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LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

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Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

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From the Editor's Desk

Dear Friends and Colleagues,

It is truly our privilege to present to you the August issue of the "Bulletin on Adverse Drug Reactions".

You are aware that ADR monitoring is not only related to pharmaceutical drugs but it also includes safety monitoring for blood and blood products. This is dealt under a separate programme of pharmacovigilance called as Haemovigilance. The first article in this issue gives an overview on this topic. There are a number of other related aspects to this topic and will be dealt with in the subsequent issues.

We have also made a small change in our section of Summary of ADRs. We have analyzed the same and presented the data in easy chart form for your quick review and may also be used for comparison with the ADR trends in your institute.

I am also happy to inform you that we are receiving articles from many other medical colleges and we are delighted to include their case study and review article in this issue.

I hope the readers find all the section of this bulletin interesting and informative.

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

Thank you

Dr. Sudhir Pawar

HAEMOVIGILANCE: A GLOBAL PERSPECTIVE

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Introduction

Blood transfusions are used in a variety of medical conditions to replace lost components of the blood. Transfusion of blood and blood products is not without risks as it can lead to complications. Haemovigilance is thus important as it is a tool to improve the quality of the blood transfusion chain, primarily focusing on safety. The word 'haemovigilance' is derived from the already existing term pharmacovigilance. The pioneer work on haemovigilance started in France in 1991, with a set up of monitoring systems by Blood Transfusion Committees in 1992.[1]

Definition

According to the International Haemovigilance Network (IHN), 'Haemovigilance' is defined as 'a set of surveillance procedures covering the entire transfusion chain from the collection of blood and its components to the follow-up of its recipients, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence.[1] Haemovigilance also focuses on complications in donors related to blood donation, "near-miss events", registration of unwanted events and further action to be taken to prevent adverse consequences.[1] Haemovigilance is applicable to transfusion of whole blood and also the labile blood components used for transfusion.

Types of Blood products:

Early transfusions used whole blood, but modern medical practice commonly uses components of the blood. The list of some commonly used blood products is given below.

Blood Products used in transfusion:

- Packed Red blood cells
- Whole blood
- Platelets

- 4% Albumin
- 20% Albumin
- Fresh frozen plasma
- Cryoprecipitate
- Intravenous Immunoglobulin
- Human prothrombin complex.

Incidences of Adverse Drug Reactions in Recipients:

There are many different types of transfusion reactions, which can be classified in several ways according to their occurrence [acute (< 24 h after transfusion) and delayed (> 24 h after transfusion)], and according to the pathogenesis and / or symptoms.[1] According to their pathogenesis, adverse reactions can be divided in infectious and noninfectious adverse reactions.

Infectious ADRs	**Acute**	Bacterial contamination of the blood component
	Delayed	Viral (e.g. hepatitis B/C, HIV) or parasitic (e.g. malaria) transmission.
Non-Infectious ADRs	**Acute**	Acute haemolytic transfusion reactions (AHTR), Febrile non-haemolytic transfusion reactions (FNHTR), Allergic reactions including anaphylactic reactions, Transfusion associated acute lung injury (TRALI), Transfusion-associated circulatory overload (TACO), Hypotensive reactions hyperkalemia
	Delayed	Delayed haemolytic transfusion reactions (DHTR), Delayed serological transfusion reactions (DSTR), Post-transfusion purpura (PTP), Transfusion-associated graft versus host disease (TAGVHD) Haemosiderosis

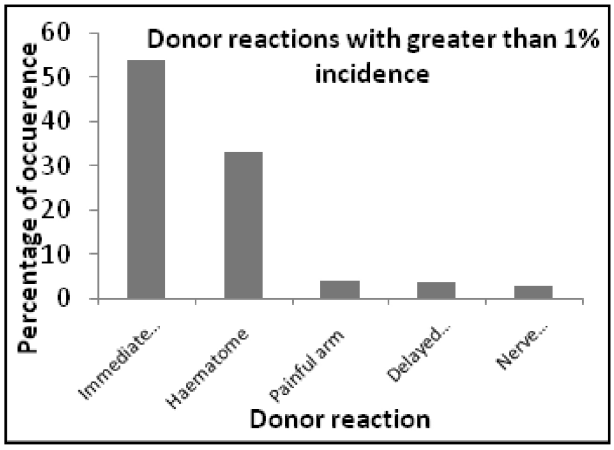
With stringent protocol for blood collection, testing and transfusion the incidences for transfusion related ADRs particularly the infectious type has reduced over a period of time. Data from a recent Indian study on transfusion related ADRs found that allergic/ anaphylactic reactions comprised 50% and febrile reactions 43.7% of the total ADRs.[2]

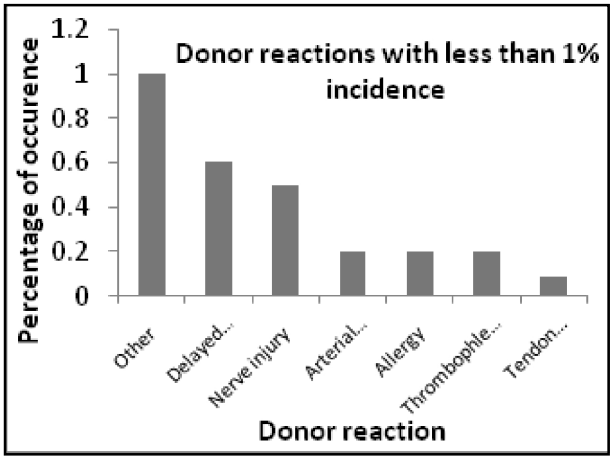
Donor Complications:

The adverse events occur not only in the recipients but also in the donors. Adverse reactions in a donor are called complications, because both the setting and the etiology are quite different from those in a recipient. They are classified as local reactions related to needle insertion (vessel injuries, nerve injuries, other), general reactions (vasovagal immediate and delayed type) and

some other rare complications[1] as given in Figure 1.

Figure 1: Percentage of donor complications of total 1,82,470 blood donations reported in New Zealand Blood Service: Seventh Annual Haemovigilance report New Zealand; 2011[3]





Need for Haemovigilance:

The main aim of haemovigilance is to detect and analyse all untoward effects of blood transfusion and to prevent recurrence, thus improving the safety of blood transfusion. However, it also extends to the following areas:[1,3,4]

- Haemovigilance implies methods for identifying errors, adverse events and reactions including alert systems, investigation of complaints, traceability systems, notification systems and audits of practice.
- It includes the identification, reporting, investigation and analysis of adverse reactions and events in recipients and blood donors as well as incidents in manufacturing processes and, eventually errors and "near-misses". Near-miss events includes those which are discovered before the start of the transfusion (wrong product issued, red cells almost transfused to wrong patient, etc.).
- It forms an integral part in assessing quality and safety of blood products and the overall transfusion process.
- Reporting the adverse reactions in a timely manner can ensure effective risk management and can help target improvement efforts and system changes to reduce the likelihood of injury to future patients.

