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BULLETIN ON ADVERSE DRUG REACTIONS

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From the Editor's Desk

Dear friends and colleagues,

It is a great pleasure to put forth this first issue of Bulletin on Adverse Drug Reaction of this year.

The mortality and morbidity due to cardiovascular diseases is increasing day by day leading to increase in the use of drugs like warfarin and aspirin to curb the impending catastrophic events. At the same time cases of bleeding due to these drugs are also being commonly reported. The first article deals with the drugs which are frequently associated with bleeding risk and the strategies to decrease this risk by a balanced approach keeping in mind the overall benefit to the patient.

Our second article attempts to explains the process and importance of "signal generation" which is the most important reason for conducting the pharamcovigilance activity. The articles highlights importance of reporting every single ADR.

Also included in this issue is an interesting case report of clomiphene induced ovarian hyper stimulation syndrome in an oocyte donor. Other features include comprehensive analysis of ADRs of our institute and the brainstorming crosswords and puzzle.

I hope the readers find this issue of bulletin interesting and a knowledge feast.

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

Thank you.

Dr. Sudhir Pawar

DRUG INDUCED BLEEDING

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Introduction

Blood dyscrasias are a rare, yet extremely serious, adverse effect of drug treatment. Although anecdotal reports of drug-induced blood disorders are common in the literature, they often have speculative mechanisms and questionable causality.[1] The exact incidence of drug induced blood disorders is under estimated.[2]

Drugs can have differing effects on the various cell types, at differing stages in cell development. Such diversity of effects leads to a wide spectrum of potential blood disorders depending on where and at what point in the production of the cell line the drug acts upon.[1] Drug-induced hematological disorders can span almost the entire spectrum of hematology, affecting red cells, white cells, platelets, and the coagulation system which presents commonly as anemia, cytopenias and bleeding disorders.[3]

Drug induced acute hemorrhages accounts to 71.3% of the adverse drug reactions seeking emergency hospitalization of which more than 70% are for intracranial hemorrhages, gastrointestinal hemorrhages, and hemoptysis. Of these cases warfarin and antiplatelet agents are the most frequently encountered culprit medications.[4] During routine adverse drug monitoring in our institute we commonly encounter cases of drug induced bleeding. Hence the purpose of this review is to provide a comprehensive overview of bleeding due to some commonly offending drugs.

What is major and minor bleeding?

For research purposes, the definition has varied widely: some investigators have defined major bleeding as any intracranial bleeding or a fall in either adjusted haemoglobin of >5g per dl or haematocrit of >15 per cent, while others have defined it as any bleeding requiring transfusion of >2-4 units of blood/ blood products or requiring surgical intervention, retroperitoneal bleeding, or any spontaneous or nonspontaneous blood loss with a decrease in haemoglobin of >3g per dl.[5]

Clinically examples of major bleeding are intracranial (CT or MRI documented), retroperitoneal (CT or MRI documented), intra-ocular (excludes conjunctival), spontaneous muscle haematoma associated with compartment syndrome, pericardial, non-traumatic intra-articular, any invasive procedure to stop bleeding and active bleeding with either BP < 90 mmHg systolic, oliguria, or > 2 g/dl fall in haemoglobin. Whereas minor bleeding is any other bleeding that would not influence the decision to anticoagulate a patient.[6]

Salient feature of the drug classes commonly implicated

Anticoagulants

Anticoagulant therapy is the mainstay of treatment and prevention of thrombosis in diverse clinical settings, including acute venous thromboembolism (VTE), atrial fibrillation, acute coronary syndrome (ACS), and in patients undergoing invasive cardiac procedures. Omission of appropriate anticoagulant prophylaxis is a widely recognized medical error. Bleeding is the primary complication of anticoagulant therapy, and is a risk of all anticoagulants, even when maintained within usual therapeutic range.[7] The annual risk of intracranial haemorrhage is increased in patients taking warfarin group leading to death in 13% to 33%, and morbidity as high as 15%.[8]

Traditional anticoagulants comprise of unfracntionated heparin (UFH) and warfarin. Newer anticoagulants approved or undergoing clinical studies include both direct and indirect inhibitors of coagulation factors. The indirect (antithrombin-dependent) inhibitors include the low molecular- weight heparins (LMWHs), such as enoxaparin, dalteparin, and tinzaparin; heparin-like compounds, such as danaparoid; as well as the selective factor Xa inhibitors fondaparinux and idraparinux. Like UFH, the LMWHs inhibit both factors Xa and IIa (thrombin), whereas fondaparinux and idraparinux primarily inhibit factor Xa. The direct thrombin inhibitors (DTIs), which include lepirudin, argatroban, bivalirudin, dabigatran and directly bind to and inhibit thrombin.[7] Apixaban and rivaroxaban are selective inhibitors of factor Xa.[9] These direct inhibitors of thrombin and factor Xa are usually referred as newer anticoagulant (NOAC). Newer anticoagulants like dabigatran and rivaroxaban have also been associated with increased risk of gastrointestinal bleeding.[10]

The risk factors for anticoagulant related bleeding are advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents.[8]

Non steroidal anti inflammatory drugs (NSAIDs)

Aspirin as low as 30mg is sufficient to suppress prostaglandin synthesis in the gastric mucosa, while 75-100mg inhibits platelet cyclooxygenase (COX) resulting in suppression of thromboxane A2-dependent platelet aggregation. This is responsible for the two-fold increase in the risk of upper gastro-intestinal bleeding at antithrombotic doses of aspirin which is self-limited in majority of patients, but it can result in peptic ulcers in some patients that may be complicated by gastro-intestinal hemorrhage, perforation and death.

The incidence of major hemorrhage with aspirin monotherapy has been estimated to be 1.5 per cent per year. The risk of ulcer complications rises sharply with dose for both aspirin and other NSAIDs.[5] NSAIDs differ in their risks for causing gastrointestinal bleeding, piroxicam having the highest risk followed by diclofenac, sulindac, naproxen, indomethacin and ketoprofen whereas ibuprofen is associated with the lowest risk.[11]

Anitplatelet drugs

Antiplatelet therapy has a key role in preventing atherothrombotic events in patients with coronary artery disease (CAD). Aspirin, a cyclooxygenase-1 (COX-1) inhibitor, and clopidogrel, an adenosine diphosphate (ADP) P2Y12 receptor inhibitor, are the antiplatelet agents most commonly used in clinical practice in CAD patients. In fact, the degree of platelet inhibition in patients treated with the same antiplatelet treatment regimen is highly variable. Therefore, in some patients a given treatment regimen may lead to no or very little response ("hypo-responders"), while in others this may induce profound platelet inhibitory effects ("hyper-responders").[12] The risks of major bleeding with other antiplatelet agents are generally similar to those of aspirin. A recent meta-analysis showed that GPIIb/IIIa inhibitors are associated with a small but significant increase in major bleeding rates but no increase in intracranial bleeding.

