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BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

Department of Pharmacology

LTMMC & LTMGH, Sion, Mumbai - 22

Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk . . . . ✍

Dear Friends and Colleagues,

I am delighted to put forth a second issue of Bulletin on Adverse Drug Reaction for the current year.

In today's medical world monoclonal antibodies are finding therapeutic and diagnostic value in various clinical conditions. With the increasing clinical applications we are facing arena of adverse effects with these drugs. Our very first article elaborates on these effects, its mechanism and management. This comprehensive write up will elucidate the risk benefit profile for the monoclonal antibodies.

The second review article highlights the ADRs that occur due to excipients in the drug formulations and their mechanisms and preventive strategies.

In this issue we also discuss an interesting case of atropine induced psychosis after topical administration. We also have a summary of analysis of ADRs from our institute to provide the glimpse of pharmacovigilance activity at our institute. The puzzle and crossword will surely make it more interesting.

I hope all the readers find this issue informative and interesting.

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

Thank you.

Dr. Sudhir Pawar

ADVERSE EFFECTS OF MONOCLONAL ANTIBODIES

Dr. Abhilasha Rashmi

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

Introduction

In 1975, monoclonal antibody (mAb) technique was created by Georges Köhler, César Milstein, and Niels Kaj Jerne by using mouse x mouse hybridoma. They shared the Nobel Prize in Physiology and Medicine in 1984 for the discovery. In 1992, FDA approved first therapeutic mAb Muromonab-CD3 to reduce acute rejection in patients with organ transplants. Since then, panels of mAbs are approved by international regulatory agencies for the treatment of malignancies, transplant rejection, autoimmune and infectious diseases, as well as a range of new indications. As of May 1, 2016, FDA has approved 62 therapeutic mAbs.[1]

After the production of mouse monoclonal antibodies, technical advances have allowed the transition from mouse, via chimeric and humanized, to fully human mAbs. According to the INN (International Nonproprietary Names) system, in 1990, "mab" was introduced as a stem for Monoclonal antibodies. INN substem for Chimeric antibodies is kept as "xi" (examples- Abciximab, Rituximab etc.), "zu" for Humanized antibodies (examples- Bevacizumab, Trastuzumab) and "u" for Human antibodies (examples- Adalimumab, Ipilimumab etc.).[2,3]

With the ongoing development of mAbs as novel therapeutic strategies for a wide variety of diseases, their clinical use has been associated with the development of a variety of adverse effects in human patients among which those involving the immune system can be considered to be the most frequent.[4] This review discusses a range of adverse effects encountered with mAb therapy.

Adverse effects

1. Immune reactions

Monoclonal antibodies contain elements that may be recognized by the recipient as foreign and can therefore cause activation of immune and innate reactions.[5] Acute reactions following infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions, serum sickness, Tumor Lysis Syndrome and Cytokine Release Syndrome.[6]

a. Acute anaphylaxis

A generalized symptomatic anaphylactic response to infusion of mABs typically occurs within the first two hours, but may be delayed up to 14 days after treatment. The highest risk of a reaction is during the first or second exposure to the mAb.[7] Monoclonal Antibodies most commonly associated with early infusion reactions are infliximab, rituximab, gemtuzumab, alemtuzumab, trastuzumab, cetuximab

and ofatumumab. Common signs and symptoms include fever, flushing, rigors, chest discomfort, abdominal pain, nausea, vomiting, diarrhea and rashes.[8] Pharmacologic prophylaxis with antihistamines and acetaminophen with or without a glucocorticoid is suggested for high-risk agents.[9] Initial management of suspected anaphylaxis is to stop the infusion. Then intramuscular injection of epinephrine should be given and volume resuscitation, intravenous antihistamines, and bronchodilators are to be administered.[10]

b. Serum sickness

Serum sickness, a classical Type III hypersensitivity reaction due to protein antigen-antibody complexes, which occurs as a response to foreign antigens, can also be caused by mAb therapy. Symptoms, which typically appear 6-21 days after drug administration, include lymphadenopathy and fever. Cutaneous symptoms, often urticarial and morbilliform eruptions and sometimes erythema and petechiae, occur in up to 95% of patients.[11] This has been noted especially for chimeric mAbs.[12]

c. Cytokine Release Syndrome (CRS)

Cytokine Release Syndrome is a prominent feature in the context of therapy with CD3 specific (muromonab), CD52 specific (alemtuzumab) and CD20 specific (rituximab) mAbs. They trigger the release of a range of cytokines; causing a cytokine storm.[6] Clinical events have been divided into four phases. First, a systemic inflammatory response consisting of high levels of cytokines in the blood, accompanied by headache, myalgias, nausea, diarrhoea, erythema, vasodilation and hypotension. Second phase presents as pulmonary infiltrates and lung injury; renal failure and disseminated intravascular coagulation. Third, severe blood lymphopenia and monocytopenia. Fourth, prolonged cardiovascular shock and acute respiratory distress syndrome.[13] Treatment of CRS depends upon the grade the patient is classified into. Tocilizumab, corticosteroids, IV fluids and vasopressors are the major treatment modalities. Tocilizumab is a humanized, immunoglobulin G1k (IgG1k) antihuman IL-6R mAb which prevents IL-6 binding to both cell-associated and soluble IL-6Rs and inhibits it. Emerging clinical experience has concluded that it is an effective treatment for severe or life-threatening CRS. In patients with CRS who respond to Tocilizumab, fever and hypotension often resolve within a few hours. If the patient's condition does not improve within 24 hours of the Tocilizumab dose, administration of a second dose of Tocilizumab and/or a second immunosuppressive agent, such as corticosteroids, should be considered.[14]

d. Tumor Lysis Syndrome (TLS)

Tumor Lysis Syndrome is a potentially life-threatening complication that can occur early with mAb therapy for neoplastic conditions.[6] It is an onco-metabolic emergency resulting from rapid cell death. Treatment of established TLS includes aggressive hydration, use of loop diuretics (especially for the patients prone to fluid overload), use of phosphate binders, use of uric acid lowering agents (preferably rasburicase) and dialysis in refractory cases.[15]

2. Infections

Infectious diseases are a well-described side effect of certain mAbs, and they are a reflection of an acquired immunodeficiency.[6] Latent infections like herpes zoster may manifest in the immunocompromised state induced by monoclonal antibodies. TNF-alpha inhibitors commonly used to treat inflammatory conditions like rheumatoid arthritis or seronegative spondylo arthropathies are associated with increased risk of latent tuberculosis (TB).Therefore, while using TNF-alpha inhibitors such as infliximab, adalimumab, golimumab the patient should undergo a chest x-ray and placement of purified protein derivative (PPD) before initiating therapy.[8]

Other infectious complications including bacterial and fungal opportunistic infections, such as histoplasmosis, listeriosis, aspergillosis, candidiasis, pneumocystis carinii pneumonia and coccidioidomycosis have also been reported in association of anti-TNF mAbs.[16,17] Agents targeting B-cells like rituximab are associated with reactivation of latent hepatitis B and Creutzfeldt Jacob virus infections (causes progressive multifocal leukoencephalopathy, PML).[18] Natalizumab, marketed for treatment of relapsing remitting multiple sclerosis (MS), a mAb that inhibits leukocyte migration has been associated with over 100 cases of PML.[19] In high risk patients, pneumocystis jiroveci prophylaxis with trimethoprim-sulfamethoxazole and cytomegalovirus prophylaxis with ganciclovir should be considered.[8]