Haemovigilance Milestones:[5]

Since its inception, the concept of Haemovigilance has progressed a long way with many committees established and activities undertaken. Few milestones are listed below.

YEAR	EVENT
1993	French Haemovigilance system established by Transfusion Safety Act.
1996	United Kingdom SHOT scheme formally established
1999	The National Haemovigilance Office was officially launched by the Minister for Health and Children in November 1999 in the Republic of Ireland
2002	European Union (EU) Directive 2002/98/EC identifies requirement for haemovigilance systems.
2002	European Haemovigilance network established, collaborative professional activities including common definitions.
2005	EU Directive 2005/61 implements formal requirement for haemovigilance schemes in member states.
2008	US Biovigilance initiative announced.
2012	National Institute of Biologics; India starts a centralized haemovigilance programme under overall ambit of Pharmacovigilance Program of India (PvPI), which is being coordinated by Indian Pharmacopoeia Commission (IPC)

What and When to report:

- All adverse events irrespective of their causality should be reported.
- Details of the transfusion reaction along with details of the patient and the blood product should be obtained and imputability (Causality assessment) scores related to the reaction should be assessed.
- The following details should be obtained:
    - o Patient details: Name, age, sex, blood group, Rh factor, and donor units.
    - o Blood product details: Product/Component name, total volume transfused, manufacturer, batch no. and expiry date, transfusion start and completion time and transfusion rate.
    - o Clinical observation: General condition; Pre, during and post transfusion.[4]
- Adverse events such as near misses and errors with or without clinical implications occur much more often than adverse reactions. The advantage of reporting adverse events is

that these reports offer learning opportunities, improve awareness and it also improves the existing systems. However it requires more resources.

- Adverse events in recipients as well as donors should be reported. Donor vigilance may contribute to reduced complications, lead to increased frequency of donation and improved donor satisfaction.
- Based on European Union regulations, each EU member state has to provide the European Commission annually with product-related incidents. In principle, haemovigilance systems should cover the whole transfusion chain.[1]

International Guidelines:

The **European Haemovigilance Network** was founded in 2002 in France. This later became The **International Haemovigilance Network (IHN)** in 2009. It includes European countries like Germany, Spain and Italy to other countries like Japan, Canada, Australia, New Zealand and USA.

The **IHN** and **ISBT (International Society of Blood Transfusion)** working party on haemovigilance are working together to develop standard definitions on adverse reactions, adverse events and near-miss events, nature of the event, severity of the event and imputability (Causality of the reaction).[5] The list of few international guidelines is as follows:

- **Serious Adverse Blood Reactions and Events (SABRE):** Deals with a user guide for mandatory haemovigilance reporting in the UK. The SABRE report then prompts access to report to the SHOT (Serious Hazards of Transfusion).[6]
- The **US Biovigilance-Haemovigilance Module** has developed guidelines for Standard definitions and criteria for categorising and reporting adverse reactions and incidents since February 2010.[5]
- **South African National Blood Service (SANBS)** is a member of the International Haemovigilance Network and one of the key objectives of this working party is "To develop a global haemovigilance, surveillance and alert network, which would provide a platform to countries for sharing key information on blood safety and availability issues and build a timely response in addressing emerging threats".[7]

The **'Haemovigilance program of India'** is run by the **National Institute of Biologics** under the aegis of **Indian Pharmacopeia Commission.** It is also included under the **Pharmacovigilance program of India** since November 2012.

The Haemovigilance programme of India is working towards becoming a part of the International Haemovigilance Network (IHN) which presently has 28 countries as its members and provides a global forum for sharing best practices and benchmarking of Haemovigilance data.

The National Institute of Biologics (http://www.nib.gov.in/haemovigilance.html) runs the Haemovigilance program that provides **Transfusion Reactions Reporting Form (TRRF)** for Blood and Blood Products and Guidance Document for reporting serious adverse reactions in blood transfusion service. It also provides the ***Haemo-vigil software*** for uploading blood transfusion reactions with an instructions manual for the same. The guidance document deals with the current list of hospitals and medical colleges enrolled under the Haemovigilance Program, documentation of serious transfusion related reactions, role of nursing staff and physicians in filling the TRRF with respect to the patient, blood product and reaction related details, maintaining privacy of the data. The guidance document also mentions the role of National Coordinating Centre for PvPI, NIB, Dept. of Transfusion reaction, CDSCO and Technical Associates appointed at the ADR monitoring centres.[4]

Conclusion:

Haemovigilance is a tool to improve the quality of the blood transfusion chain, primarily focusing on safety. It also highlights the importance of the role of effective education and training to implement safe transfusion. Various Haemovigilance programs running worldwide have been able to contribute to better transfusion practices and predicting and avoiding certain adverse transfusion reactions. Moreover, WHO initiatives have been established to support developing countries in setting up National Haemovigilance Systems. The goal of these initiatives is to strengthen and expand national systems for data collection, management, risk assessment, surveillance and vigilance for policy decisions and programme planning for safe blood transfusion in these countries.

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20 Document.

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DRUG INDUCED NEPHROTOXICITY

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Drug-induced Nephrotoxicity is a common condition and is responsible for a variety of pathological effects on the kidneys. It can be defined as renal disease or dysfunction that arises as a direct or indirect result of exposure to drugs.[1] The incidence of drug-induced nephrotoxicity has been increasing with the increasing use of drugs and with their easy availability as over-the-counter medications especially Non- Steroidal Anti-Inflammatory Drugs (NSAIDs), antibiotics etc.[2]

Drug-induced acute renal failure (ARF) accounted for 20% of all ARF cases in an Indian study.[3] Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 %, due to higher incidence of diabetes and cardiovascular diseases compelling them to take multiple medications. Although renal impairment is often reversible, it may still require multiple interventions and hospitalization.[4]

Most of the drugs which are found to be nephrotoxic, exert toxic effects by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Knowledge of offending drugs and their particular pathogenic mechanisms of renal injury are critical for recognizing and preventing drug-induced renal impairment.[1]

Risk factors

We are exposed to a variety of potential nephrotoxic substances on a rather frequent basis in the form of therapeutic agents, while most of them are prescribed, many others are available to the general population as over-the-counter medication. Herbal remedies, natural products, and nutritional supplements that are widely available at most health food stores are also potentially nephrotoxic. More concerning are the harmful contaminants and chemicals contained in the products that are not listed on the label[5, 6]. Some of the risk factors are listed in Table No.1.

Table 1: Risk factors that increase renal vulnerability to Nephrotoxins [7]

Susceptible kidney	Advancing age, prior renal insufficiency, and renal transplantation.
Co morbid condition	Diabetes mellitus, multiple myeloma, SLE, dehydration, sepsis, shock, vascular disease. etc.
Sodium retaining state	Cirrhosis, CHF, Nephrotic syndrome. etc.
Electrolyte disturbance	Metabolic acidosis, hypokalemia, hypomagnesemia, etc

Drugs Causing Nephrotoxicity[3]

Some drugs having a potential to cause nephrotoxicity are listed in Table no 2.