Factors that have been identified as independent risk factors include older age, renal dysfunction, female gender, low body weight and low platelet count. In particular, low levels of platelet inhibition increase the risk of recurrent ischaemic events, while high inhibition increases the risk of bleeding. Therefore, the objective of antiplatelet therapies should be to inhibit platelet function to an extent that the risk of ischaemic as well as bleeding outcomes is minimised.[12]

Combine therapy of Warfarin and Aspirin

Mechanical heart valve patients have a clear overall benefit from combining aspirin with warfarin therapy. However, post-MI patients probably have a reduced risk of thromboembolic events but appear to have no decrease (and perhaps an increase) in overall mortality. For other routine warfarin indications, there is no adequate data to guide this common clinical decision.[13]

For individuals at high cardiovascular risk but at low risk for bleeding (for example, a 58-year-old man with diabetes and congestive heart failure), adding warfarin to standard aspirin therapy could avert 83 myocardial infarctions and 43 strokes per 1000 patient-years of therapy at a cost of just 6 major bleeding episodes. Benefits of warfarin plus aspirin may exceed harm in patients with the acute coronary syndrome who are not stented and do not have high bleeding risks.[14]

Thrombolytics

Bleeding is the primary complication of thrombolytic therapy, with stroke being one of the greatest concerns. The primary mechanism of all thrombolytics is the conversion of plasminogen to the active form, plasmin, which then degrades fibrin. This proteolysis can occur with fibrin-bound plasminogen on the surface of thrombi and the unbound form within the plasma. The unbound plasmin generated degrades fibrin but also fibrinogen, factor V, and factor VIII. Unlike streptokinase and urokinase which are not fibrin specific, agents such as t-PA, tenecteplase, reteplase, and desmoteplase are

referred to as fibrin-specific lytics because of a higher affinity for fibrin-bound plasminogen compared with free plasminogen. Theoretically, higher fibrin specificity may reduce bleeding complications due to direct effect desired site of action and less depletion of circulating procoagulant factors. The risk factors for bleeding include advanced age (>75 years), female gender, African American race, low body weight, medical history (acute myocardial infarction, poorly controlled hypertension, aortic dissection, acute pancreatitis, dementia), surgical history, bleeding history, deranged liver functions and invasive devices.[15]

Selective serotonin reuptake inhibitors

Serotonin released from platelets following vascular injury causes vasoconstriction and platelet aggregation. SSRIs inhibit serotonin reuptake by platelets, depleting platelet serotonin and impairing their ability to form clots. Several studies have also shown that the risk of bleeding may be higher in drugs with an increased affinity for the serotonin transporter such as clomipramine, fluoxetine, sertraline and paroxetine, while citalopram fluvoxamine and venlafaxine have intermediate activity.[16]

Clinical presentation

The signs and symptoms of various forms of bleeding are mention in Table 1

Table1: Clinical presentation of various forms of bleeding [5]

Site	Symptoms	Signs
Intra-abdominal • upper GI bleeding	haematemesis pallor melaena	pallor, dyspnoea shock: tachycardia, hypotension, clammy skin, confusion or decreasing alertness, weakness
• lower GI bleeding	haematochezia: bright red blood or fresh clots per rectum nausea, vomiting abdominal pain/swelling	signs of shock (as above) tender abdominal mass
• retroperitoneal blee ding (rare)	limb weakness	leg pain/paresis
Intracranial (intracerebral, subdural)	headaches and vomiting, changes in behaviour, sudden weakness in arm or leg, difficulty walking neck pain or stiffness double vision convulsions or seizures	altered mental state & focal neurological signs, altered consciousness
Genitourinary	haematuria	pallor, shock if severe
Respiratory	epistaxis	pallor, shock if severe

Site	Symptoms	Signs
Puncture sites, surgical	localised bleeding	pallor, shock
Joints (haemarthrosis)	joint pain/swelling	joint effusion/tenderness
Intraocular (rare)	visual disturbances	decreased visual acuity
Cardiac (rare)	haemopericardium	cardiac tamponade, shock

Prevention and Management

Anticoagulants

Quantifying the absolute risk of bleed for an individual receiving anticoagulation treatment is important because it can help clinicians in identification of high risk patients, assessing risk benefit ratio and helps in communicating the same to patients who need anticoagulants. Steps to prevent anticoagulant related bleeding are:

- Avoid high initial warfarin loading doses; a 5 mg starting dose is generally preferable and an even lower starting dose may be appropriate for older people, who are generally more sensitive to warfarin.
- Identify and address correctable risk factors for bleeding
    - o Use bleeding risk tools such as HAS-BLED scores to identify and correct risk factors but not to withhold anticoagulant treatment - people at high risk of bleeding are also at high risk of stroke.
    - o Continue to assess risk factors for bleeding in all patients taking warfarin; this may influence clinical monitoring intervals.
- Replace medicines that interact with warfarin when possible.
    - o Avoid concomitant use of NSAIDs and certain antibiotics with warfarin. Drugs thought to increase bleeding risk or interact with anticoagulants are antiplatelets (aspirin, dipyramidole, clopidogrel), non-steroidal anti-inflammatory drugs, corticosteroids, statins, antidepressants, antiepiletics (carbamazepine, phenytoin), verapamil, amiodarone, antifungals and antimicrobials (rifampicin, quinidine, chloramphenicol, clarithromycin).
    - o Avoid concomitant antiplatelet therapy except when clinical benefit is known, such as with mechanical heart valves, acute coronary syndrome or recent coronary stents.
- Discuss the key points of warfarin management with the patient: ensure patients understand the importance of dosing and monitoring; provide educational materials on dietary, alcohol and drug (including complementary, alternative and over-the-counter medicines) interactions that influence INR.[17, 18, 19, 20]

The effects of UFH can be readily reversed with protamine sulfate, and vitamin K is a specific antidote for coumarin. Approximately 60% of the anticoagulant effect of LMWH can also be neutralized by protamine.[6]

Warfarin reversal:[18]

For most warfarin indications, the target international normalised ratio (INR) is 2.0-3.0 (venous thromboembolism and single mechanical heart valve excluding mitral). For mechanical mitral valve or combined mitral and aortic valves, the target INR is 2.5-3.5.

- For patients with elevated INR (4.5-10.0), no bleeding and no high risk of bleeding, withholding warfarin with careful subsequent monitoring seems safe.
- Vitamin K1 can be given to reverse the anticoagulant effect of warfarin. When oral vitamin K1 is used for this purpose, the injectable formulation, which can be given orally or intravenously, is preferred.
- For immediate reversal, prothrombin complex concentrates (PCC) are preferred over fresh frozen plasma (FFP). Prothrombinex-VF is the only PCC routinely used for warfarin reversal. It contains factors II, IX, X and low levels of factor VII. FFP is not routinely needed in combination with Prothrombinex-VF. FFP can be used when Prothrombinex-VF is unavailable. Vitamin K1 is essential for sustaining the reversal achieved by PCC or FFP.
- Surgery can be conducted with minimal increased risk of bleeding if INR < 1.5. For minor procedures where bleeding risk is low, warfarin need not be interrupted. If necessary, warfarin can be withheld for 5 days before surgery, or intravenous vitamin K1 can be given the night before surgery.

