremia (such as hyponatremia associated with congestive cardiac failure or cirrhosis of liver) and euvolemic hyponatremia (such as hyponatremia associated with Syndrome of Inappropriate ADH Secretion). Aquaretics like tolvaptan and conivaptan increase renal free water excretion with little or no change in electrolyte excretion. As they tend, not to affect sodium reabsorption, they do not stimulate the TGF (Tubulo-glomerular feedback) mechanism. Thus, the glomerular filtration rate (GFR) remains unchanged.[4]

The most serious adverse effect with the use of vaptans is Osmotic demyelination syndrome or ODS. It is known to occur when hyponatremia is corrected too rapidly (ie. increase in plasma sodium concentration > 8-10 mM in 24 hours or > 18 mM in 48 hour). Hence, cases of symptomatic hyponatremia, requiring initiation of therapy with vaptans, should be managed by closely monitoring plasma sodium concentration and liberalisation of fluid intake (> 2 L/day).[5]

The next significant adverse effect with vaptans is polyuria, which occurs due to inhibition of ADH (Anti-Diuretic Hormone) mediated water reabsorption in collecting duct. The exact incidence of this ADR is not known. This polyuria may lead to dehydration, dizziness, hypotension, increased thirst, xerostomia etc.[6] Our patient presented with massive polyuria following the second dose of tablet tolvaptan. Improvement in polyuria was seen after 2 days of stopping this drug.

Existing literature revealed a similar case, reporting massive aquaresis following tolvaptan therapy. The case, reported by Cho C et al. described a patient of alcoholic cirrhosis, being treated for hepatic encephalopathy. Preliminary investigations detected a serum sodium level of 120 mEq/dL, a urine sodium concentration of 94 mEq/L and urine osmolality of 754 mOsm/kg. The hyponatremia was

subsequently managed by initiation of tablet tolvaptan 30 mg. An increase in urine output to 200 to 300 ml per hour was observed. This was followed by an increase in serum sodium level and decrease in urine osmolality. A 25% albumin infusion was started 5 hours after tolvaptan administration, as part of the management, for the case. However, it was noted that there was a sudden increase in urine output to 500 to 900 mL/h at the end of the albumin infusion (ie, 6 hours later). Further, it was noted that, the aquaretic effect of tolvaptan abruptly stopped at 16 hours, with the urine output falling to 115 ml/h and 10 to 50 ml/h subsequently.[7]

The maximum water clearance of this patient, after tolvaptan therapy was estimated at 675 ml/h as compared to only 68 ml/h, reported by a meta-analysis. Such a massive polyuria was however, not attributed to tolvaptan alone. The sequence of events, led the authors to believe that this could have been contributed by a rise in oncotic pressure of intravascular fluid by the IV infusion of albumin. This polyuria, warranted an intensive monitoring of serum sodium levels and administration of intravenous hypotonic fluid to avoid rapid corrections of hyponatremia.[7]

Tolvaptan acts at the level of the collecting duct of a nephron. However, responsiveness to tolvaptan has been known to be unpredictable. For example, in acute kidney injury (AKI), which is often associated with severe tubular dysfunction, including the collecting ducts, tolvaptan may not show any response. This was reported in a 16-year-old girl who was suffering from heart failure and AKI. Authors Imumura et al. reported a decline in urine output in this patient, even after administration of tolvaptan. Since, urine osmolality reflects the activity of collecting ducts, it has been proposed that measuring the same may predict the responses of tolvaptan.[8]

Patients of tolvaptan induced polyuria may be managed by primarily withholding the offending drug. An adequate water intake is sufficient for recovery of most of the cases. In addition, drugs may also be used to treat this polyuria. Thiazide diuretics are commonly used to treat polyuria.

Conclusion

Tolvaptan is a vasopressin type 2 receptor antagonist, that has been demonstrated to be effective in hypervolemic, hyponatremic states. An unexpected response of massive polyuria may require intensive monitoring of serum sodium levels and administration of intravenous hypotonic fluid. This would avoid rapid correction of hyponatremia and prevent any subsequent life-threatening events. Further, since the response to tolvaptan remains unpredictable, monitoring urine osmolality has been proposed to be a valuable parameter for the prediction of responses to tolvaptan.

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PUBLISHED LITERATURE ON DRUG INDUCED POLYURIA

Compiled by Dr. Avishek Mukherjee* & Dr. Prathamesh Avhad*

First year residents, Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Polyuria Related to Dexmedetomidine

Anesth Analg. 2013;117(1):150-2.