Table 2: Drug Causing Nephrotoxicity

Nephrotoxic Agents (Class)	Examples
Antibiotics	Aminoglycosides, Sulfonamides, Amphotericin B, Foscarnet, Rifampicin, Tetracycline, Acyclovir, Pentamidine, Vancomycin.
Antineoplastics & Immunosuppressants	Cisplatin, Methotrexate, Mitomycin, Cyclosporine, Ifosphamide, Zoledronic Acid, Sirolimus, Calcineurin Inhibitor
Analgesics	NSAIDS, Selective COX-2 Inhibitors, Phenacetin, Mesalamine
Herbals	Aristolochic Acid, Ephedrasp Glycyrrhizasp, Datura, Taxus Celebica
Contrast Agents	Radiocontrast, Gadolinium 44
Anti Hypertensives	Angiotensin converting enzyme inhibitors (ACE-I), Angiotensin II receptor blockers (ARBs) [under predisposing conditions]
Anti Hyperlipidemics	Statins, Gemfibrozil
Others	Heavy Metal Poisoning, Proton pump inhibitors (PPIs), Cocaine, Heroine, Laxatives, Chinese Herbs, Gold, Haloperidol, Allopurinol, Phenytoin, Quinine

Features of some common nephrotoxic drugs are as follow:

Aminoglycosides (AMG)

AMG are prototype drugs having nephrotoxicity as major side effect. Nephrotoxic risk increases with Na+ and K+ depleted state, renal ischemia, increasing age, liver disease, concomitant use of diuretics and nephrotoxic agents and with duration of therapy (50% when given for 14 days or more).[9]

(Relative toxicity: Neomycin> Gentamicin> Tobramycin> Netilmicin >Amikacin> Streptomycin)

Clinical Features

It presents as acute tubular necrosis, showing features such as non-oliguric ARF, proximal tubular dysfunction, proteinuria, glycosuria, hypokalemia, hypocalcaemia and hypomagnesemia.[8]

Mechanism of Toxicity

AMG gets actively concentrated in the renal cortex and proximal tubular cells. It then binds to lysosomes, leading to formation of myeloid bodies/secondary lysosomes, which is believed to interfere with the phosphatidyl-inositol pathway. Thus momentary high drug concentrations as achieved immediately after intravenous injection result in saturation of the uptake mechanism. Hence, multiple dosing is more deleterious than single dose bolus injection.[8, 9]

Prevention and Precautions

To prevent aminoglycoside-induced nephrotoxicity in clinical practice, the following points need emphasis[10-18]

- AMG nephrotoxicity is directly dependent on the dose and duration of therapy. Thus, nephrotoxicity is more likely to occur if large doses are given over prolonged periods, or usual doses are given to patients with underlying renal disease. Hence use the lowest dose and shortest possible course of therapy.
- Use AMG as a once daily dose rather than divided dose especially in high-risk individuals.
- Serial monitoring of renal function (serum creatinine every other day) should be carried-out for early detection of nephrotoxicity.
- Avoid combination of aminoglycosides with other potential nephrotoxins (amphotericin, cisplatin, diuretics, contrast material, etc.).
- During AMG therapy, ensure adequate hydration especially in the elderly.

NSAIDS

Over-the-counter availability of these drugs puts a large population at risk. Higher than usual dose, volume depletion, congestive heart failure, nephrotic syndrome, cirrhosis particularly with ascites, pre-existing renal disease and age > 65 years are the factors which increases its toxicity.[4, 19]

Clinical features

It presents with oliguric ARF, hyperkalemia, sodium and water retention, hypertension, heavy proteinuria, fever, rash, eosinophilia etc. Classically seen with consumption of any NSAID for over 20 years, especially with aspirin.[19]

Mechanism of toxicity

Nephrotoxicity is due to delayed hypersensitivity response, with shunting of arachidonic acid metabolites to lipoxygenase pathway. Leukotrienes mediate chemotaxis for WBCs leading to cellular infiltrates (T-cell and eosinophils). Analgesic nephropathy is a chronic interstitial nephritis associated with capillary sclerosis of the vessels of renal pelvis and

renal papillary necrosis followed by calcification. It is due to medullary ischaemia induced by loss of vasodilatory effects of prostaglandins on vasa recta.[19]

Prevention and Management

- Recognize the risk (situational factors) for nephrotoxicity and take corrective action to minimize nephrotoxic potential.
- Avoid chronic (habitual) use of NSAIDs.
- Avoid combinations of analgesics and monitor use of drugs when consumption is mandatory.
- All available analgesics have a nephrotoxic potential and should be carefully considered before usage.
- Early intervention can prevent its progression. Stop NSAIDs, if patients develop any evidence of renal insufficiency and ensure adequate hydration before and during therapy.

Cisplatin

Nephrotoxicity is the major side effect of this drug, but it is cumulative and dose-related (> 25-33 $mg/m^2/wk$).[18]

Clinical features

Acute tubular necrosis or tubulointerstitial disease with symptoms of azotemia and fluid loss. Biochemical tests usually show tubular proteinuria with prominent tubular casts. Increase in blood urea nitrogen (BUN), serum creatinine and low serum Na^+, K^+, Mg^{+2}, Ca^{+2} occur due to proximal tubular damage especially at S3 portion.[20]

Prevention and Management[18]

- Prevention of toxicity is by avoidance of other nephrotoxic drugs like AMG.
- Diuresis should be started immediately after drug administration; maintaining urine output of 100 mL/hr, can decrease nephrotoxicity. Mannitol may be helpful.
- When administered with hypertonic saline, cisplatin is better tolerated.
- Sodium-thiosulfate i.v. should be added if > 200 mg/m2 of cisplatin is used[3]
- Anti oxidant drugs causing free radical scavenging may play an important role in renoprotection.[18]

Cyclosporine(CS-A)

Acute reversible & chronic irreversible nephrotoxicity are the two forms of cytotoxicity known

with cyclosporine.

Acute form

It is seen mostly in transplant recipients manifesting as acute renal failure, due to vasoconstriction and also due to vasospastic products of arachidonate metabolism specially thromboxane-A2.[4, 19]

Clinical features

Sudden onset hypertension within weeks of transplant. Urine volume and Na^+ excretion are preserved but GFR and renal plasma flow are decreased with no change in the filtration fraction along with hypertension. [19]

Prevention and Management

- Rapid improvement seen with reduction of dose. GFR progressively reaches to baseline as blood levels of CS-A fall to trough levels.
- Calcium channel blockers provide protection and ameliorate early & long term cyclosporine toxicity and improve graft survival.
- Prostaglandin analogue, misoprostol also helps in reversal of vasoconstrictive effects.