New oral anticoagulants (NOACs) mediate their anticoagulant effect by directly inhibiting their target coagulation factors. Accordingly, a successful strategy to reverse NOACs would require either removing the drugs from circulation or overcoming their inhibitory effects. A specific NOAC reversal agent (or "antidote") is not available for clinical use to date. Clinical trials assessing the efficacy of PCCs or recombinant factor VIIa (rFVIIa) in bleeding patients taking NOACs are also scarce. Though, NOACs have shorter half-lives than warfarin, and are not associated with a higher risk of bleeding, it may be necessary to reverse the effect of NOACs in cases of life-threatening bleeding, or in cases where other clinical factors are preventing timely clearance of a NOAC.[21]

Antiplatelets

There is a strong correlation between bleeding risk of GPIIb/IIIa inhibitors and concomitant administration of heparin. It is therefore important that only specifically recommended heparin regimens should be used. In the event of bleeding, the infusion should be discontinued and transfusions of blood and/or platelets should be considered.[5]

NSAIDs

For NSAID's induced gastro-intestinal bleed, oral or intravenous administration of omeprazole following endoscopic haemostatic therapy in patients with evidence of active or recent peptic ulceration reduces the risk of continued bleeding or re-bleeding.[5]

Thrombolytics

Strategies to minimize risk of bleeding with thrombolytics are use of fibrin specific agents, weight-adjusted doses and administration techniques like bolus dosing of alteplase and catheter directed therapy may be helpful.[15]

Management of bleeding complications depends on the causative drug, the degree of bleeding and the hemodynamic stability of the patient. Of paramount importance is the need to discontinue the drug and stabilize the patient using intravenous fluids, blood or platelets as appropriate, with subsequent measures aimed at reversing the hemorrhagic effects of the drug.

Conclusion

Thus, drug induced bleeding is a common adverse effect encountered with drugs altering coagulation cascade or platelet aggregation. There is a very thin line of distinction between desired therapeutic effect and threat of bleeding. Thus, balancing the risk benefit of therapy and tailoring it as per the patient characteristics is the key to safe treatment.

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ROLE OF SAFETY SIGNAL IN PHARMACOVIGILANCE

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Introduction

A single drug sees the light of clinical utility after undergoing about 15 years of various scrutiny tests including in-vitro, animal and human studies and at the cost of about one billion of dollars for the development. Although a great deal of information on the product's safety and efficacy is gathered during clinical development, it is not possible to characterize fully the safety profile of the drug in premarketing studies. This is because the phases of clinical studies includes only about few hundred to few thousand patients and are conducted in groups that are largely homogeneous in characteristics and hence unable to capture rare adverse effects.[1]A number of drugs such as valdecoxib (causing Stevens-Johnson syndrome), troglitazone (causing hepatotoxicity)and rofecoxib (causing myocardial infarctions) have been withdrawn from the market because of adverse reactions that were unknown or not fully characterized when the drug was approved[2] and these were detected after the product launched for general population.

Hence the role of Pharmacovigilance is emphasised which helps in understanding and confirming the safety profile of a drug after its launch.

The most important role of Pharmacovigilance principally is to identify and evaluate "safety signals". The WHO defines a safety signal as "the reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously"[3]. Usually more than a single report is required to generate a signal, depending upon the event and quality of the reports available. When a signal is detected, further investigation is warranted to determine whether an actual causal relationship exists. There are various sources from where safety information can be derived for signal generation. However with spontaneous reporting, a minimal number of case reports - in the range of about 3 to 9 are usually needed for a signal generation.[4] Signal detection speed depends on the proportion of doctors contributing to the reporting system even if it is as low as few cases reported per product. These adverse reactions reports are collected in large databases and which themselves form important source of safety information. Four major databases are currently operating having a large number of adverse reaction records. The World Health Organization for International Drug Monitoring (Uppsala Monitoring Centre) has VigiBase™, which was started in 1968 and contains over 7 million individual case safety reports from 144 member countries [WHO 2012]. The United States Food and Drug Administration (FDA) has the Adverse Event Reporting System (AERS), which was started in 1969 and contains over 4 million reports [FDA 2011a], and the Vaccine Adverse Event Reporting System (VAERS) [VAERS 2013], which was started in 1990 and contains over 400,000 reports. The European Medicines Agency (EMA) has EudraVigilance, which was started in 2001.[2]

Safety signal can be detected very early and through all the phases (phase I to phase IV) of clinical studies and all has their significance in drug's safety detection. In this article we will be considering only the safety signals related to phase IV of drug development. The following table gives the examples of drugs whose suspected adverse reactions were highlighted by quantitative screening of individual case reports which were communicated to national pharmacovigilance centres and relevant pharmaceutical companies, and finally supported by scientific publications.

Table 1: Examples of ADRs identified earlier and confirmed after marketing[5]

Drug	Suspected ADR	Highlighted	Communicated	Supported
Topiramate	Glaucoma	2nd quarter 2000	April 2001	October 2001
Infliximab	Vasculitis	2nd quarter 2000	September 2002	August 2004
Infliximab	Pericardial effusion	4th quarter 2001	December 2002	August 2004
SSRIs	Neonatal convulsions	4th quarter 1999	December 2001	May 2005
Abacavir	Myocardial infarction	2nd quarter 2000	May 2005	April 2008

ADR - adverse drug reaction; SSRI - selective serotonin reuptake inhibitor.

Steps of the signal management process

The signal management process includes set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed.[6] The table below gives the various sources from where signal can be derived. One of the strengths of these adverse event reporting systems is that they collect data from patients who would not normally be included in clinical trials indicating the scenario of exposure to a heterogeneous population against to the segregated population of clinical studies.[2]

Table 2: Sources of signals[4]

Observations in patients (qualitative signals)	**Observations in populations (quantitative signals)**
Spontaneous-reporting systems Anecdotal literature reporting Intensive hospital monitoring Prescription event monitoring Follow-up studies Monitored release programmes **Experimental findings** Clinical trials In vitro experiments Animal toxicology	Large data resources on morbidity and drug use (Including record linkage) Case-control studies; case-control surveillance Follow-up studies Prescription event monitoring Intensive hospital monitoring Large spontaneous-reporting systems (e.g. World Health Organization, US Food and Drug Administration)

The qualitative and quantitative methods include either the clinical-pharmacological or quantitative/ epidemiological aspects respectively, which contribute towards signal detection.[7] Spontaneous reporting of case reports or case series are highly sensitive in picking up qualitative signals and serves as an early warning related to drugs reactions. On the other hand, they are limited in their ability to provide quantitative information. Quantitative approaches in signal detection unify the qualitative and quantitative aspects of signal detection.[8] Although the concept of quantitative signal detection originates from more than 30 years ago, its application and further development has been boosted in recent years mainly due to the general availability of powerful information technology. The quantitative methods are based on the disproportionate numbers of adverse clinical events that are present in the database which may reveal an important signal and serves important method for confirmation of the drug-ADR association.[8]

The signal management processes include all steps from *initial signal detection; through their validation and confirmation; analysis and prioritisation; and signal assessment to recommending action.*

Let us understand the process of signal generation with the help of an example of temsirolimus and myocardial infarction as recently published in a WHO newsletter.[9]

Temsirolimus and Myocardial infarction: the following is the evaluation of 17 individual case safety reports of myocardial infarction in patients how received Temsirolimus with other drugs or alone. The individual case safety reports were received at the WHO Global ICSR Database, VigiBase, from different countries worldwide.

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin) and indicated for treatment of adult patients with advanced renal cell carcinoma (RCC) and also for adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

By 6 May 2014, 17 ICSRs in the WHO Global ICSR Database, VigiBase® of myocardial infarction and temsirolimus were received from the United States (9 reports), Germany (4 reports), and Austria, Canada, Greece and Japan (1 report each). The patients ranged in age from 51 to 78 years with a median of 64 years in the 11 cases which provided the information. There were 13 males and three females in the 16 reports which contained these details. Time to onset was reported in 11 of the reports and ranged from 1 day to 9 months (median 2.5 months).Temsirolimus was given for various indications and the adverse reaction reported included cardiac conditions along with many other systems involvement. Temsirolimus was the only drug "suspected" in eight of the 17 cases.