3. Pulmonary Complications

Some mABs like rituximab and trastuzumab are associated with an increased risk of direct interstitial lung disease (ILD). Symptoms of ILD are high fever, dyspnea, and cough.[20] Patients should be treated with glucocorticoids after infectious etiologies are excluded. Empiric antibiotics against atypical pathogens can also be used to reduce secondary infection.[8] Patients treated with mAbs targeting epidermal growth factor receptors used in colorectal cancers (cetuximab and panitumumab) are also known to cause pulmonary toxicity rarely.[21]

4. Platelet and thrombotic disorders

An acute, severe, self-limiting thrombocytopenia can be caused by infliximab (TNF-alpha), efalizumab (CD11a specific) and rituximab (CD20-specific); however the mechanisms of action remain obscure.[6] Acute thrombocytopaenia develops after first infusion of abciximab (an antiplatelet glycoprotein IIb/IIIa, chimeric Fab antibody) in about 1% of patients and in more than 10% of patients after a second infusion.[22] Thrombocytopenia has also occurred in around 3% of subjects receiving Alemtuzumab for multiple sclerosis.[23,24] Bevacizumab, a humanized mAb against vascular endothelial growth factor (vEGF) has been associated with arterial thromboembolic events.[25]

5. Autoimmune diseases

Monoclonal antibodies have the capacity through their immunomodulatory actions, to cause various autoimmune conditions. Use of TNF-specific mAbs for rheumatic diseases has been associated with the development of anti-nuclear antibodies and antibodies to double-stranded DNA, and also with lupus-like syndromes.[23]Alemtuzumab is a potent immunosuppressive mAb used in multiple sclerosis, but can also cause antibody-mediated thyroid autoimmunity.[26]

6. Cancer

The use of mAbs may increase the risk of future malignancies. Monoclonal antibodies that target TNF-alpha were found in post marketing safety analysis to be associated with malignancies especially lymphomas.[8] Hepatosplenic T-cell lymphoma has been associated with use of infliximab in young patients with inflammatory bowel disease.[27]

7. Dermatotoxicity

EGFR is a promising target on many solid tumours. The EGFR-specific mAbs cetuximab and panitumumab are effective therapies for refractory metastatic colorectal cancer. These mAbs commonly cause a skin rash on the face and upper torso, although dermatitis can present as dry skin, pruritus and erythema.[6] The dermatitis is thought to be part of the pharmacodynamic action of this agent, as EGFR is a transmembrane glycoprotein that is widely expressed on epithelial cells.[6] Prophylactic oral minocycline has shown some efficacy in decreasing the severity of skin reactions in the first month of Cetuximab therapy.[28,29]

Paronychia involving the great toe is often the first sign, and secondary bacterial infection (often with staphylococcus aureus) is also not uncommon in patients treated with cetuximab.[9] Other less common specific cutaneous reactions include erythematous exanthem caused by cytomegalovirus, Stevens-Johnson syndrome, toxic epidermal necrolysis, which has been reported in a small number of patients treated with Ipilimumab for metastatic melanoma.[30] Treatment options include topical antibiotics, topical corticosteroids, and/or electrodessication of larger lesions.[9]

8. Cardiotoxicity

Trastuzumab is a humanized mAb used successfully in women with estrogen receptor positive metastatic breast cancer.[31] Cardiac dysfunction caused by trastuzumab is most commonly an asymptomatic decrease in left ventricular ejection fraction that tends to be reversible. However, if cardiac failure develops, this responds well to standard medical management.[6]

9. Pulmonary Adverse effects

There are several complications associated with the use of mAbs that affect the lungs, including interstitial lung disease (ILD), hemorrhage, trachea-esophageal fistula and thromboembolic disease. Since the mechanisms underlying such lung injuries have generally not been uncovered, any classification on the basis of pathogenesis is difficult. Adverse events can be grouped into 4 main categories: interstitial pneumonitis and fibrosis, acute respiratory distress syndrome (ARDS), bronchiolitis obliterans organizing pneumonia and hypersensitivity reactions.[9]

Rituximab is the most implicated mAb, inducing a heterogeneous spectrum of lung disorders.[32] Interstitial lung disease (ILD) has been reported in treatment with Cetuximab and Transtuzumab.[33,34,35] Discontinuation of mAb is advised in any patient who develops ILD or ARDS during treatment. Improvement following treatment with glucocorticoids has been reported.[9]

10. Enterotoxicity

Enterocolitis, colitis, and gastrointestinal perforation are common gastrointestinal adverse effects of mAbs. All VEGF targeted therapies, including bevacizumab, can cause gastrointestinal perforation. Non gastrointestinal fistula formation also has been observed; most commonly within the first 6 months of treatment.[9] To minimize the risk of gastrointestinal perforation and fistula formation, at least 28 days should elapse between surgery and last dose of bevacizumab, except in emergency situations.[36]

Table 1: Common adverse effects seen with Monoclonal Antibodies [6,8,9,11]

Target	Monoclonal Antibody	Common side effects
Platelet glycoprotein IIb/IIIa	Abciximab- Chimeric Antibody fragment	• Hypersensitivity and immunogenicity • Increased risk of bleeding • Thrombocytopenia
Tumour Necrosis Factor-alpha	Adalimumab- Fully human Certolizumab- Humanized Infliximab- Chimeric	• Infusion reactions and immunogenicity • Hypersensitivity reactions • Immunosuppression and infections (tuberculosis) • Anaemia, leukopaenia and thrombocytopaenia • Worsening heart failure • Malignancy, lymphoma and lymphoproliferative disorders • Elevated liver transaminases • Increased nuclear-specific antibodies
CD52 on mature B, T and natural killer cells	Alemtuzumab- Humanized	• Infusion reactions • Hypersensitivity and immunogenicity • CRS

		• Tumour lysis syndrome • Immunosuppression and opportunistic infections • Pancytopaenia, lymphopaenia and thrombocytopaenia • Autoimmune haemolytic anaemia • Thyroid disorders • Cardiotoxicity
Interleukin-2 receptor-alpha on activated lymphocytes	Basiliximab- Chimeric Daclizumab- Humanized	• Severe acute hypersensitivity reactions • CRS and immunogenicity • Immunosuppression and infections • Local skin reactions
Vascular Endothelial Growth Factor	Bevacizumab- Humanized	• Infusion reactions and immunogenicity • Local complications at tumour site • Arterial and venous thromboembolic events • Haemorrhage • Severe hypertension • Cardiac failure • Reversible posterior leukoencephalopathy syndrome • Slower wound healing and GI perforation
	Ranibizumab- Humanized	• Conjunctival haemorrhage • Intraocular inflammation • Increased intraocular pressure • Retinal detachment • Endophthalmitis
Complement C5	Eculizumab- Humanized	• Meningococcal and Neisseria infection • Intravascular hemolysis
CD11a	Efalizumab- Humanized	• First-dose reaction complex • Immunosuppression • Serious opportunistic infections • PML • Guillain-Barré syndrome, encephalitis, meningitis • Immune haemolytic anaemia • Immune thrombocytopaenia
CD3 antigen on T cells	Muromonab CD3- Mouse	• Severe acute infusion reactions • Immunosuppression and infections • Immunogenicity • Cardiovascular side effects • Hepatitis