Chronic form

CS-A nephrotoxicity typically manifests after one year; mimics chronic rejection.

Clinical features

Hypertension, mild proteinuria, rarely hematuria, with marked decline in GFR. Haemolytic uraemia syndrome is a rare arteriopathy with severe renal impairment.

Mechanism of toxicity

It is due to obliterative arteriolopathy, tubular atrophy and interstitial fibrosis. Tubular atrophy with diffuse fibrosis may appear as stripes (striped interstitial fibrosis-characteristic of CS-A). Severe lesions are seen in patients with cumulative dose of more than 1.8 g/kg over six months, associated with thrombosis in renal microcirculation along with thrombocytopenia and haemolytic anemia.[3]

Prevention and Management [3,4,19]

- Start CS-A on 5th day post-surgery at the lowest dose with upward titration to reach ideal trough concentration in 1-2 months with meticulous monitoring of Serum Creatinine and blood pressure.
- Calcium channel blockers are beneficial in initial stages of acute hypertension.

- Avoid drugs such as cimetidine, ranitidine, diltiazem, verapamil, erythromycin, metoclopramide, anabolic steroids and oral contraceptives which raise CS-A concentration.
- Micronized forms of CS-A are beneficial as total dose required is less and also lower nephrotoxicity.

Amphotericin-B (Am-B)

It contains hydrophilic as well as lipophilic regions. Risk factors for toxicity remain the same as for any toxic nephropathy but sodium deficiency is important especially in patients on diuretics, Those with cumulative doses of 3-4g have greater risk.[9, 18]

Clinical features

Azotemia with inability to concentrate urine, increasing the urinary loss of K^+ and Mg^{+2}.

Mechanism of toxicity

It easily mingles with cellular membranes, disrupts them & damages the endothelium, which not only increases the permeability but also causes vasoconstriction of afferent and efferent arterioles, decreasing GFR and leading to oliguric ARF, which may progress to tubular toxicity.[4]

Prevention and Management[4]

- Prevention is the key in managing these patients.
- Dopamine agonist and salt supplementation may exert protective role.
- Liposomal Amphotericin B reduces the renal toxicity. A higher total dose of 5 mg/kg/day compared to a maximum of 0.5 to 1.5 mg/kg/day with hydrophilic Am-B can be achieved without risking the renal tissue.

Biomarkers of drug induced kidney damage[20]

Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. The existing biomarkers such as serum creatinine and blood urea nitrogen, to monitor renal safety are insensitive and show limited specificity. In the past decade, several efforts have been undertaken to identify better markers of nephrotoxicity using genomics and proteomics approaches. These new markers are more sensitive and can detect damage earlier than BUN and creatinine levels. Some of these biomarkers are mentioned in table 3.

Table 3: Biomarkers of nephrotoxicity [20]

Biomarkers	Source	Significance
Albumin	Glomerulus PCT	Pathological urinary excretion of albumin >20 mg/l after 100- 150 mg/m2 Elevated in response to cisplatin, gentamicin, carbapenems, thioacetamide, hexachlorobutadiene
ß2 microglobulin	Glomerulus	Increased in response to ochratoxin A, depleted uranium, cisplatin, chlorotrifluoroethylene, 1,1-dichloro- 2,2-difluoroethylene
Cystatin C	Glomerulus PCT	Elevated during chromium nephropathy
Clusterin	PCT, DCT	Increased following renal ischemia, unilateral urethral obstruction or in response to various nephrotoxins, e.g. gentamicin, ochratoxin A, sevoflurane, cisplatin, vancomycin, bacitracin
Kim-1(kidney injury molecule)	PCT,DCT	Elevated in response to gentamicin, mercury, chromium, cadmium
L-FABP (fatty acid binding protein-liver type)	PCT	Levels may predict adverse outcome (death); increased urinary levels in acute liver injury may limit specificity

(PCT- Proximal Convoluted Tubule, DCT-Distal Convoluted Tubule)

Conclusion

Emerging data demonstrate that even small reversible changes in renal function in critically ill patients are associated with adverse outcomes. Medication-related renal dysfunction is common in critically ill for a number of possible reasons, including increased patient complexity with other coexistent risk factors for AKI (e.g., sepsis, hypotension) and polypharmacy. Overestimation of pre-existing renal function, particularly in elderly patients; and inaccurate and insensitive methods of assessing acute changes in renal function can make early diagnosis difficult. Surprisingly little information is available to guide us with respect to avoiding these complications in critical illness.

"Always be Precautious and Preventive"

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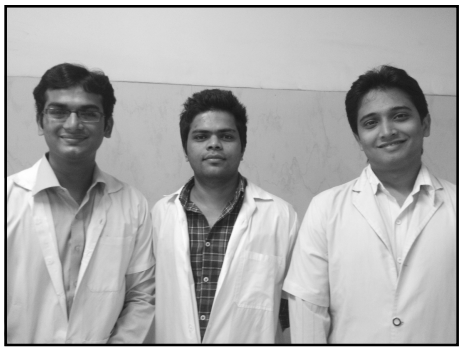
ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED (March 2013 - June 2013)



Compiled by Smruti Mulgaonkar*, Dr Swati Patil, Dr Neha Kadhe***, Dr Sudhir Pawar******

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Total cases reported: 94

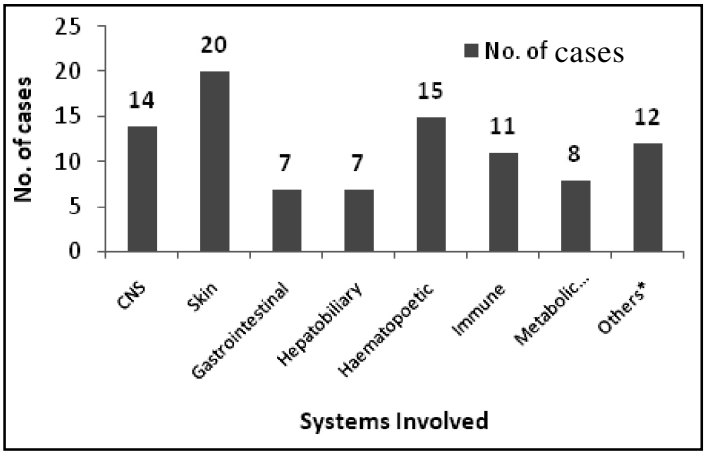
I. Age and Gender distribution

Age groups	Number of patients	Males	Females
<3yrs	11	4	7
3 - 17yrs	23	14	9
18 - 44yrs	28	14	14
45 - 60yrs	15	4	11
> 60yrs	17	8	9
Total	94	44	50