Case reports in VigiBase® suggest that there is a possible signal for the association of temsirolimus and MI. Time to onset of cardiac adverse reaction is consistent with a drug-induced effect and although onset is very short in some cases, this may be explained by the presence of free fatty acids. Temsirolimus is known to induce high levels of cholesterol and particularly triglycerides and this is a plausible

mechanism for the development of MI in some patients. In the six cases with recovery, temsirolimus was either withdrawn or the course discontinued in four cases and the fate of the drug was unknown in the other two cases. In the three cases where the outcome of the MI was death, the drug was withdrawn or discontinued in two cases and the fate of the drug was unknown in the other case. Although there are alternative explanations for MI in some reports and advanced disease may make a contribution in others, the use of temsirolimus appears to be a possible signal.

Literature and Labeling: previous product literature does not refer to MI associated with temsirolimus. The only cardiac disorder that was reported in clinical trials was pericardial effusion which was reported uncommonly. Vascular disorders such as venous thromboembolism (including deep vein thrombosis and venous thrombosis), thrombophlebitis and hypertension were reported commonly. There are also no reports in the published literature which link MI with temsirolimus. In a phase I clinical trial of temsirolimus and bevacizumab in the treatment of salivary duct carcinoma, however, one of the two patients treated died as a result of an MI although it was considered unrelated to the study drugs. Hence in the absence of any mention in the literature this is considered as new finding.

In summary, there are 17 reports associating MI with the use of temsirolimus. Temsirolimus was the only drug suspected in eight of the 17 cases. Temsirolimus is known to induce high levels of cholesterol and particularly triglycerides and this is a plausible mechanism for the development of MI in some patients. Time to onset is consistent with a drug-induced effect and although onset is very short in some cases, this may be explained by the presence of free fatty acids.[9]

Hence this analysis can be considered for the generation of signal however the confirmation of association of temsirolimus with the ADR can only be done after further studies and signal follow-up.

Table below gives the points to be considered to analyse the association of the adverse reaction and the drug for signal generation based on a number of quantitative and qualitative criteria.[4]

Table 3: The balance of evidence in a signal

- Quantitative strength of the association
  - Number of case reports
  - Statistical disproportionality
- Consistency of the data (pattern)
- Exposure-response relationship
  - Site, timing, dose, reversibility
- Biological plausibility of hypothesis
  - Pharmacological, pathological
- Experimental findings
  - e.g. dechallenge, rechallange, blood levels, metabolites, drug-dependent antibodies
- Analogies
- Nature and quality of the data
  - Objectivity, documentation, causality assessment

As defined previously, a signal in pharmacovigilance is more than just a statistical association. It consists of a hypothesis together with data and arguments; either in favour or against the hypothesis. These relate to numbers of cases, statistics, clinical medicine, pharmacology (kinetics, actions, and previous knowledge) and epidemiology, and may also refer to findings with an experimental character. Hence out of the signal generated all may not be indicative of the association of drug and the adverse reaction. It is important to follow up for confirmation of the association and the adverse reaction.[4]

Signal follow up and action

The discovery of a drug-induced disorder, from the earliest suspicion via a credible signal to a fully explained and understood phenomenon, is a lengthy process. Though the first and the important step is reporting an adverse reaction even if it a single incidence, it may take some time until the symptoms, frequency, mechanism and risk factors of an adverse reaction have been fully recognised and the causal connection has been definitely established. These signals should be scientifically proven for necessary actions to be taken. Therefore, signals need follow-up with regard to both scientific credibility and clinical and regulatory relevance.[4]

Signal follow up

There is a possibility that a signal which consists of only a few case reports may not be statistically significant. Hence when a signal has been recognised and assessed, it needs to be followed up to observe how it evolves over time as regards to absolute numbers of cases, the statistical parameters, exposure to the drug (utilisation) and the consistency of the reporting pattern. Various methods have been described for the confirmation including comparison of the reported adverse reaction in different countries, targeted comparisons, nested case control studies, using the support of active surveillance and comparing with other databases to name a few.[10, 11]

Actions based on safety signals

Once the drug - adverse reaction association is confirmed, the information is communicated to the national regulatory body and/ or other institutes. Further actions includes initiation of further study (hypothesis testing), e.g. follow-up study, cross sectional study and publication (newsletter, article) Based on the evidence, the regulatory body may take further action including withdrawal of the drug or marketing with black box warning to general patients or in specific groups of patients.

Conclusion

One of the important aspect of pharmacovigilance is to identify the safety signals which can start from as early as pre-clinical or phase I studies. For the rare adverse reactions the safety signals can be identified in the post marketing phase with the contribution of even a few numbers of case reports which are compiled together and analysed for a meaningful interpretation. Various automated method

are developed for the identification of a safety signal form a large number of cases. It is important to note that notifying even a signal case report by the clinician can contribute to better understanding of the safety profile of a drug.

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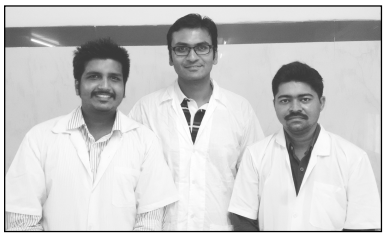
ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED



(November 2014 - February 2015)

Compiled by Dr. Shivkumar Shete
Technical Associate - Pharmacovigilance.

Department of Pharmacology, LTMMC & GH, Sion, Mumbai-400022

Total Case Reports: 102

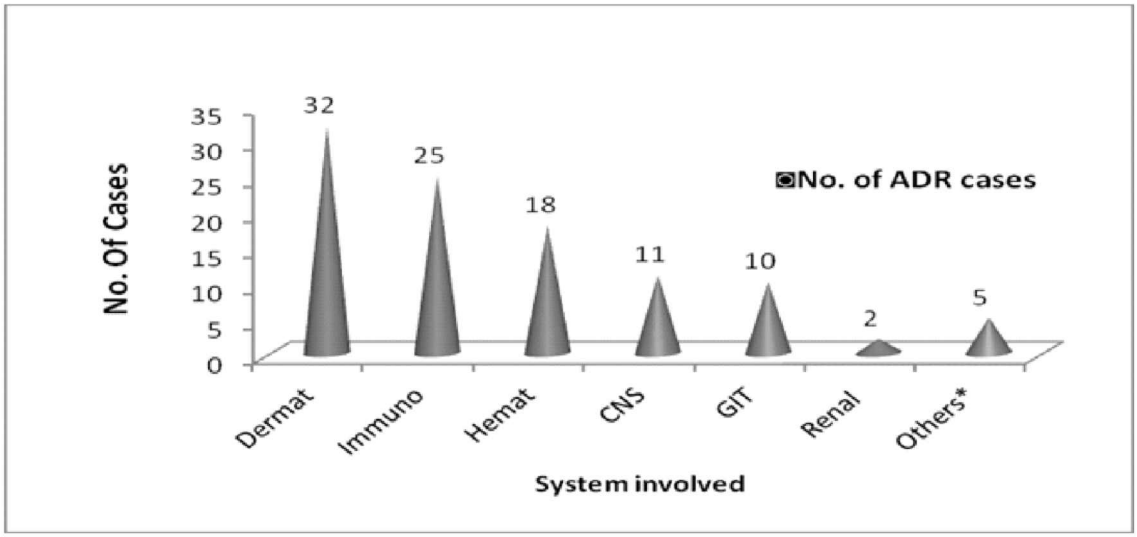
I. Age and Gender distribution

Age groups	Number of patient	Males	Females
<3yrs	7	4	3
3-17yrs	16	9	7
18-44yrs	46	21	25
45-60yrs	17	8	9
>60yrs	16	12	4
total	102	54	48