alpha 4 Integrin	Natalizumab- Humanized	• Infusion and hypersensitivity reactions • Immunogenicity • PML (0.1%) and immunosuppression • Hepatotoxicity
Immunoglobulin E (IgE)	Omalizumab- Humanized	• Anaphylaxis (0.1%) • Injection site reactions • Immunogenicity • URTI • Churg-Strauss syndrome (rare)
Fusion protein on RSV	Palivizumab- Humanized	• Anaphylaxis and apnoea (rare) • Fever, injection site reactions
CD20 on B cells	Rituximab- Chimeric	• Prominent acute infusion reactions • CRS • Tumour lysis syndrome • Transient hypotension • Immunogenicity • Serum sickness • Severe mucocutaneous reactions • Immunosuppression • Hepatitis B reactivation with fulminant hepatitis • PML • Renal toxicity • Cardiac arrhythmias
EGFR	Panitumumab Fully human	• Infusion reactions • Skin rashes in most patients (90%) • Diarrhoea (60%), nausea and vomiting • Hypomagnesaemia (2%)
	Cetuximab- Chimeric	• Severe infusion reactions • IgE against oligosaccharides • Urticaria and dermatological toxicity • Bronchospasm and pulmonary toxicity • Hypomagnesaemia
	Trastuzumab- Humanized	• Hypersensitivity and infusion reactions • Cardiotoxicity • Skin reactions • Pulmonary toxicity • Hypomagnesemia
Interleukin-6 receptor	Tocilizumab- Humanized	• Anaphylaxis and anaphylactoid reactions • URTI • Headache • Serious infections • Abnormal liver function, neutropaenia and dyslipidemia

Conclusion

Monoclonal antibodies represent an important and growing category of targeted therapeutic agents. We need to recognize which types of risks apply to a particular mAb, and take steps to identify and minimize potential adverse effects. Increasing the safety of mAbs is vital for a greater use of mAb-based therapy in the treatment of diseases.

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ADVERSE REACTIONS DUE TO EXCIPIENTS

Dr Jaisen Lokhande

Assistant Professor, Department of Pharmacology, LTMMC and GH, Sion

Excipients are substances mixed with the active pharmaceutical ingredients (API) in a formulation and which provide some functions through their physical and chemical properties.[1] In many of the formulations they are present in greater quantity compared to the active ingredient.[2] The FDA has approved 773 chemical agents for use as excipients in pharmaceutical formulations and these are added for stability reasons, as a preservative, flavouring agent or dye.[1] According to the international pharmaceutical excipient council (IPEC) of America and IPEC Europe Excipients are defined as "substance(s) other than the API which has been appropriately evaluated for safety and is included in a drug delivery system to either aid processing of the system during manufacturing or protect, support or enhance stability, bioavailability or patients compliances or assist in product identification and enhance any other attributes of overall safety and effectiveness of drug product during storage or use".[3] Excipients have well established uses in drug formulary however they are also implicated to cause adverse reactions. The following section gives an overview of the uses, adverse reactions, diagnosis and some preventive measures to the adverse reactions due to drug excipients.

Classification and Uses of Excipient

Excipients are generally added to the active pharmaceutical ingredients in order to protect, support or enhance stability of the formulation; improve patient acceptance; help improve bioavailability of active drug and enhance overall safety and effectiveness of the formulation during its storage and use.[2] Excipients are used in almost all the formulations including tablets, liquids or injectable. Tablets are the most widely used dosage form and the details of various uses and examples of excipients used in tablets are given in Table 1.[4] Excipients are classified based on their uses, origin, source or based upon their chemical class.[5]

Table 1: Classification and functions of common excipients used in tablets

Excipient	Function	Examples
Diluents	Provide bulk and enable accurate dosing of potent ingredients	Sugar compounds e.g. lactose, dextrin, glucose, sucrose, sorbitol inorganic compounds e.g. silicates, calcium and magnesium salts, sodium or potassium chloride
Binders compression aids, granulating agents	Bind the tablet ingredients together giving form and mechanical strength	Mainly natural or synthetic polymers e.g. starches, sugars, sugar alcohols and cellulose derivatives

Disintegrants	Aid dispersion of the tablet in the gastrointestinal tract, releasing the active ingredient and increasing the surface area for dissolution	Compounds which swell or dissolve in water e.g. starch, cellulose derivatives and alginates, crospovidone
Glidants	Improve the flow of powders during tablet manufacturing by reducing friction and adhesion between particles. Also used as anti-caking agents.	Colloidal anhydrous silicon and other silica compounds
Lubricants	Similar action to glidants, however, they may slow disintegration and dissolution. The properties of glidants and lubricants differ, although some compounds, such as starch and talc, have both actions.	Stearic acid and its salts (e.g. magnesium stearate)
Tablet coatings and films	Protect tablet from the environment (air, light and moisture), increase the mechanical strength, mask taste and smell, aid swallowing, assist in product identification. Can be used to modify release of the active ingredient. May contain flavours and colourings.	Sugar (sucrose) has now been replaced by film coating using natural or synthetic polymers. Polymers that are insoluble in acid, e.g. cellulose acetate phthalate, are used for enteric coatings to delay release of the active ingredient.
Colouring agents	Improve acceptability to patients, aid identification and prevent counterfeiting. Increase stability of light sensitive drugs.	Mainly synthetic dyes and natural colours. Compounds that are themselves natural pigments of food may also be used.

Type of Interactions due to Excipient

Even though considered inert substance, these excipients have the tendency to cause some interactions (Table 2) directly or due to the various impurities which they contain, which may result in decomposition of the active pharmaceutical ingredients in the formulation thus altering the shelf life of the formulation (Table 3). The various type of interactions that an excipient can undergo are termed as drug-excipient interactions; excipient-excipient interactions and package-excipient interactions. Drug excipient interactions are further classified as:[2]

- Physical interactions
- Chemical interactions
- Biopharmaceutical interactions including premature breakdown of enteric coat.

One has to note that not all the interactions are harmful or abnormal. Some of the interactions are beneficial and intended to be so. Table 2 gives an overview of physical interactions which may have beneficial or detrimental effects on drugs.[2]

Table 2: Physical interactions

Interaction	Beneficial effect examples	Detrimental effect examples
Complexation:- Usually binds reversibly with drugs to form complex, sometimes insoluble complexes are formed which lead to slower dissolution and decreased absorption of drug. Result observed in such cases is detrimental	Cyclodextrin is often used to improve bioavailability of poorly water soluble drugs. This increases bioavailability and increases rate and extent of drug dissolution by increasing mucosal permeability or increasing stability of drug.	Tetracycline formed insoluble complex with calcium carbonate leading to slower dissolution and decreased absorption.
Complexing agents can also be used to increase bioavailability of poorly water soluble drugs Result observed in such case is beneficial	Complexation of Cyclodextrin with ursodeoxycholic acid increased bioavailability caused by increased dissolution.	Formulation of chlorpromazine with polysorbate 80 and sodium lauryl sulphate decreased membrane permeability of drug.
Adsorption:- Adsorption of drug by excipient can lead to reduced bioavailability as the drug is not available for dissolution.	Formulation of Indomethacin (NSAID) using kaolin as adsorbent increased its dissolution rate which leads to increase in bioavailability of drug.	1) Cetyl Pyridinium chloride cations get adsorbed on the surface of magnesium stearate which acts as a lubricant in tablet containing Cetyl pyridinium chloride. This leads to marked reduction in the antibacterial activity of the drug.
Adsorption of drug on excipient surface can assist in increasing surface area of drug available for dissolution which eventually increases bioavailability.		2) Decrease in absorption of dicumarol in the formulations containing excipients like Aluminum hydroxide, Starch, Talc, owing to the adsorbing properties of excipients
Solid dispersion:- This kind of interactions improves the dissolution and bioavailability of hydrophobic drugs. Sometimes solid dispersion interactions can result in slow dissolution of drugs.	Improved dissolution rates of drugs like Piroxicam, Norfloxacin, Nifedipine and Ibuprofen were observed when these drugs were formulated into solid dispersions using Polyethylene glycol of different molecular weights.	Solid dispersion product formed due to interaction between Povidone and Stearic acid in a capsule showed slow dissolution of drugs.