Pratt A, Aboudara M, Lung L.

Dexmedetomidine has become a popular sedative in the intensive care unit for patients undergoing mechanical ventilation because of its highly selective alpha-2 agonism, which exerts a combination of anesthetic, analgesic, and anxiolytic effects. Bradycardia and hypotension have been reported as the most common side effects of its use in large studies. Dexmedetomidine has been reported to induce polyuria by suppressing vasopressin secretion and increasing permeability of the collecting ducts in a dose-dependent fashion. We report a case of dexmedetomidine related polyuria in an intensive care unit (ICU) patient with agitated delirium due to alcohol withdrawal. Polyuria occurred with a high-dose continuous infusion and subsequently resolved with discontinuation of the drug.

Lithium-induced Nephrogenic Diabetes Insipidus: Renal Effects of Amiloride

Clin J Am Soc Nephrol 2008; 3:1324-1331

Bedford J, Weggery S, Ellis G, McDonald F, Joyce PR, Leader J, and Walker RJ.

Polyuria, polydipsia, and nephrogenic diabetes insipidus have been associated with use of psychotropic medications, especially lithium. The impact of psychotropic medications on urinary concentrating ability and urinary aquaporin 2 (AQP2) excretion was investigated after overnight fluid deprivation, and over 6 h after 40 μg of desmopressin (dDAVP), in patients on lithium (n =45), compared with those on alternate psychotropic medications (n=42). Those not on lithium demonstrated normal urinary concentrating ability (958 ± 51mOsm/kg) and increased urinary excretion of AQP2 (98±21 fmol/μmol creatinine) and cAMP (410±15 pmol/μmol creatinine). Participants taking lithium were divided into tertiles according to urinary concentrating ability: normal, >750 mOsm/kg; partial nephrogenic diabetes insipidus (NDI), 750 to 300 mOsm/kg; full NDI, <300 mOsm/kg. Urinary AQP2 concentrations were 70.9 ±13.6 fmol/ μmol creatinine(normal), 76.5 ±10.4fmol/μmol creatinine (partial NDI), and 27.3 fmol/μmol creatinine (full NDI). Impaired urinary concentrating ability and reduced urinary AQP2, cAMP excretion correlated with duration of lithium therapy. Other psychotropic agents did not impair urinary concentrating ability. Eleven patients on lithium were enrolled in a randomized placebo-controlled crossover trial investigating the actions of amiloride (10 mg daily for 6 wk) on dDAVP-stimulated urinary concentrating ability and AQP2 excretion. Amiloride increased maximal urinary osmolality and AQP2 excretion. Amiloride-induced reduction of lithium uptake in the principal

cells of the collecting duct improves responsiveness to AVP-stimulated translocation of AQP2 to the apical membrane of the principal cells.

Case report: a thiazide diuretic to treat polyuria induced by tolvaptan

BMC Nephrol. 2018;19(1):157.

Kramers BJ, van Gastel MDA, Meijer E, Gansevoort RT.

Currently, the vasopressin V2 receptor antagonist tolvaptan is the only available treatment for autosomal dominant polycystic kidney disease (ADPKD), but there are tolerability issues due to aquaretic side effects such as polyuria. A possible strategy to ameliorate these side-effects may be addition of a thiazide diuretic, this is an established treatment in nephrogenic diabetes insipidus, a condition where vasopressin V2 receptor function is absent. We describe a case of 46-year-old male ADPKD-patient, who was prescribed tolvaptan, which caused polyuria of around 5L per day. Hydrochlorothiazide was added to treat hypertension, which resulted in a marked decrease in urine production. While using tolvaptan, rate of eGFR decline was 1.35 mL/min/1.73m^2 per year, whereas after hydrochlorothiazide was initiated this was 3.97 mL/minute/1.73m^2 per year. This case report indicates that while addition of hydrochlorothiazide may improve tolerability of vasopressin V2 receptor antagonists, co-prescription should only be used with great scrutiny as it may decrease tolvaptan effect on rate of ADPKD disease progression.

Bendamustine-induced nephrogenic diabetes insipidus?

Clin Nephrol. 2017;87 (2017) (1):47-50.

Derman BA, Jain M, McAninch EA, Gashti C.