II. Seriousness of reactions reported

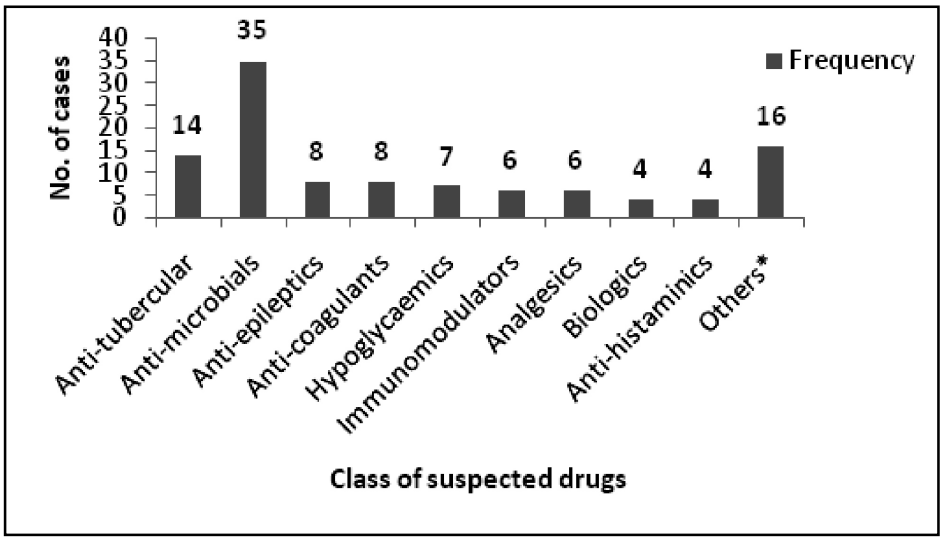
Seriousness of the reactions	Number of cases (Approx %)
Yes	81(84)
No	13 (14)

III. System wise distribution of the adverse drug reaction:



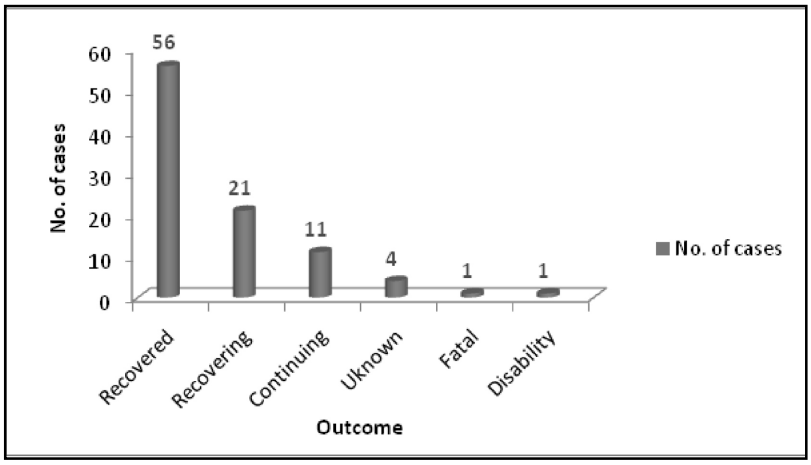
*Others include cases involving cardiovascular, endocrine, ocular and urinary system.

IV. Class of Suspected Drugs:

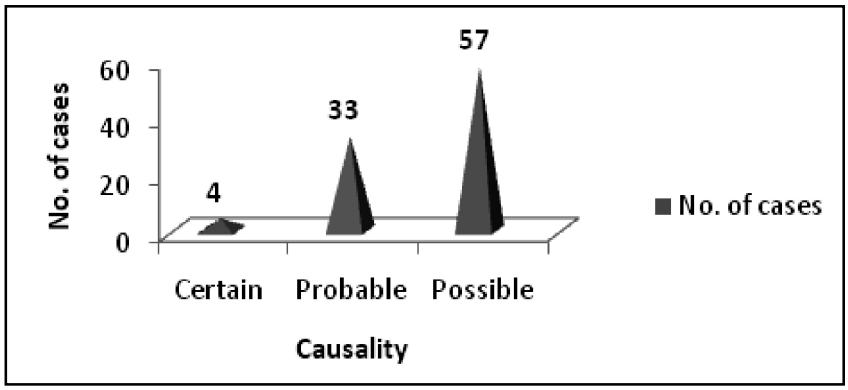


*Others include drug classes like Steroids, haematinics, sedatives, anti-retrovirals, anti-hypertensives, anti-leprosy and anti-cholinergics.

V. Outcome of the reaction



VI. Causality assessment (WHO causality assessment scale)



EVALUATION OF A CASE

Allopurinol induced Toxic Epidermal Necrolysis (TEN): A rare adverse drug reaction

Dr. Ranjana Kale*, Dr. Satish Bahekar, Dr. Anil Rapelliwar***, Dr. Sushil Kumar Varma******

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Case history

A 32-year-old woman presented to the emergency unit with the symptoms of fever, extensive erythematous rash with slight epidermal detachment all over the body, oral lesions, and swollen eyes with watery discharge causing impairment in vision. She was having difficulty in deglutition and talking since 3 days and aggravated since 12 hours. She was immediately referred to dermatology ward and hospitalized.

According to the history given, she is a case of post-thyroidectomy hypothyroidism since five years and regularly on tablet Levothyroxine sodium (100mcg per day). Ten days prior to admission, she visited her orthopedician for the complaints of joint pain and was diagnosed as gout with increase in serum uric acid level for which she was prescribed tablet Allopurinol (300mg per day). On day 8, she suffered from mild fever and mild pruritic rash over her face which rapidly progressed into erythematous rash and in the next two days it spreads over the body. Oral lesions also started to develop in the form of ulcerations and crusts over oral mucosa leading to difficulty in deglutition and even talking. Both eyes were swollen with continuous discharge leading to impairment in vision.

On general examination, patient was having low grade fever but was conscious and well oriented. Vital parameters like heart rate, blood pressure etc. were within normal limits.

On cutaneous examination, her face was puffy. Extensive erythematous rash associated with slight epidermal detachment was present over face, neck, chest region, back and abdomen. Intensity of rash was less over the legs and soles. More than 70% of body surface area was involved. Nickolsky sign was absent. Oral examination revealed oedematous lips with ulcerated and crusted oral mucosa. Tongue was swollen and excessive salivation was present. Ocular examination revealed excessive bilateral swollen eyelids with erosions, conjuctival congestion leading to redness and excessive serous watery discharge. Diagnosis of TEN was obvious on clinical examination. Biopsy of lesions was not needed.

All the necessary blood investigations like complete blood count (CBC), blood sugar, liver function tests (LFT), kidney function tests (RFT) and urine examination were done. Significant findings were increase in WBC count and eosinophil count and a decrease in platelet count. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were raised. Rest of blood parameters and urine examination were within normal limits.

In view of clinical examination and investigations, diagnosis of TEN was confirmed. Tablet Allopurinol was immediately stopped. Further, in-hospital management included pain control with analgesics, adequate intravenous hydration, injectable antibiotics and corticosteroids, skin care with local antiseptics, mouth care with gargles and oral gels and eye care with eye drops and ointments. With all these measures, patient's condition started to improve gradually. On day 5, after stopping Allopurinol, deranged blood parameters also started coming to normal range.