Excipients are rarely produced to the extremely high standards of purity that apply to drug substances (Table 3). Hence the presence of impurities rather than the material itself might be the cause of any adverse event, perhaps by inducing degradation of the drug. There may be batch differences or brand differences in excipients.[6]

Table 3: Impurities found in common excipients[7]

Excipient	Residue
Povidone, crospovidone, polysorbates	Peroxides
Magnesium stearate, fixed oils, lipids	Antioxidants
Lactose	Aldehydes, reducing sugars
Benzyl alcohol	Benzaldehyde
Polyethylene glycol	Aldehydes, peroxides, organic acids
Microcrystalline cellulose	Lignin, hemicelluloses, water
Starch	Formaldehyde
Talc	Heavy metals
Dibasic calcium phosphate dehydrate	Alkaline residues
Stearate lubricants	Alkaline residues
Hydroxypropylmethyl/ethyl celluloses	Glyoxal

ADRs due to Excipient

Many published articles highlighted the occurrence of adverse reactions to excipients. Few examples are mentioned in the following section.

One of the earliest examples of excipient toxicity was with the use of diethylene glycol used as a solvent to make sulphonamides more soluble in water. Diethylene glycol is a highly toxic substance and was responsible for the death of many children and adults in the USA in the 1930s.[8]

Benzyl alcohol which is an excipient of clindamycin injection has been identified to cause the "gasping syndrome" in many premature neonates when administered. As per the literature, benzyl alcohol gets accumulated in premature babies. The immature pathways in combination with the relatively high dose of benzyl alcohol are thought to be the cause of the gasping syndrome.[9] Previously, two groups of investigators, concluded that an IV solutions containing 0.9% benzyl alcohol led to severe metabolic acidosis, encephalopathy, respiratory depression with gasping, and perhaps other abnormalities leading to the death of a total of 16 infants.[10] After this report, the Food and Drug Administration (FDA) recommended that fluids preserved with benzyl alcohol were not to be used in premature babies.[9]

In another incidence, intravenous vitamin E preparation was used to prevent retinopathy in preterm neonates in several centres in the USA in 1983.[11] There were reports of 38 deaths and the intravenous

vitamin E preparation was withdrawn. It was suggested that excipients used were responsible for the toxicity.[12]

Another study mentions about a particular brand of phenytoin, which had been sold for many years in Australia and New Zealand. When the same was supplied to the United States, the manufacturer changed the formulation and as a result, 51 patients whose epilepsy was stable with the use of the old formulation had severe and serious adverse reactions, including coma, with the new product. In the new formulation, calcium sulfate dehydrate was replaced with lactose. However, it appeared that the calcium salt slowed absorption of the phenytoin, whereas lactose speeded it up which led to the increased incidence of adverse events.[13]

Lactose, which is seemingly harmless agent and widely used in drug formulations, foods and beverages, can causes adverse reactions usually classified as lactose intolerance or sensitivity.[13] In populations with a predominance of dairy foods in the diet, particularly northern European people, as few as 2% of the population has primary lactase deficiency.[14] A multicenter study in healthy volunteers in India showed that 66.6% people in South India and 27.4% people in North India have lactose intolerance.[15] However in this condition one has to take into account that lactose intolerance is also dependent on the load of lactose reaching the colon which would be very less as in the case of drugs excipient.

In 2007, in the United Kingdom Food Standards Agency, a study was published linking the use of six colourants (tartrazine, quinoline yellow, sunset yellow, carmoisine, ponceau 4R and allura red) with behavioural problems in children. The European Food Standards Agency reviewed these results but concluded that no change in legislation was needed.[16]

Table 4: Common examples of adverse reactions to excipients[4]

Excipient	Function	Caution in practice
Tartrazine	Colouring agent	Reported cases of hypersensitivity, and hyperkinetic activity in children
Aspartame	Sweetener	Caution in patients with phenylketonuria
Benzalkonium chloride	Preservative	Bronchoconstriction (nebuliser solutions) and ocular toxicity (soft contact lens solutions)
Sodium metabisulphite	Antioxidant	Hypersensitivity, including bronchospasm and anaphylaxis, are reported for all sulphites
Propyl gallate	Antioxidant	Contact sensitivity and skin reactions
Lactose	Tablet filler	Caution in patients with galactosaemia, glucose-galactose malabsorption syndrome, or lactase deficiency
Sesame oil	Oil (injections)	Hypersensitivity reactions reported
Lanolin (wool fat)	Emulsifier (topical products)	Skin hypersensitivity reactions, caution in patients with known sensitivity

Clinical Guidelines and Approach to identify ADRs due to Excipients

One important step in evaluation of an adverse reaction is to understand that excipients can also cause adverse reactions. A comprehensive patient history is very important with focus on timeframes and factors that can influence interpretation, e.g. a family history of atopy, underlying infections, a recent change in diet and concomitant medications or a recent change in drug brand. A rating scale has been published in article which can help the clinician to a specific diagnosis.[16] In this rating, a score is given to each positive finding, maximum score being 20. A score of 10 indicates a high level of suspicion of an excipient-related ADR. Another way to identify excipient related ADR is by a test called as Cellular Antigen Stimulation Test (CAST) can also help to confirm the diagnosis.[16] The CAST is a useful first-line test in cases where excipient-related adverse drug reactions are suspected. A high leukotriene concentration (more than 200 pg/ml) in this test is a good indication of an allergic reaction towards a specific component.[17]

The following steps may also be utilised to rule out which ingredients may be causing the adverse effects.[4]