II. Seriousness of reactions reported

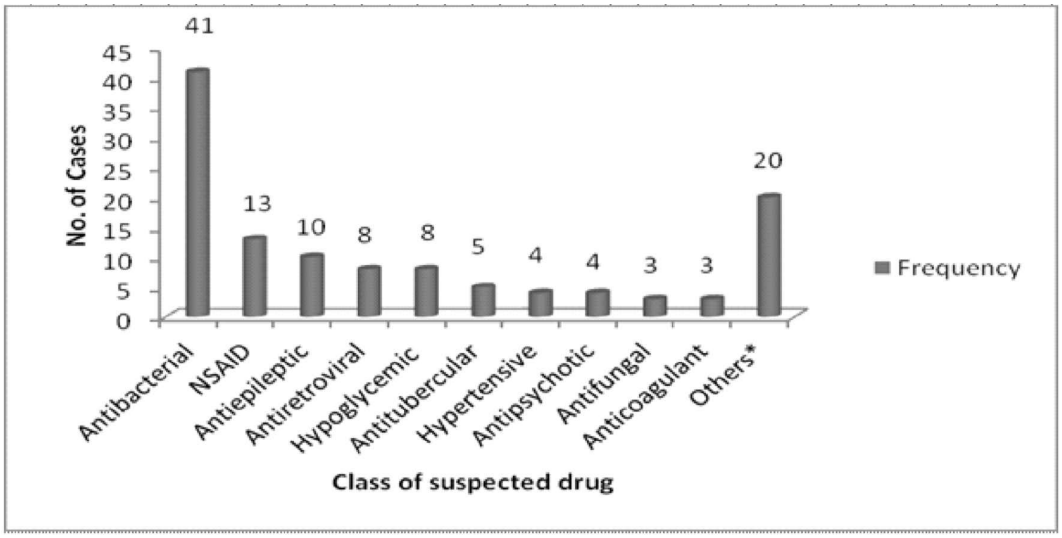
Seriousness of reactions reported	Number of cases
Yes	96
No	6

III. System of distribution of the adverse drug reaction



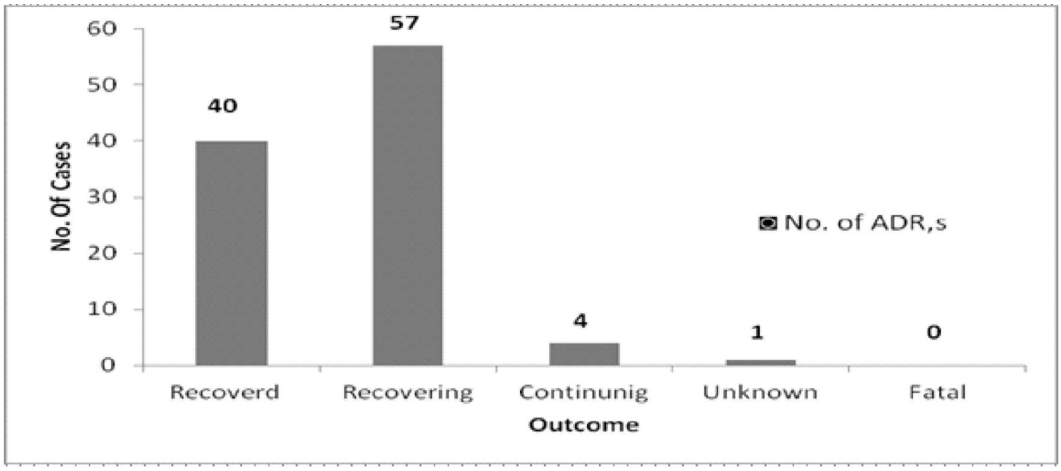
* Others include cases involving ophthalmic, cardiovascular system, musculoskeletal and genitourinary system.

IV. Class of Suspected Drugs

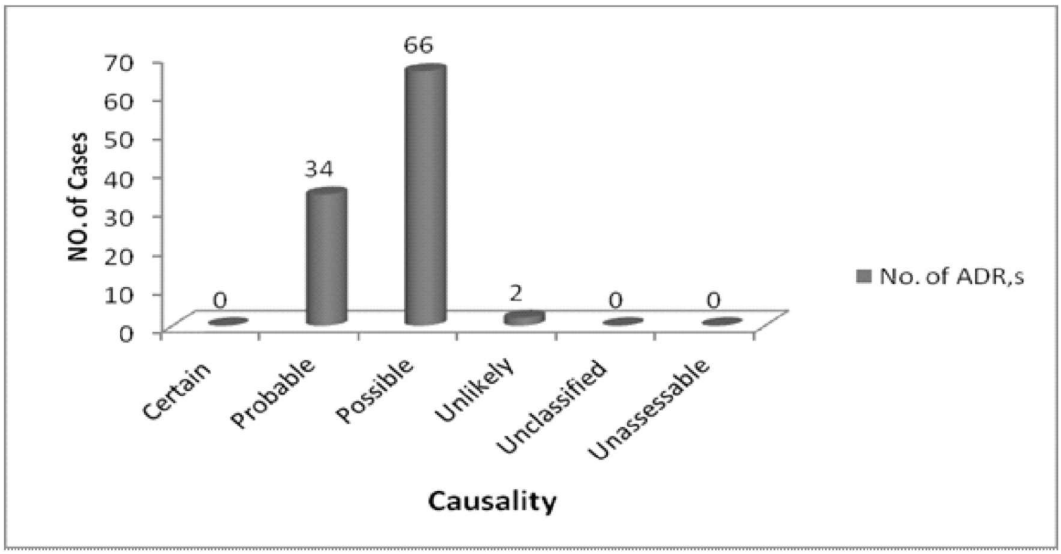


*Others include immunomodulator, intravenous fluids, anti gout, vaccine, diuretics, anticancer, anti histaminic, anti spasmodic and anti anxiety drugs.

V. Outcome of the reaction (n=102)



VI. Causality assessment (WHO causality assessment scale) (n = 102)



EVALUATION OF A CASE

Ovarian Hyperstimulation Syndrome Due To Clomiphene Citrate: A Case Report

Dr Kalpana Dudhal

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

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation but rarely it can occur spontaneously during pregnancy.[1,2] The syndrome is commonly associated with exogenous gonadotropin stimulation and is rarely observed after clomiphene citrate treatment (OHSS<1%).[3,4] OHSS is a self limiting disorder that usually resolves spontaneously within several days, but may persists for longer duration, particularly in conception cycles. The syndrome has a broad spectrum of clinical manifestations, from mild illness needing only careful observation to severe disease requiring hospitalisation and intensive care.[5] The pathophysiological hallmark of the ovarian hyperstimulation syndrome is a sudden increase of vascular permeability resulting in fluid shift from intravascular space to third space compartments and intravascular dehydration.[6] The symptoms can range from nausea, vomiting and mild abdominal discomfort to severe disease with ascites, hydrothorax and renal failure. Treatment is only supportive.[7]

We are reporting a case of OHSS due to clomiphene and discussing diagnosis and management of OHSS.