Discussion

Adverse drug reactions (ADRs) comprises of a very serious issue in modern day clinical practice. Adverse drug reaction (ADR) is defined by World Health Organization as "A response to a drug, which is noxious and unintended and which occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function".[1] With the introduction of vast amount of new drugs entry in market everyday and ever-changing prescription patterns, this risk is always on. The same principle applies to cutaneous adverse drug reactions (CADRs). These are always distressing to patients and treating physicians.

CADRs are the most frequent of all manifestations of drug sensitivity. Serious CADRs are uncommon, but can result in conditions like Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and exfoliative dermatitis sometimes proving fatal.[2] SJS and TEN are severe manifestations of cutaneous hypersensitivity reactions affecting approximately 0.4 to 6 persons per million populations each year.[3] Mortality rate of TEN varies between 16-30%. [4] Most of the cases of TEN occur mainly due to the drugs like antiepileptics, NSAIDs, sulphonamides, quinolones, and allopurinol.[5-6]

Cutaneous adverse drug reactions are common, comprising of around 10-30%.[7] SJS and TEN are the most dangerous of these leading to substantial amount of morbidity and mortality. The term TEN was first introduced by Lyell in 1956 to describe four patients with a syndrome featured by extensive mucosal membrane involvement leaving the skin surface looking scalded.[4] By definition, if the epidermal involvement is less than 10% of body surface area, it is termed as SJS. If it is more than 30%, it is termed as TEN and if in between, termed as SJS-TEN overlap.[5] In this patient, body surface area involved was more than 70% leading to the diagnosis of TEN. TEN

is an acute and life threatening skin disorder of unknown pathophysiology. Majority of the cases are almost and always due to some drugs.[8]

In the present case, there is a reasonable time relationship between the intake of the drugs (Allopurinol) and the occurrence of the ADR, the ADR is unlikely to be attributed to disease or other drugs and the patient recovered on stopping the offending drug (dechallenge positive). Based on the above and the lack of rechallenge, the ADR is considered as "Probable" for Allopurinol based on the WHO assessment scale for causality.

In this case, patient was taking tablet allopurinol since last 10 days. Allopurinol, a xanthine oxidase inhibitor, is an effective and widely prescribed uric acid lowering agent. SJS and TEN are rare skin side effects of allopurinol, most common association found in Europe and Israel.[9] This drug has been mentioned as a causative agent for TEN in various medical literatures. [5, 6,10,11,12] Cutaneous adverse drug reactions with this drug are common; affecting 2% of patients prescribed.[13]

Drug exposure and resulting hypersensitivity reactions is the main cause of majority of drug induced TEN cases.[9] The symptoms started after 7 days of the drug intake. M. Mockenhaupt et al.[14] in their study proved that, SJS and TEN most often begins between the time period of 4 to 28 days after allopurinol use. Though, exact pathophysiological basis behind allopurinol induced TEN is difficult to explain, one possible mechanism can be postulated on the background of hypersensitivity to allopurinol in some individuals. It can be attributed to complex interaction of many factors like immunological and genetic factors.[15] Also, in some cases, it can be possible because of accumulation of oxypurinol, an active metabolite of allopurinol.[15] It has a half life of 14-20 hours in normal patient. Raised levels of this metabolite have been found to be correlated with risk of developing hypersensitivity to allopurinol ultimately leading to TEN. Keiko Maekawa et al.[16] in their study suggested that, subjects with HLA-B* 5801 are genetically at high risk for the development of allopurinol induced SJS and TEN. So, involvement of genetic component in the cases of drug induced TEN can't be ignored. Improvement in the symptoms of patient on allopurinol withdrawal confirmed the association of this drug with occurrence of this ADR.

Conclusion

TEN was triggered in this case by otherwise normal dose of allopurinol and improvement was seen after withdrawal. It is otherwise commonly prescribed, useful and safe drug for hyperuricemia and this case report of TEN should not discourage its clinical use. To reiterate, the treating physician should always keep in mind the possible risk of this dangerous condition while prescribing the drug, because at times seemingly innocuous drugs can be the culprit. To

conclude, early diagnosis of adverse drug reaction and immediate withdrawal of the offending drug is essential to avoid extra complications.

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PUBLISHED STUDIES ON ALLOPURINOL AND ADVERSE REACTIONS

Compiled by **Dr Jaisen Lokhande**

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Cutaneous adverse drug reactions to allopurinol: 10 year observational survey of the dermatology department--Cagliari University (Italy).

J Eur Acad Dermatol Venereol. 2012 Nov;26(11):1424-30.

Atzori L, Pinna AL, Mantovani L, Ferreli C, Pau M, Mulargia M, Aste N.

Background: Allopurinol is extensively prescribed for conditions associated with urate excess, despite being responsible for severe cutaneous adverse drug reactions (ADR).

Objective: A cross-sectional survey of allopurinol cases observed at the main Dermatology Department with inpatients facilities in southern Sardinia. (approx 560,836 inhabitants).

Material And Methods: Data collection of all consecutive patients referred for ADR between 2001 and 2010. Causality assessment followed the WHO Collaborating Centre for Drug Monitoring criteria; illness severity score was adopted for toxic epidermal necrolysis (SCORTEN).

RESULTS: Allopurinol was the culprit drug in 84 of 780 cutaneous ADR cases (10.7%; 8.4 cases/year). Mean age was 74 years, 58% of the patients were female, 95% of patients required hospitalization. Clinical forms were maculo-papular eruptions (34 cases), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (31 cases), vasculitis (six cases), Drug Rash Eosinophilia and Systemic Symptoms (DRESS) (three cases), Acute Generalized Exanthematous Pustolosis (AGEP) (three cases), Pityriasis rosea-like eruption (three cases), lichenoid dermatitis (two cases), fixed drug eruption (one case), erythroderma (one case). The indication for allopurinol prescription was asymptomatic hyper-uricemia in 95% of the patients. Twelve patients were under allopurinol dosage adjustment according to creatinine clearance. Final causality assessment was definite for 12% of the cases and probable for the remaining 88%. Full recovery was achieved in 88% of subjects; ten SJS/TEN patients died (12% overall mortality; 32% mortality of the SJS/TEN cases).

CONCLUSION: Considering the populations size of Southern Sardinia, is plausible that 1.5/ 100,000 Sardinian will be affected by allopurinol related ADR per year. Advanced age, and inappropriate allopurinol prescription were the main conditions affecting morbidity and mortality.

Allopurinol-induced hypersensitivity syndrome

Orv Hetil. 2012 Apr 15;153(15):586-91.

Kinyó A, Lakatos A, Varga A, Gyulai R, Varga E, Bata-Csörg Z, Kemény L.