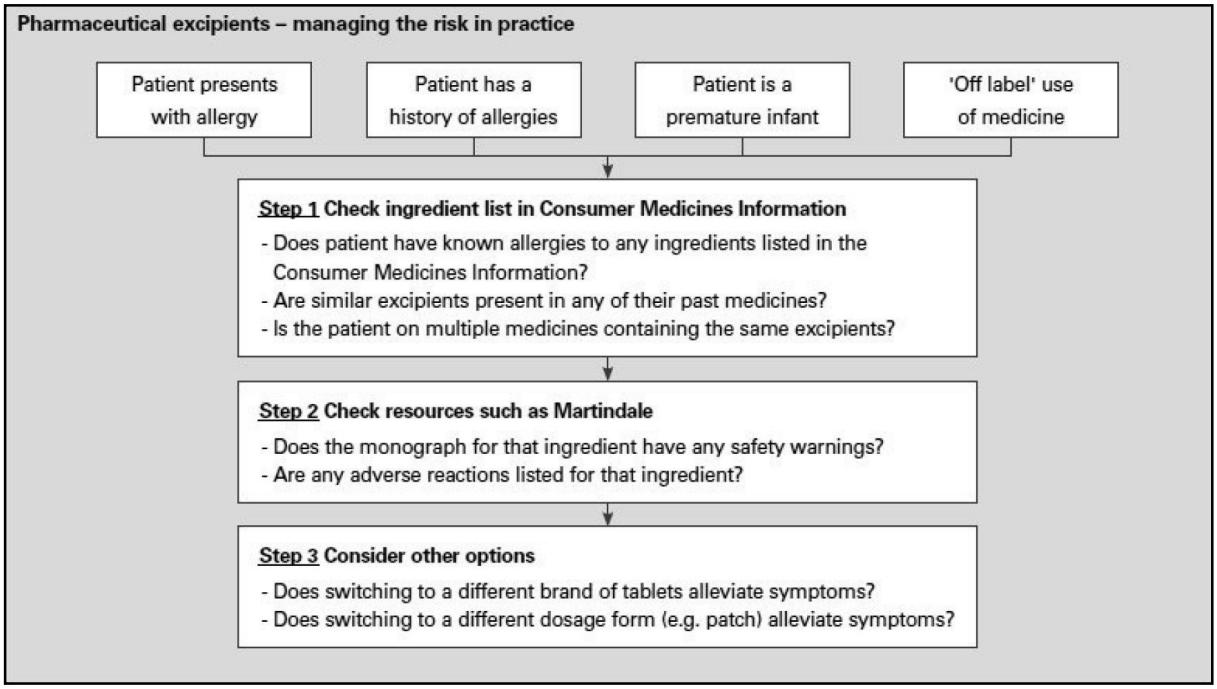

Figure 1: Steps for identification of adverse reactions due to excipients

Precautions and Preventive measures

Clinicians should keep in mind that tragic accidents have been attributed to excipients in the past. The risks of adverse reactions due to the excipients are compounded when inappropriate and inferior quality excipients are used. Preventive measures include frequent inspection and laboratory examination of imported and locally manufactured formulated drugs to monitor the safety of their excipients and the quality of the raw materials used in their manufacture.[18]

Some authors have recommended that excipients, additives and active ingredients should be listed on the label, where they can be read by physicians, nurses, pharmacists and patients or their caregivers.[13]

Conclusions

Pharmaceutical products often contain one or more than one ingredients as excipients, other than the active pharmaceutical ingredients, which are essential for their manufacture, stability and function. These ingredients may not be always be inert and may possess some features which have potential to cause adverse effects in few individuals. Identifying such reactions and finding the appropriate safety information will help to ensure a safe outcome for the patients.

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ANALYSIS OF ADVERSE DRUG REACTIONS REPORTED

(March 2016 to June 2016)

Compiled by **Swati Vaidya**

Technical Associate -Pharmacovigilance Programme of India (PvPI), Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Total Case Reports: 127

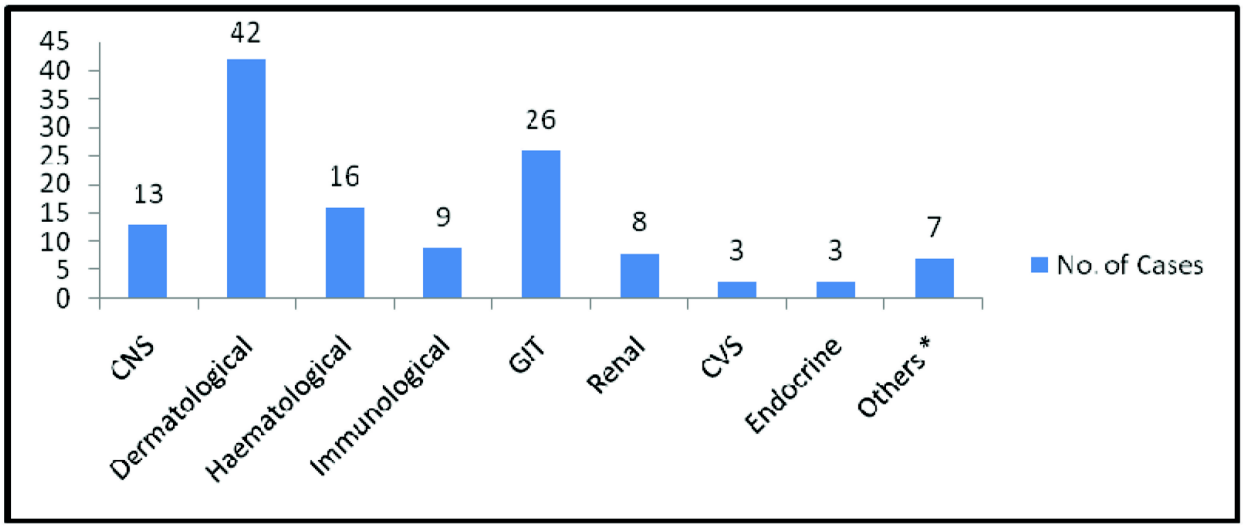
I. Age and Gender distribution:

Age groups	Number of patients	Males	Females
<3 yrs	23	7	16
3 - 17 yrs	23	14	9
18 - 44 yrs	56	29	27
45 - 60 yrs	17	7	10
>60 yrs	8	7	1
Total	127	64	63

II. Seriousness of the reaction:

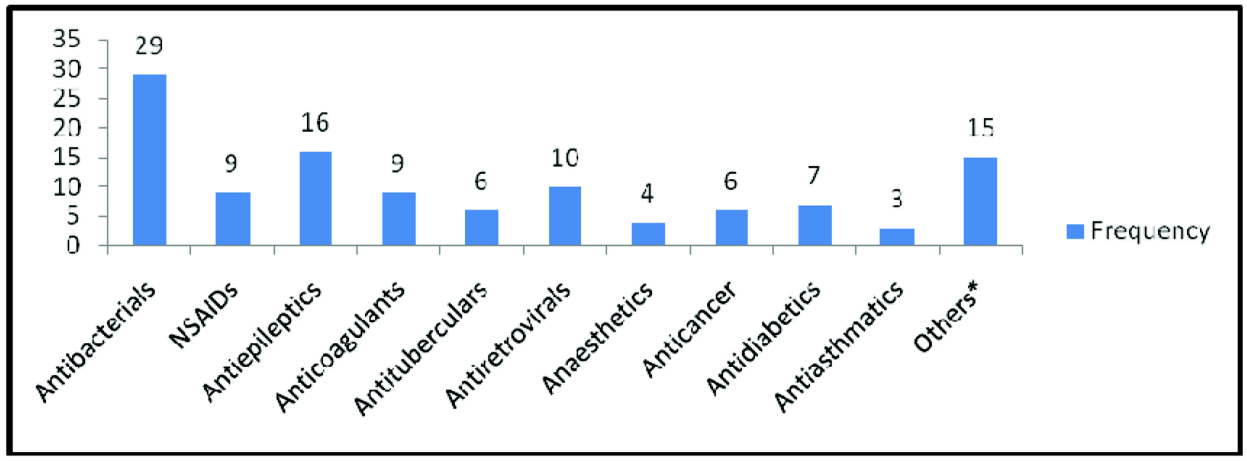
Seriousness of the ADR	No. of Cases (N=127)
Yes	113
No	14