Case report

A 23 years old female, G0 presented with complaints of nausea, vomiting and anorexia since 7 days followed by progressive abdominal distension associated with pain, constipation and breathlessness. She had no chest pain, there was no fever and cough. There was no history of other medical illness.

The patient was prescribed ovulation inducing agent for oocyte donation by a doctor from private nursing home.

She had taken clomiphene citrate, 50 mg single daily dose orally for 5 days. She was asymptomatic for 5 days after discontinuation of clomiphene. Later she started having nausea, vomiting and anorexia. Egg retrieval was done after these complaints and she was treated symptomatically for the same. While patient was taking treatment, her symptoms progressively worsened. She had progressive abdominal distension associated with other symptoms mentioned above. She came to our institute with complaints of progressed illness.

On examination she was afebrile and vitals were stable. She was breathless and signs of bilateral pleural effusion present. Abdominal examination revealed tenderness and distension with signs of ascites. Rest of the systems were normal.

Her laboratory investigations revealed hemoglobin of 16.4 gm % with total count of 16800/mm3 and platelet count 414000/mm3. Chest x-ray showed bilateral pleural effusion. Renal functions were normal. Ultrasonography revealed bilateral grossly enlarged ovaries with multiple enlarged follicles, secondary haemorrhages and gross ascites. Bilateral moderate pleural effusion was also seen on ultrasound examination. Based on these findings and clinical presentation diagnosis of ovarian hyperstimulation syndrome was done.

She was admitted and managed symptomatically for OHSS with close monitoring of vitals, urine output, renal function and abdominal girth. She was treated with antibiotics, analgesics and antiemetics. Patient gradually recovered from the illness and was discharged.

Discussion

Ovarian hyperstimulation syndrome is an iatrogenic complication of ovarian stimulation but rarely it can occur spontaneously during pregnancy in persons with mutations in follicle stimulating hormone receptor. This syndrome is typically associated with exogenous gonadotropin stimulation. It is also rarely seen with other agents like clomiphene citrate and gonadotropin releasing hormones (GnRH).[1,2,5]

In vitro fertilization techniques use GnRH agonists or antagonists and gonadotropins to stimulate the ovary. Following stimulation human chorionic gonadotropin (HCG) is used to initiate ovulation and maintain luteal phase. In rare instances the ovarian stimulation can lead to excessive ovarian response. It is characterised by ovarian enlargement accompanied by over production of ovarian hormone and ovarian vasoactive agents leading to state of increased capillary permeability. HCG induces release of vasoactive mediators.[6, 8]

Clomiphene citrate is a potent anti-estrogen that primarily is used for treatment of anovulation in the setting of an intact hypothalamic-pituitary axis and adequate estrogen production (e.g., PCOS). The drug is relatively inexpensive, orally active, and requires less extensive monitoring. OHSS is rarely seen in patients taking clomiphene citrate, usually it is mild but sometimes severe and fatal.[4]

Risk factors[1,5]

Several factors independently increase the risk of developing severe OHSS. These include the following:

- Age < 30 years
- Polycystic ovaries

- o Rapidly rising or high serum estradiol
- o Previous history of OHSS
- o Large number of small follicles (8 to 12 mm)
- o Use of hCG as opposed to progesterone for luteal phase support after IVF
- o Large number of oocytes retrieved (> 20)
- o Early pregnancy
- o Thin built

Clinical features[9]

The hallmark of OHSS is shift of fluid from the intravascular to extravascular space. Symptoms usually begin with a sensation of abdominal bloating, discomfort, nausea, vomiting and may progress to severe disease with ascites, hydrothorax and renal failure. Sometimes it may have complications like pulmonary oedema, adult respiratory distress syndrome, pulmonary embolism, atelectasis and intra-alveolar haemorrhage, venous thromboembolism.

This patient has taken clomiphene citrate as ovulation inducing agent for oocyte donation, was having young age as the only risk factor for OHSS. She improved with symptomatic treatment after discontinuation of clomiphene. There are reported cases of OHSS due clomiphene and enough evidence published in literature about OHSS due to clomiphene. Based on this and according to WHO scale of Causality assessment, the association of clomiphene with ADR can be considered to be "Probable" because of temporal relation with clomiphene as well as she improved after discontinuation of drug and she did not receive any other medications along with clomiphene.

Prevention[6,7]

OHSS prevention is a priority in current medical practice. Identification of high risk patients before initiating ovulation stimulation and best to avoid it in those patients. Prevention can be optimized by initially recognizing risk factors and individualizing ovulation induction regimens, using the minimum dose and duration of gonadotropin therapy necessary to achieve the therapeutic goal. Every patient receiving ovulation stimulation therapy needs monitoring for ovarian response (serum oestradiol levels and follicular number) and if ovarian response is high (serum oestradiol > 3000-4000 pg/ml and/or follicular number >20-25) individualization of regimen is necessary. Following factors should be considered while individualizing regimen.

1. Replacement of hCG by endogenous or exogenous LH as ovulation trigger.
2. Reducing the dose of the hCG trigger to 5,000 IU instead of the standard 10,000 IU.
3. Using progesterone and not hCG for luteal phase support.

4. Coasting-withholding the FSH injections or dose can be reduced continuing GnRH agonist administration. This allows larger follicles to continue to grow where rest of the follicles enter atresia.
5. Cancellation of cycle of treatment and continuation of down regulation until next period.
6. Using Cabergoline 0.5mg daily post oocyte retrieval where indicated.
7. Intravenous (IV) administration of prophylactic 25% albumin (20-50g) at the time of oocyte retrieval.
8. Cryopreservation of oocytes and embryos subsequent transfer in an unstimulated cycle.

Management[1,5,6,7,9,10]

There is no specific treatment for OHSS. Therapy is mainly supportive. The syndrome is self limiting and resolves spontaneously. Outpatient management is usually possible in women with mild and moderate OHSS along with careful monitoring of patient for progress of disease. Women with severe and critical OHSS should be admitted for proper monitoring, intravenous fluid therapy, early recognition and management of complications due to it.

Daily monitoring of weight, abdominal circumference, intake and output chart and signs of any complication is required. Hematological examination should include hematocrit, RBC count, WBC count, electrolytes, kidney function tests, liver enzymes, total serum protein and albumin, coagulation tests.

Pain relief

Acetaminophen is used for symptomatic relief of abdominal pain and if necessary oral or parenteral opiates can be used. Non-steroidal anti-inflammatory agents with antiplatelet properties should not be used because they may interfere with implantation and may also compromise renal function in women with severe OHSS.

Nausea and/or vomiting

Antiemetic agents considered to be safe in pregnancy should be used to alleviate nausea and/or vomiting.

Fluids and electrolytes

Women should drink according to their thirst. In addition, IV hydration with a crystalloid solution should be instituted until diuresis occurs. If clinical and laboratory findings indicate persistent intravascular

volume depletion despite aggressive IV fluid hydration, IV albumin should be initiated and repeated until hydration status improves. Diuretics should not be used as they can further deplete intravascular volume.

Paracentesis

Patients with tense ascites causing significant pain and/or respiratory compromise benefit from paracentesis. It will also improve oliguria that is secondary to reduced renal perfusion from ascites increasing intraabdominal pressure and compromising blood flow to the kidneys. The ascites output should be recorded daily. Drainage of ascites will also generally resolve a pleural effusion.