A 59-year-old man presented with polyuria and polydipsia immediately following his sixth cycle of rituximab and bendamustine for chronic lymphocytic leukemia. He initially compensated by increasing his oral fluid intake at home, but later developed septic shock and was admitted with orders to be kept nil per oral (NPO). This prompted an episode of acute hypernatremia during which he exhibited continued polyuria with inappropriately dilute urine. Desmopressin challenge yielded no response in the urine osmolality, indicating a nephrogenic source of his diabetes insipidus (DI). He had no known exposure to other causative agents and had demonstrated a robust response to chemotherapy. The patient became eunatremic once oral intake was resumed and his infection was treated. Two months after presentation, he remained symptomatic. A trial with hydrochlorothiazide resulted in a significant increase in urine osmolality and subsequent decrease in urine output. To our knowledge, this is the first case of nephrogenic diabetes insipidus after rituximab and bendamustine exposure. We propose that bendamustine, similar to the alkylating agent ifosfamide, is toxic to the glomerulus and proximal tubule cells and is the most likely cause of the patient's nephrogenic DI.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr. Smita Mali

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

FDA Drug Safety Podcast: FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

On August 29, 2018, FDA warned that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (or SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We await the addition of a new warning about this risk, to the prescribing information of all SGLT2 inhibitors and to the patient 'Medication Guide'.

SGLT2 inhibitors are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin etc. which lower blood sugar by causing the kidneys to remove sugar from the body through the urine.

Health care professionals should assess patients for Fournier's gangrene and if suspected, start treatment immediately with broad-spectrum antibiotics and surgical debridement, if necessary. Futher management would include discontinuation of the SGLT2 inhibitor, closely monitor blood glucose levels and provide appropriate alternative therapy for glycemic control. Fournier's gangrene is an extremely rare but life-threatening bacterial infection of the tissue under the skin that surrounds muscles, nerves, fat, and blood vessels of the perineum. It is reported to occur in 1.6 out of 100,000 males annually in the U.S., most frequently in males 50-79 years of age. From March 2013 to May 2018, we identified 12 cases, 7 men and 5 women, of Fournier's gangrene in patients taking an SGLT2 inhibitor.

Reference : [**]FDA Drug Safety Podcast: FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes [Internet]. [Cited in Dec 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm619444.htm .

FDA Drug Safety Podcast: FDA warns about increased risk of cancer relapse with long-term use of azithromycin antibiotic after donor stem cell transplant

On August 3, 2018, FDA warned that the antibiotic azithromycin should not be given long-term to prevent a certain inflammatory lung condition in patients with cancers of the blood or lymph nodes who undergo a donor stem cell transplant. Results of a clinical trial found an increased rate of relapse in cancers affecting the blood and lymph nodes, including death, in these patients. We are reviewing additional data and will communicate our conclusions and recommendations when our review is complete.The serious lung condition for which long-term azithromycin was being studied called bronchiolitis obliterans syndrome (BOS) is caused by inflammation and scarring in the airways of the lungs, resulting in severe shortness of breath and dry cough. Cancer patients who undergo stem cell transplants from donors are at risk for BOS. Azithromycin is not approved for preventing BOS and there are no known effective prophylactic antibiotic treatments. Health care professionals should not prescribe long-term azithromycin for prophylaxis of BOS to patients who undergo donor stem cell transplants because of the increased potential for cancer relapse and death.

Reference : FDA Drug Safety Podcast: FDA warns about increased risk of cancer relapse with long-term use of azithromycin (Zithromax, Zmax) antibiotic after donor stem cell transplant [Internet]. [Cited in Dec 2018]. Available from:https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm615935.htm.

FDA Drug Safety Podcast: FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Alemtuzumab

On November 29, 2018 FDA warned that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in patients with multiple sclerosis or MS shortly after they received alemtuzumab. These problems can lead to permanent disability and even death. As a result, we have added a new warning about these risks to the prescribing information in the drug label and to the patient Medication Guide. We have also added the risk of stroke to the existing Boxed Warning, FDA's most prominent warning.

Since its approval in 2014 to treat relapsing forms of MS, we identified 13 worldwide cases of ischemic and hemorrhagic stroke or arterial dissection occurring shortly after the patient received alemtuzumab. Twelve of these cases reported symptoms within 1 day of receiving alemtuzumab and one reported symptoms occurring 3 days after treatment. Health care professionals should advise patients at every alemtuzumab infusion to seek immediate emergency medical attention if they experience symptoms of ischemic or hemorrhagic stroke or cervicocephalic arterial dissection. The diagnosis is often complicated because early symptoms such as headache and neck pain are not specific.