III. System involved in the ADR : N=127



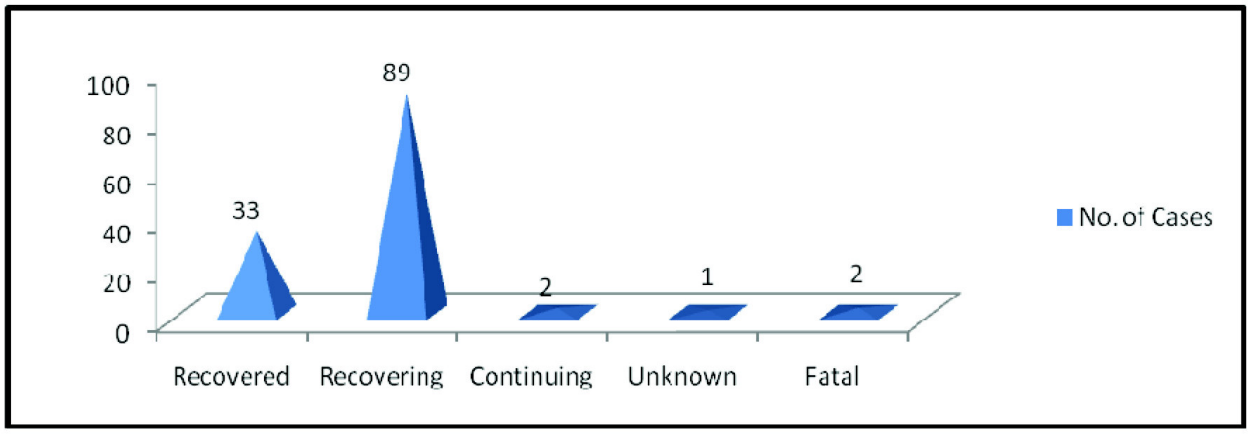
*Others include ENT, musculoskeletal system, electrolyte disturbances and respiratory system.

IV. Class of the Suspected drug: N=127

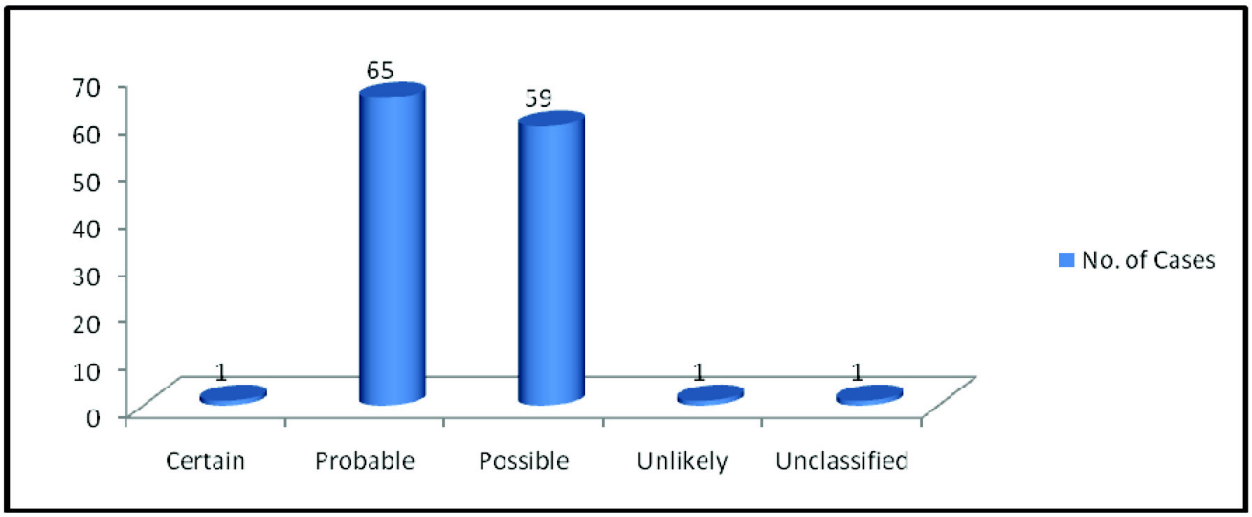


*Other drugs includes antifungals, antivirals, antihypertensives, antipsychotic, haematinics, diuretics, radiocontrast media, sedatives, prokinetics and antispasmodics.

V. Outcome of the reaction : N=127



VI. Causality assessment (WHO UMC Classification): N= 127



EVALUATION OF A CASE

Atropine induced Psychosis

Dr Vaibhav Hublikar*, Dr Anupama Mauskar#, Dr Prachi Karnik##, Dr Neha Kadhe, Dr Swati Patil***, Dr Mamta Manglani###, Dr Sudhir Pawar******

** - 3rd year Resident, Department of Pharmacology; # - Additional Professor, Department of Pediatric; ## - Assistant Professor, Department of Pediatric;*

*** - Additional Professor, Department of Pharmacology;*

**** - Assistant Professor, Department of Pharmacology;*

- Professor and Head, Department of Pediatric;

***** - Professor and Head, Department of Pharmacology, LTMMC and GH, Sion*

Introduction

Atropine is a natural anticholinergic alkaloid used as a preanaesthetic medication to reduce secretions, in intestinal and renal colic as an anti-spasmodic, as a cardiac vagolytic. In ophthalmology, it is used for its mydiatric, cycloplegic for testing errors of refraction. Atropine ointment 1% is used for this purpose. Its long lasting mydiatric-cycloplegic and local anodyne actions on cornea makes it valuable in treatment of iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer[1]

Adverse effects of systemically administered atropine on the central nervous system are well documented. At few instances atropine has also been incriminated for producing delirious states with minor or absent peripheral signs of intoxication and severe mental retardation following routine instillation as an eye drop or ointment.[2]

Here we describe a case of acute toxic psychosis caused by use of atropine ointment in the eye during the course of treatment of hypopyon corneal ulcer.

Case description

A 5 year old male child weighing 8.4 kgs was admitted to the paediatrics ward for acute gastroenteritis. He was started on injectable antimicrobials i.e. cefotaxime, metronidazole and amikacin. Along with these appropriate fluid and electrolyte replacement was administered. On ophthalmic examination, he was found to have conjunctival xerosis in both eyes and hypopyon corneal ulcer in the right eye. He was started on ointment atropine sulphate 1% for local application twice a day. Concomitantly, azithromycin 1% thrice a day and tobramycin 1% thrice a day ointments and carboxy methyl cellullose eye drops were started. A regimen of injection vitamin A 50000 IU was given on day 0, 1 and 14 of admission. He was also a known case of thalassemia major for which he was receiving blood transfusion at regular intervals.

Patient developed fever and irritable behavior 10 days after starting atropine sulphate ointment. Patient's behavior deteriorated in the next 4 days and he had a psychotic spell in the form of biting, mouthing, restlessness, excessive crying, decreased duration of sleep and failure to recognize his parents.

Psychiatric opinion was taken. A diagnosis of atropine induced psychosis was made. A differential diagnosis of dyselectrolytemia due to decreased potassium levels and re-feeding syndrome was also suspected. Psychosis due to dyselectrolytemia was ruled out as patient's potassium levels at the time of presentation of psychotic symptoms were normal and refeeding syndrome was ruled out as patient phosphate and magnesium levels were within normal limits. Suspecting drug induced psychosis, atropine was stopped after 14 days of initiation of atropine therapy. Other antimicrobial and supportive treatment was continued and patient was shifted to intensive care. Patient's condition improved in the next 3 days.