Abstract: Allopurinol is an effective urate lowering drug, which is usually well-tolerated with no adverse effects in most cases, but about 2% of the treated patients develop a skin rash, and patients may experience severe allopurinol-induced hypersensitivity syndrome.

AIMS: The aim of the authors was to summarize and present the clinical manifestations of allopurinol-induced hypersensitivity in patients treated at the Department of Dermatology and Allergology, University of Szeged in order to identify potential associations with this syndrome.

METHODS: Retrospective review of all patients who were referred to the department with allopurinol-induced hypersensitivity syndrome in the last four years.

RESULTS: During four years, 11 patients were treated with allopurinol-induced hypersensitivity syndrome. The average age was 70.3 years. Before the initiation of allopurinol therapy, 36% of patients had already suffered from various degrees of renal impairment, and 72% of them had been taking thiazide diuretics. Cutaneous manifestations were mainly generalized, erythematous, maculopapular exanthemas (9 patients, 82%), and two patients showed signs of erythema multiforme (18%). Asymptomatic hyperuricemia was the indication for allopurinol therapy in all patients.

CONCLUSIONS: Allopurinol-induced hypersensitivity syndrome is a severe, life-threatening disease. Administration of allopurinol should be initiated with clear indications in appropriate dose. Old age, underlying renal impairment and concomitant thiazide diuretic intake should be considered as potential risk factors for developing hypersensitivity syndrome.

Hypersensitivity syndrome during therapy with allopurinol in asymptomatic hyperuricemia with a fatal outcome

Dtsch Med Wochenschr. 2001 Nov 23;126(47):1331-4.

Hammer B, Link A, Wagner A, Böhm M.

History and Admission Findings: A 86-year-old woman with chronic renal failure was treated with allopurinol for asymptomatic hyperuricemia. After one week she developed quickly progressive exanthema, bullous eruptions, epidermolysis, fever of 39.1; C and dyspnoea at rest.

Diagnosis, Treatment And Course: The diagnosis of an allopurinol-induced hypersensitivity syndrome with toxic epidermal necrolysis was made from the history, the typical clinical picture and a skin biopsy. Initial therapy starts with steroids. Because of a lack of clinical improvement therapy was changed to immunoglobulins. In addition, systemic analgesia and cardiocirculatory supportive therapy were given. Because of increasing somnolence and severe pain intubation and controlled artificial ventilation were initiated. Despite intensive therapy progressive multi-organ failure developed and the patient died 3 weeks after start of symptoms.

Conclusions: The life threatening hypersensitivity syndrome with fever, eosinophilia, hepatitis, renal failure and skin eruptions as severe as epidermal necrolysis is the most dangerous complication of therapy with allopurinol. The trigger seems to be oxipurinol, the main metabolite of allopurinol, which particularly accumulates in patients with renal failure and concomitant therapy with thiazides. There is no specific treatment of the disease. The use of allopurinol in patients with asymptomatic hyperuricaemia is not indicated in most cases. Dose adjustment according to the clearance of creatinine is mandatory.

A whole-genome association study of major determinants for allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients.

Pharmacogenomics J. 2013 Feb;13(1):60-9.

Tohkin M, Kaniwa N, Saito Y, Sugiyama E, Kurose K, Nishikawa J, et al.

Abstract :

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are severe, cutaneous adverse drug reactions that are rare but life threatening. Genetic biomarkers for allopurinol-related SJS/TEN in Japanese were examined in a genome-wide association study in which Japanese patients (n=14) were compared with ethnically matched healthy controls (n=991). Associations between 890 321 single nucleotide polymorphisms and allopurinol-related SJS/TEN were analyzed by the Fisher's exact test (dominant genotype mode). A total of 21 polymorphisms on chromosome 6 were significantly associated with allopurinol-related SJS/TEN. The strongest association was found at rs2734583 in BAT1, rs3094011 in HCP5 and GA005234 in MICC (P=2.44 × 10(-8); odds ratio=66.8; 95% confidence interval, 19.8-225.0). rs9263726 in PSORS1C1, also significantly associated with allopurinol-related SJS/TEN, is in absolute linkage disequilibrium with human leukocyte antigen-B*5801, which is in strong association with allopurinol-induced SJS/TEN. The ease of typing rs9263726 makes it a useful biomarker for allopurinol-related SJS/TEN in Japanese.

REGULATORY UPDATE

Series of FDA Drug Safety Communication

Compiled by **Dr Jaisen Lokhande**

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FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil

The U.S. Food and Drug Administration (FDA) has approved changes to the labels for olmesartan medoxomil which can cause intestinal problems known as sprue-like enteropathy.

The enteropathy may develop months to years after starting Olmesartan with symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The drugs should be discontinued if no other cause of the above symptoms is found and therapy with another antihypertensive started. Sprue-like enteropathy has not been detected with other angiotensin receptor blockers (ARB) than olmesartan.

FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. [homepage on the Internet]. 2013 [cited 2013 Jul 25]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm359477.htm

FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after the zolpidem CR formulation

The U.S. Food and Drug Administration (FDA) approved label changes regarding new dosing for zolpidem because of the known risk of next-morning impairment with these drugs.

FDA warns that patients on zolpidem extended-release either 6.25 mg or 12.5 mg should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities.

The updated label also includes dosing recommendations:

- initial dose of immediate-release zolpidem - 5 mg for women and either 5 mg or 10 mg for men.
- initial dose of zolpidem extended-release - 6.25 mg for women and 6.25 or 12.5 mg for men.

- if doses ineffective (5 mg for immediate-release, 6.25 mg for extended-release) - increased to 10 mg for immediate-release products and 12.5 mg for zolpidem extended-release. However, the higher dose can increase risk of next-day impairment of driving and other activities that require alertness.

FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. [homepage on the Internet]. 2013 [cited 2013 Jul 25]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm

FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies

The U.S. Food and Drug Administration (FDA) advises against using magnesium sulfate injection for more than 5-7 days to stop pre-term labor in pregnant women which is an off-label indication. Magnesium sulfate (MgSO4) injection administered longer than 5-7 days may lead to low calcium levels osteopenia or fractures in the developing baby or fetus. The shortest duration of treatment that can result in harm to the baby is not known.

In light of this new safety information, the following is being included to the drug label for Magnesium Sulfate Injection, USP 50%:

- Warning stating that continuous administration of MgSO4 injection beyond 5-7 days in pregnancy can cause low calcium levels and bone changes in the baby.
- Teratogenic Effects section conveying the potential harm to developing babies by changing the Pregnancy Category to D from A which also includes concerns under the new Warning. (Pregnancy Category D means there is positive evidence of human fetal risk, but the potential benefits from using the drug in pregnant women may be acceptable in certain situations despite its risks).
- Labor and Delivery section emphases continuous administration of MgSO4 injection for pre-term labor is not approved and the safety and efficacy for this indication are not established.