Reference : FDA Drug Safety Podcast: FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis drug Lemtrada (alemtuzumab).[Internet]. [Cited in Dec 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm627618.htm.

FDA Drug Safety Podcast: FDA warns about severe worsening of multiple sclerosis after stopping the medicine Fingolimod.

On November 20, 2018 FDA warned that when the multiple sclerosis (MS) drug Fingolimod is stopped, the disease can become much worse than before the drug was started or while it was being taken. This MS worsening is rare but can result in permanent disability. As a result, we have added a new warning about this risk to the prescribing information of the fingolimod drug label and patient Medication Guide.

Health care professionals should inform patients before starting treatment about the potential risk of severe increase in disability after stopping fingolimod. When fingolimod is stopped, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately. Patients should be advised to seek immediate medical attention if they experience new or worsened symptoms of MS after fingolimod is stopped.

Reference : FDA Drug Safety Podcast: FDA warns about severe worsening of multiple sclerosis after stopping the medicine Gilenya (fingolimod). [Internet]. [Cited in Dec 2018]. Available from: https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm626599.htm

MATCH THE FOLLOWING DRUG WITH IT'S SPECIFIC ADR

Dr Sharmada Nerlekar*, Dr Abhilasha Rashmi*

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

1	Carbamazepine	A	Hemorrhagic pancreatitis
2	Tegaserod	B	Dose related metabolic acidosis
3	Rimonabant	C	Gall stones
4	Cyclophosphamide	D	Pulmonary hypertension
5	Tacrine	E	Capillary leak syndrome
6	Carboprost	F	Activation of latent tuberculosis
7	Octreotide	G	Hemorrhagic cystitis
8	Quinacrine	H	Prolonged hypotension
9	Etanercept	I	Dose related diplopia
10	Asparginase	J	Suicidal tendencies
11	Nesiritide	K	Peripheral neuropathy
12	Bortezomib	L	Skin atrophy
13	Tacrolimus	M	Hepatotoxicity
14	Zonisamide	N	Hyperkalemia
15	Aldesleukin	O	Skin discoloration
16	Clobetasol	P	Unpredictable cardiotoxicity

Answers : 1 - I, 2 - P, 3 - J, 4 - G, 5 - M, 6 - D, 7 - C, 8 - O, 9 - F, 10 - A, 11 - H, 12 - K, 13 - N, 14 - B, 15 - E, 16 - L.

ALPHABET 'T' PUZZLE

Dr. Abhilasha Rashmi*, Dr. Sharmada Nerlekar*
**Associate Professor, Department of Pharmacology,*
LTMMC & GH, Sion, Mumbai - 22.

1 T									
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Clues

1. A prostanoid with ocular hypotensive effect similar to Latanoprost but causes less corneal irritation than it.
2. Vomiting and diarrhea due to this Ubiquinone (Coenzyme Q) analog, used for malaria chemoprophylaxis, may decrease drug absorption leading to therapeutic failure.
3. Lofexidine, a Clonidine derivative, is FDA approved for use in opioid _____ syndrome because it suppresses many of the autonomic symptoms related to the condition.
4. _____acetate, an immunomodulator polypeptide, is having best safety profile in pregnant females with Multiple Sclerosis.
5. The most common cause of Serotonin syndrome in patients taking MAO inhibitors is the accidental administration of an SSRI or _____.
6. There is a warning issued by FDA that _____ Peptidase-4 inhibitor group of drugs, used to treat Type 2 Diabetes Mellitus, are associated with severe joint pain.
7. For treatment of localized plaque psoriasis, topical corticosteroids improve the efficacy & reduce the side effects of burning, itching and skin irritation commonly associated with this topical retinoic acid derivative.
8. A Ritonavir analog, but better tolerated than ritonavir and not a CYP enzyme inducer, which is used as a pharmacokinetic enhancer to HIV Protease inhibitor drugs.
9. Along with common adverse effects like somnolence, fatigue, weight loss, nervousness and renal calculi, this antiepileptic drug is also associated with change in taste of carbonated beverages.
10. Though considered safe for pediatric psoriasis, injection site reactions are seen in about one third patients of rheumatoid arthritis when treated with this TNF-alpha inhibitor.

ALPHABET 'T' PUZZLE: ANSWERS :

1. Travo/Taflupr ost
2. Atovaquone
3. Withdrawal
4. Glatiramer
5. Tryptophan
6. Dipeptidyl
7. Tazarotene
8. Cobicistat
9. Topiramate
10. Etanercept

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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