According to WHO UMC causality scale atropine was probably associated with psychosis as drug and adverse event had a temporal relationship, de-challenge test was positive and the reaction could not be attributed to any other cause or drug.

Discussion

Adverse ocular reaction to topical application of atropine ophthalmic preparations could be allergic or toxic.[3,4,5]. The allergic reaction, includes local manifestation, like dermatitis over the eyelids, with erythema, itching and local edema. It can also manifest systemically in the form of anaphylaxis.[6,7]

Toxic reactions are most common and are due to actions on post-ganglionic cholinergic fibres or due to direct CNS effect. These effects are subjected to interpersonal variation and can occur at therapeutic doses as well.[6,7,8] .In mild cases there is dryness of skin, mouth and throat, flushed skin of face and neck and tachycardia. In more severe cases of intoxication, patient is excited, confused and exhibits muscular incoordination and weakness. Giddiness, staggering gait may be present. Ataxia comes up early and can be so severe that the patient is unable to stand or sit without support. Nystagmus and tremors may be present.[9,10]

The signs and symptoms of atropine induced psychosis appear within minutes to hours after the administration of the eye drops/ ointment. In our patient psychotic symptoms developed after 10 days of daily atropine ointment administration.

The chances of toxicity to atropine increase in pediatric and geriatric age groups patients because of higher susceptibility.[11] In Down's syndrome patients, there is increased sensitivity to atropine due to pharmacogenetic abnormality caused by genetic imbalance imposed by extra chromosome 21 which causes increased susceptibility to toxicity.[11] Additionally mongols and blondes have also shown increased reports of toxicity.[12,13,14] Older anti-psychotics and tricyclic anti-depressants have anti-muscarinic effects and are thus prone to develop the reaction when used concomitantly with atropine.[15]

Little amount of atropine ocular preparation is absorbed directly into the general circulation through the conjunctival membrane but mainly the drug mixed with tears reaches the nasal mucosa and the intestinal tract via the nasolacrimal ducts. This is of importance in preventing the toxic symptoms. In 1% atropine sulphate, each drop contains 1/110 gr. (0.6 mg.). Assuming complete absorption, three drops in the normal subject will produce parasympathetic paralysis, six drops restlessness, and 15 drops mental symptoms and ataxia.[2] The amount of atropine in the 1% atropine ointment could vary depending on the amount applied. Approximately one centimeter length of the ointment contains 0.5 mg of the drug (equal to one drop of 1% eye drops). Any child can be exposed to as high as 3 mg of the drug in a single day.[16]

The diagnosis made is mainly based on clinical signs and symptoms. There is usually a history of ingestion and/or use of medication. According to DSM-IV criteria our patient fits the diagnosis of drug/substance induced psychosis. Hospitalization is indicated for all patients. Management includes a quiet darkened room with avoidance of unnecessary stimuli which are essential to quieten the patient. During acute phase, constant supervision, padding of cots and sometimes bodily restraint are advisable to prevent physical harm to the patient and his attendants.[2, 12] General measures include maintenance of adequate fluid intake and control of high temperature by sponges and salicylates, sedatives like short acting barbiturates. Physostigmine 1-3 mg subcutaneously is sufficient usually to counteract almost all the effects of atropine.[11] Stimulants such as caffeine should be given and artificial respiration and oxygen inhalation should be started when indicated.[12,14] Our patient was shifted to intensive unit and was monitored and symptomatic treatment was given for fever. No specific antidote was given.

The toxic effects of atropine eye drops can be prevented if slight pressure is exerted on the inner canthi of the eyes after instillation of atropine drops. This prevents the tears from reaching the nasolacrimal duct and diminishes absorption. The use of newer cycloplegics which do not contain atropine or homatropine will lessen the chances of such toxic effects and patients should be advice to discontinue taking medication at the first sign of undesired effect.[11]

Conclusion

Systemic adverse effects of atropine are well documented in cases of organophosphorus poisoning. Similar toxicity after topical use emphasizes on vigilant approach in use of mydriatic eye drops and proper patient education pertaining techniques of using ophthalmic preparations to curb systemic absorption are also very important.

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PUBLISHED CASE REPORTS ON ANTICHOLINERGIC'S INDUCED PSYCHOSIS

Compiled by Dr. Swati Patil

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

Neurotoxic effects induced by the topical administration of cycloplegics. A case report and review of the literature.

Rev Neurol. 2006 Nov 16-30;43(10):603-9.

Jiménez-Jiménez FJ, Alonso-Navarro H, Fernández-Díaz A, Adeva-Bartolomé MT, Ruiz-Ezquerro JJ, Martín-Prieto M.

A 61 year-old man who developed in two occasions confusion, disorientation and vivid visual hallucinations following exposure to a cyclopegic eye drop containing atropine 2%, scopolamine 0.5% and phenylephrine 4%. We performed a literature search regarding neurological complications of cycloplegic eye drops using the PubMed Database and the services of the Virtual Library 'Agencia Lain Entralgo'. The clinical features of all reports in which the original document was obtained are analyzed and summarized. We have summarized the clinical features of 29 patients with neurotoxicity due to cyclopentolate, 19 to atropine, 18 to scopolamine, 7 to homatropine, and 2 to tropicamide. Our patient should be the fourth reported in Spain, being the offending drug in the four cases the same eye drop. The most commonly reported symptoms are visual hallucinations, behavioral disorders/ acute psychosis, alterations of consciousness/confusion, restlessness/hyperactivity, ataxia and speech disorders. Many of the patients reported are children and elder. There have been reported some fatal cases, specially related with atropine.Neurotoxicity related with anticholinergic effects of cycloplegic agents is not infrequent, although it is not well known in our setting; and can cause death in some cases. Exposure to these drugs should be taken in account in the differential diagnosis of acute confusional syndromes.

Delirium due to scopolamine patch in a 4-year-old boy.

J Formos Med Assoc. 2011 Mar; 110(3):208-11.

Lin YG, Chen PH, Chang FY, Wu LT, Liao KY, Wu TC.

The scopolamine patch is usually used to reduce postoperative nausea and vomiting associated with anesthesia and/or surgery. It is also commonly used for the prevention of motion sickness. Transdermal scopolamine patches have been used for decades and there are few reports in the literature of toxic psychosis associated with the product. Most documented cases of acute psychosis following administration of scopolamine or other anticholinergic agents have been from the adult population. Here we present a 4-year-old boy with deteriorated cognitive function and changed mental status acutely. Besides flushing skin and psychotic behaviors including bizarre actions, hallucinations, aggressive behavior, hyperactivity, and incoherent speech were also noticed. Symptoms and signs were resolved after removal of scopolamine patch and conservative management. This case is possibly one of the

youngest patients to exhibit such toxic effects. We hope to relay information about common agents with anticholinergic effects to clinical practitioners and remind that drug-induced psychosis should be considered in children with acute changes in behavior.

Psychotic disorder induced by oxybutynin: Presentation of two cases.

Clin Drug Investig. 2006;26(10):603-6.

Gulsun M, Pinar M, Sabanci U.