Management of Complications

Hospitalized patients should be considered at risk of thrombosis secondary to hemoconcentration and immobilization. Daily prophylactic doses of low-molecular weight heparin and use of thromboembolic deterrent stockings should be considered on admission and continued until discharge. Renal failure, thromboembolism, pericardial effusion, and acute respiratory distress syndrome are potential life-threatening complications of OHSS. These conditions should be diagnosed early and managed by a multidisciplinary team possibly in an ICU setting.

Counselling

Women should be counselled, and their partners should be made aware, that the management of OHSS is primarily supportive until the condition resolves spontaneously. Women should be counselled regularly about the natural history of OHSS and advised that their clinical course may be prolonged. Women should be reassured that pregnancy may continue normally despite OHSS, and there is no evidence of an increased risk of congenital abnormalities.

Conclusion

OHSS is a complication of ovarian stimulation therapy, so it is necessary to identify women at increased risk. Knowledge of OHSS risk factors, clinical presentation, and careful assessment of severity are essential to the effective diagnosis and management of this condition.

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PUBLISHED CASE REPORTS ON CLOMIPHENE CITRATE INDUCED OVARIAN HYPERSTIMULATION SYNDROME

Compiled by Dr Jaisen Lokhande

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

Adnexal torsion in a woman undergoing ovarian hyperstimulation with clomiphene citrate therapy: a case report and review of the literature.

Arch Gynecol Obstet. 2012 Jan;285(1):271-3.

Shiau CS, Huang YH, Chang MY, Lo LM, Hsieh TT, Hsieh CL.

Ovarian stimulation is a unique aid for patients treated for anovulation and an important tool in various assisted reproduction treatments. Clomiphene citrate, an orally active, non-steroidal triphenylethylene derivate, is a commonly prescribed agent for ovulation induction. Clomiphene citrate is considered a safe agent and has rarely been associated with significant side effects. This report describes a case of unilateral adnexal torsion after ovulation induction with clomiphene citrate; we performed unwinding of the adnexum, which appeared ischemic via laparoscopy. Unfortunately, the affected adnexum became hemorrhagic after this approach, which invariably led to its resection.

Ovarian hyperstimulation syndrome associated with clomiphene citrate.

West Indian Med J. 2001 Sep;50(3):227-9.

Mitchell SY, Fletcher HM, Williams E.

Ovarian hyperstimulation is a recognized complication of ovulation induction with gonadotropins. The syndrome is becoming more common as the number of women undergoing in-vitro fertilization increases. It is rarely seen in conjunction with clomiphene citrate usage. This case report is of moderate to severe ovarian hyperstimulation in a patient who was treated with clomiphene citrate because of infertility secondary to anovulation. She presented with amenorrhoea for five weeks, lower abdominal pain and a positive urinary human chorionic gonadotropin (hCG) test. Pelvic ultrasonography was suggestive of a possible ectopic pregnancy with a differential diagnosis of a ruptured ovarian cyst. Diagnostic laparoscopy was done followed by laparotomy. Oophorectomy was performed because the ovary was thought to be complex with solid areas. However, conservative management with avoidance of laparotomy is the recommendation in confirmed cases of ovarian hyperstimulation but this requires a high level of suspicion in patients who have ovulation induction.

Clomiphene, ovarian hyperstimulation syndrome and pregnancy

Georgian Med News. 2009 Jan;(166):26-9.

Samsonia MD, Lesnovskaia EE, Kandelaki MA

In case of an ovarian hyperstimulation syndrome surgical treatment causes the regress of symptoms much faster than pharmacotherapy--during the resection of an ovary the concentration of oestrogens in blood is effectively reduced. Frequent use of ovulation inductors (Clomiphene / Gonadotropin) is accompanied by ovarian hyperstimulation syndrome. It is characterized by the increase of sizes of ovaries; the formation of ascites and hydrothorax, by the thromboemboli of main blood vessels and etc. Clomiphene accelerates the maturation process of follicles, but contributes to the increase of concentration of oncomarker CA-125 in blood. This makes it difficult to verify the diagnosis of ovary cancer, particularly among pregnants. The case report of infertility treatment with Clomiphene is depicted. Woman became pregnant after three courses of infertility treatment, but pregnancy was complicated with cardiac and lung insufficiency; the suspicion of stage III ovarian cancer aroused. Serious threat to health of a woman resulted in prevention of pregnancy. Right side adnexectomy was conducted. Surgical treatment led to improvement and after four years the patient delivered a healthy child.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr Jaisen Lokhande

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

Aceclofenac - Updated cardiovascular advice in line with diclofenac and COX-2 inhibitors: The Medicines and Healthcare products Regulatory Agency (MHRA) has announced that aceclofenac is now contraindicated in patients with certain established cardiovascular diseases. Even though there are limited data available regarding the arterial thrombotic effects of aceclofenac, the regulation was based on aceclofenac's structural similarity to diclofenac and its metabolism to diclofenac. When using aceclofenac to relieve pain and inflammation in various indications, prescribers should consider; that aceclofenac is now contraindicated in patients with established, ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, congestive heart failure (NYHA, classification II-IV), switching patients with these conditions to an alternative treatment at their next routine appointment. It is recommended to start aceclofenac treatment after careful consideration of any significant risk factors for cardiovascular events, e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking.

Reference: *WHO Pharmaceuticals Newsletter [homepage on the Internet]. 2015 [cited 2015 Jul 13].(2) Available from: World Health Organization, Web site: http://www.who.int/medicines/publications/Pharm_Newsletter2_2015.pdf?ua=1*

Donepezil - Risk of rhabdomyolysis and neuroleptic malignant syndrome: Health Canada has issued an Information Update on the risks of rhabdomyolysis and/or Neuroleptic Malignant Syndrome (NMS) for donepezil after conducting a safety review. The prescribing information for donepezil has been updated to include the possible risks of rhabdomyolysis and NMS. It is advised that the health-care professionals be aware of the possibility of these rare serious reactions, and for steps to be taken for their early detection.

Reference: *WHO Pharmaceuticals Newsletter [homepage on the Internet]. 2015 [cited 2015 Jul 13].(2) Available from: World Health Organization, Web site: http://www.who.int/medicines/publications/Pharm_Newsletter2_2015.pdf?ua=1*