FDA Drug Safety Communication: FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies. [homepage on the Internet]. 2013 [cited 2013 Jul 25]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm353333.htm

CROSSWORD

Dr Sharmada Nerlekar*, Dr Abhilasha Rashmi**

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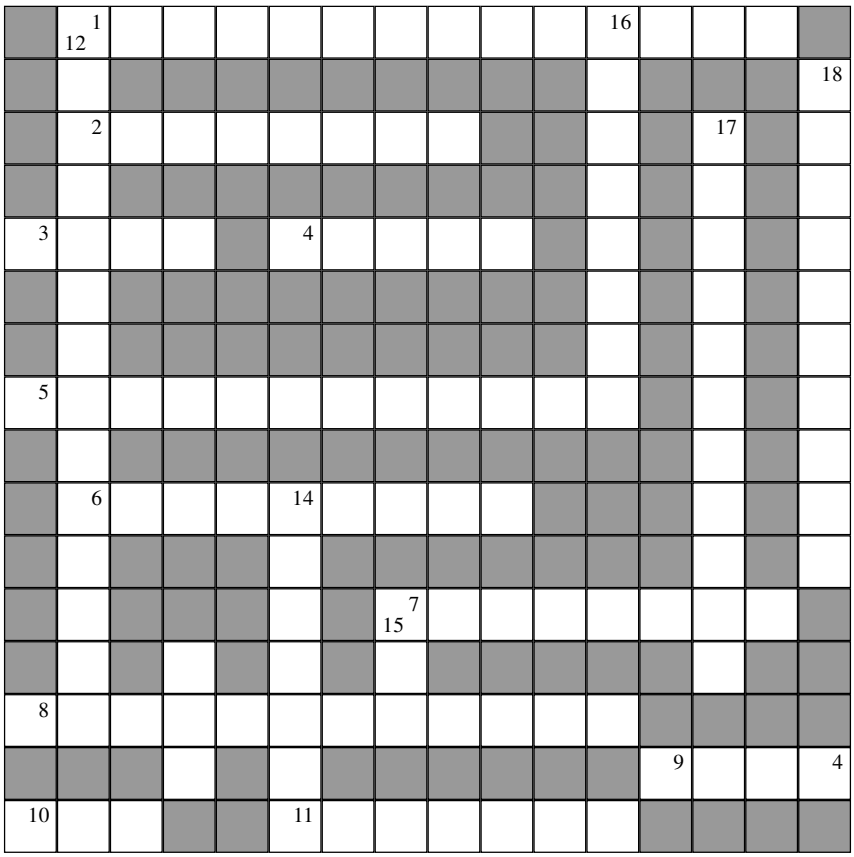

Across

Q1. Elderly are more sensitive to halothane and are more prone to its -------(14).

Q.2. Finasteride on long term use surprisingly increases the risk for----- cancer.(8).

Q.3. Vitamin E interferes with oral absorption of -----(4).

Q.4. Amifostine can be used to prevent----- toxicity due to cisplatin.(5).

Q.5. ----- a platelet inhibitor can cause coronary steal phenomenon in the elderly.(12).

Q.6. ----- hydroxide containing antacids can cause hypophosphatemia.(9).

Q.7. Acrolein, a nephrotoxic metabolite of cyclophosphamide, can lead to serious haemorrhagic -----(8).

Q.8. This fluoroquinolone may cause episodes of dysglycemia-----(12).

Q.9. Sitagliptin and vildagliptin, which are ----- inhibitors can cause nasopharyngitis due to substance P as an adverse effect.(4).

Q.10. Pyrimethamine-Sulfadoxine combination can cause serious cutaneous reactions including-----(3).

Q.11. -----, an atypical NSAID, is contraindicated in patients of MI and epilepsy.(7).

Down

Q.12. Using thiazides frequently and in high doses is likely to cause-----(14).

Q.13. Trastuzumab can show adverse effects like cardiomyopathy and toxicity of-----(3).

Q.14. EXUBERA and AFREZZA have been approved by FDA as inhaled----- preparations as they have lesser chance of causing pulmonary fibrosis.(7).

Q.15. Diacerein, an atypical NSAID, does not inhibit----- but inhibits IL1 and has a peculiar ADR of urine discolouration.(3).

Q.16. -----release syndrome is the common ADR of Antithymocyte Globulin(8).

Q.17. Orlistat, is contraindicated in patients with malabsorption of fats or-----(11).

Q.18. -----, used to treat CMV retinitis in AIDS patients,can produce iritis, vitreitis and raised IOP(10).

ANSWERS

1 Hepatotoxicity
2 Prostate
3 Iron
4 Renal
5 Dipyridamole
6 Aluminium
7 Cystitis
8 Gatifloxacin
9 DPP4
10 SJS
11 Nefopam
12 Hypercalcaemia
13 GIT
14 Insulin
15 COX
16 Cytokine
17 Cholestasis
18 Fomivirsen

ALPHABET 'D' PUZZLE

Dr Abhilasha Rashmi*, Dr Sharmada Nerlekar,**

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1 D									
2	**D**								
3		**D**							
4			**D**						
5				**D**					
6					**D**				
7						**D**			
8							**D**		
9								**D**	
10									**D**

1. Local adverse effects of topical corticosteroids include skin atrophy, steroid rosacea, acne, hypopigmentation, hypertrichosis and perioral & allergic contact _____.
2. The anti TNF- α monoclonal antibody, used as a DMARD, _____, is found to be less immunogenic than Infliximab.
3. _____, a halogenated hydroxyquinoline, and a luminal amoebicide, can lead to iodine toxicity like dermatitis, urticarial, pruritus or fever.
4. A gap of at least 6 hours should be given between intake of a nitrate and this PDE-5 inhibitor, as cases of severe hypotension & myocardial infarction have been reported in men taking both drugs.
5. Dose related pulmonary toxicity is the most important ADR of this broad spectrum Class III antiarrhythmic.
6. This Dopamine D1 receptor agonist, used for treatment of hypertensive emergencies, should be avoided in patients of glaucoma as it increases intraocular pressure.
7. A reversible positive Coombs' test occurs in 10-20% of patients with this centrally acting sympathoplegic drug.
8. _____ is an antipsychotic butyrophenone used as antiemetic only in resistant cases because it may result in fatal ventricular tachycardia.
9. The synthetic form of BNP ,_____, approved for use in acute heart failure, should be used with great caution as there are reports of excessive hypotension and renal damage.
10. Nephrotic syndrome and aplastic anemia may occur after the use of this uricosuric drug for treatment of Gout.

ANSWERS:

1. DERMATITIS 2. ADALIMUMAB 3. IODOQUINOL 4. SILDENAFIL 5. AMIODARONE
6. FENOLDOPAM 7. METHYLDOPA 8. DROPERIDOL 9. NESIRITIDE 10. PROBENECID

NOTES

NOTES

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

Please feel free to contact us for the same.

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