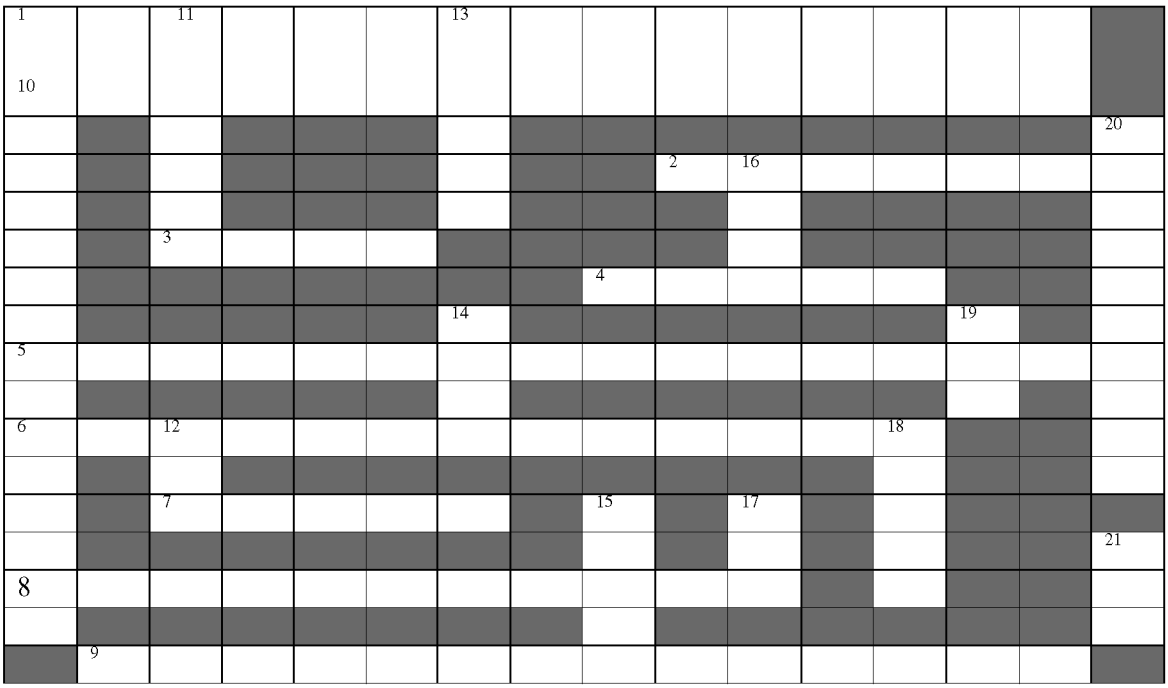
Hydroxyzine - Risk of QT interval prolongation and Torsade de Pointes : The MHRA has issued a warning not to prescribe hydroxyzine to people with a prolonged QT interval or risk factors for QT interval prolongation, and has decreased the maximum adult daily dose of hydroxyzine to 100 mg. The MHRA has informed health-care professionals to consider for various risks factors before prescribing to patients. The maximum daily dose is now: 100 mg for adults, 50 mg for the elderly (if use cannot be avoided), 2 mg per kg body weight for children up to 40 kg in weight and recommended to prescribe the lowest effective dose for as short a time as possible.

Reference: *WHO Pharmaceuticals Newsletter [homepage on the Internet]. 2015 [cited 2015 Jul 13].(3) Available from: World Health Organization, Web site: http://www.who.int/medicines/publications/Pharm_Newsletter3_2015.pdf?ua=1*

CROSSWORD PUZZLE

Dr. Sharmada Nerlekar *, Dr Abhilasha Rashmi**

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



ACROSS

Q1. Side effects with Deferiprone are joint pain, reversible neutropenia & rarely _____. (15)

Q2. Estramustine, used to treat advanced prostate cancer, has estrogenic adverse effects like, gynaecomastia, impotence & impaired_____ tolerance. (7)

Q3. Interstitial _____ disease is an infrequent but serious complication of Gefitinib, a drug used to treat advanced lung cancers. (4)

Q4. The major dose related toxicity with didanosine is peripheral neuropathy also called stocking and_____ neuropathy. (5)

Q5. The significant adverse effect of sirolimus is that, it mainly causes_____. (16)

Q6. The prominent adverse effects of _____ mofetil are vomiting, diarrhea, leucopenia and predisposition to CMV infection. (13)

Q7. Prolonged use of albendazole as in cysticercosis has caused headache, alopecia, jaundice, neutropenia and_____. (5)

Q8. Lindane being highly lipophilic can produce systemic toxicity in the form of vertigo, cardiac arrhythmias and_____ especially in children. (11)

Q9. _____ is a dose related adverse effect of epirubicin. (14)

BELOW-

Q10. _____ given 30 minutes before dimercaprol injection, reduce the intensity of its adverse effects. (15)

Q11. Penicillamine produces prominent dermatological, haematological and_____ toxicities. (5)

Q12. Imatinib, the drug of choice in c-kit-positive Gastro Intestinal Stromal Tumour, has adverse effects of fluid retention, liver damage and _____. (3)

Q13. Sulfadoxine & sulfamethoxypyrazine, classified as _____ acting sulfonamides, have caused serious cutaneous reactions. (4)

Q14. The most important toxic potential with primaquine is _____ related haemolysis, methemoglobinemia, tachypnoea and cyanosis. (4)

Q15. _____ sensitivity can occur with saquinavir. (5)

Q16. The adverse effect of _____ dystrophy is least likely with abacavir. (4)

Q17. Fluoroquinolones are known to produce ____ toxicity in the form of dizziness, headache, restlessness and anxiety.(3)

Q18. Patients belonging to_____ age group are at a greater risk of developing bone marrow toxicity from cotrimoxazole. (5)

Q19. Toxicity of zidovudine is mainly due to partial inhibition of cellular mitochondrial _____ polymerase Ý leading to anaemia and neutropenia. (3)

Q20. The most prominent adverse effect of bortezomib, used in the treatment of multiple myeloma, is peripheral ____.(10)

Q21. The adverse effects of Interferon ? include _____ like symptoms.(3)

ALPHABET 'H' PUZZLE

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

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

1 H									
2	H								
3		H							
4			H						
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6					H				
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9								H	
10									H

1. During treatment with this topical antifungal drug, irritation, pruritus, burning sensation and sometimes exacerbation of the lesion occurs, especially on the foot if occlusive footgear is worn.
2. This live attenuated vaccine affords protection from the disease for 10 years after its single dose, but is contraindicated within one month of measles vaccination and in those with lymphocytopenia.
3. The incidence of optic neuritis by this antitubercular drug is proportional to its dose i.e. seen in 15% patients receiving 50 mg/kg/day, 5% patients receiving 25 mg/kg/day and less than 1% patients receiving 15mg/kg/day.
4. When a drug is terminated suddenly, the appearance of this syndrome is the only actual evidence of Physical Dependence, and the symptoms tend to be opposite to the effects produced by the drug.
5. When given in full therapeutic dose, the triad of dose-related toxicity seen with Quinine is _____, hypoglycemia and hypotension.
6. In post operative period, Meperidine is preferred over other opioids due to its capacity to reduce shivering, which is a common problem during emergence from _____.
7. Torsades de pointes type of cardiac _____ is the major toxicity (up to 6%) seen with Ibutilide, which requires immediate cardioversion in affected patients.
8. Concurrent administration of this antimalarial drug with drugs prolonging QT interval, like Astemizole, Phenothiazines etc. may increase the risk of cardiac conduction defects.
9. Peripheral sensory _____ is the most serious dose and duration dependent adverse effect seen in 10-30% of patients of Multiple Myeloma treated with Thalidomide.
10. No injectable drug should be added to the infusion, as being incompatible with many drugs, this colloidal plasma expander can precipitate allergic reactions.

ALPHABET 'H' PUZZLE:

1. Haloprogin 2. Chickenpox 3. Ethambutol 4. Withdrawal 5. Cinchonism 6. Anesthesia 7. Arrhythmia 8. Artemether 9. Neuropathy 10. Hetastarch

---

CROSSWORD ANSWERS

(1) AGRANULOCYTOSIS (2) GLUCOSE (3) LUNG (4) GLOVE (5) THROMBOCYTOPENIA (6) MYCOPHENOLATE (7) FEVER (8) CONVULSIONS (9) CARDIOTOXICITY (10) ANTIHISTAMINICS (11) RENAL (12) CHF (13) LONG (14) DOSE (15) PHOTO (SENSITIVITY) (16) LIPO (DYSTROPHY) (17) CNS (18) ELDER (19) DNA (20) NEUROPATHY (21) FLU

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

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