Anticholinergic agents are muscarinic receptor antagonists that suppress the activity of the acetylcholine system in the brain. Some of these agents also increase the concentration of dopamine in the synaptic cleft, which may result in psychotic symptoms. Oxybutynin is an antimuscarinic drug that may have adverse effects on the CNS, including memory impairment, confusion, delirium and hallucinations in elderly patients. To date, several case reports have been published about the association between oxybutynin and psychotic symptoms in elderly subjects, but we were unable to find any case reports describing oxybutynin-induced psychotic disorders in young people. Here we report on two patients, a 7-year-old boy and a 21-year-old man, who developed a brief psychotic disorder that may have been caused by oxybutynin. The first patient was kept under observation with vital functions supported but no medication. All his psychotic symptoms regressed and his general condition improved. The second patient was treated with olanzapine 10 mg/day. His psychotic symptoms resolved within 3 weeks. Our two case reports provide evidence that oxybutynin may induce psychotic disorders, and in younger patients.

A Case Report On Atropine Induced Psychosis

IJPSR 2016; 7(1): 387-391.

Tom NR, Varghese GH, Alexander H, Swethalekshmi V, Kumar TRA and Sivakumar T

The administration of atropine to a large population for treatment of intoxication carries the risk of allergic or toxic reactions in a small number of patients. It has been reported rarely in the literatures .We describe a cases of atropine-induced psychotic disorder in a substance abused patient and different approaches of management. Dryness of the mouth, blurred vision, photophobia and tachycardia commonly occur with chronic administration of doses. In addition psychotic symptoms such as restlessness and excitement, hallucinations, delirium may occur due to atropine. This is a study of a 55 year old female patient who manifested with visual and auditory hallucination, fatigue, anxiety, headache visual disturbances and chest tightness after intake of atropine. To manage this adverse drug reaction the dose of atropine was progressively reduced to 1ml/hr and 0.5ml/hr and discontinued after appearance of signs of complete atropinization. Patient was given with IV morphine 2 mg/hr to manage agitation and IV haloperidol 5mg as required to managing the psychiatric effects. Physostigmine, scopolamine or glycopyrrolate was given in some cases as replacement of therapy in atropine-induced psychosis. In this case, symptomatic treatment is appropriate as it is substance abused patient, no long term therapy is needed for the patient and anticholinergic toxicity is likely to resolve within days of discontinuing the offending agent.

REGULATORY UPDATES AND MEDICAL NEWS

Compiled by Dr. Swati Patil

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

FDA Drug Safety Communication: FDA to review study examining use of oral fluconazole in pregnancy

The U.S. Food and Drug Administration (FDA) is evaluating the results of a Danish study1 that conclude there is a possible increased risk of miscarriage with the use of oral fluconazole for yeast infections. They are also reviewing additional data and will communicate our final conclusions and recommendations when the review is complete.

Health care professionals should be aware that the Centers for Disease Control and Prevention guidelines recommend only using topical antifungal products to treat pregnant women with vulvovaginal yeast infections, including for longer periods than usual if these infections persist or recur.

The current FDA drug label states that data available from studies in people do not suggest an increased risk of problems during pregnancy or abnormalities in developing babies when women are exposed to a single 150 mg dose of oral fluconazole to treat vaginal yeast infections. However, high doses of oral fluconazole (400-800 mg/day) taken by pregnant women for much longer than a single dose have resulted in reports of abnormalities at birth. In the Danish study,1 most of the oral fluconazole use appeared to be one or two doses of 150 mg. Until FDA's review is complete and more is understood about this study1 and other available data, they have advised cautious prescribing of oral fluconazole in pregnancy.

FDA Drug Safety Communication: FDA to review study examining use of oral fluconazole (Diflucan) in pregnancy.[Internet]. [Cited in August 2016]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm497482.htm.

Food and Drug Administration (FDA) approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection).

Fluoroquinolones are antibiotic medicines that work by killing or stopping the growth of bacteria that can cause illness. They are FDA-approved to prevent or treat certain serious bacterial infections.These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. Fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis, (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

The labels of fluoroquinolone medicines already have a Boxed Warning for tendinitis, tendon rupture, and worsening of myasthenia gravis. The labels also include warnings about the risks of peripheral neuropathy and central nervous system effects. Other serious risks associated with fluoroquinolones are described in the labels, such as cardiac, dermatologic, and hypersensitivity reactions. After FDA's

2013 review that led to the additional warning that peripheral neuropathy may be irreversible. The side effects occurred within hours to weeks after starting the fluoroquinolone, and at the time we received the reports, the side effects had continued for an average of 14 months to as long as 9 years after stopping the medicines. Several cases reported that some side effects stopped or improved after discontinuation of the medicine; others reported the side effects worsened or continued.

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects.[Internet]. [Cited in August 2016]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm.

Canagliflozin: Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations

FDA is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with the diabetes medicine canagliflozin. FDA has not determined whether canagliflozin increases the risk of leg and foot amputations. FDA is currently investigating this new safety issue and will update the public when we have more information. Canagliflozin is a prescription medicine used with diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin lowers blood sugar by causing the kidneys to remove sugar from the body through the urine. Health care professionals should follow the recommendations in the canagliflozin drug labels. Monitor patients for the signs and symptoms described above and advise patients to seek medical advice if they experience them.

Canagliflozin (Invokana, Invokamet): Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations. [Internet]. [Cited in August 2016]. Available from: http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm501565.htm.

MATCH THE FOLLOWING DRUG WITH ITS SPECIFIC ADR

Dr SharmadaNerlekar*,Dr AbhilashaRashmi**

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

1.	Lamotrigine	A.	Hypoprothrombinaemia
2.	Cilostazol	B.	Stroke in elderly.
3.	Tibolone	C.	Hypokalaemia
4.	Erlotinib	D.	Intraoperative Floppy Iris Syndrome
5.	Cefoperazone	E.	Dose related neurotoxicity
6.	Naltrexone	F.	Unpredictable Cardiotoxicity
7.	Thioridazine	G.	Risk of prostrate cancer
8.	Tamsulosin	H.	Interstitial lung disease
9.	Heparin	I.	Increased risk of bleeding
10.	Olanzapine	J.	Eye damage on long term use
11.	Tegaserod	K.	Severe rash in kids.
12.	Finasteride	L.	Vaginal spotting
13.	Gossypol	M.	Haematuria
14.	Carbamazepine	N.	Headache
15.	Ginkgo biloba	O.	Hepatotoxicity

ANSWERS

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

ALPHABET 'M' PUZZLE

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

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

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

1. Reversible but severe CNS toxicity like seizures, acute psychosis & vertigo are seen in 0.5% of patients after administration of this quinoline antimalarial drug.
2. Corneal Verticillata, which are brown whorl-like pigmentary deposits in the corneal epithelium, are seen with the use of this antiarrhythmic drug.
3. Iritis in 25%, raised intraocular pressure in 15-20% of patients, cataracts & vitritis are the major ocular adverse effects of this antisense oligonucleotide when administered intravitreally for treatment of cytomegalovirus retinitis.
4. Clinically significant thrombocytopenia occurs in about 10% of patients receiving this "Inodilator" for treatment of heart failure.
5. Hemolytic Uremic Syndrome, which occurs due to drug induced endothelial damage, is the most dangerous toxic effect seen with this anticancer antibiotic.
6. Auditory impairment is associated with this glycopeptide antimicrobial agent if its plasma concentration rises above 60 µg/ml.
7. Tendency to develop renal calculi, probably due to inhibition of carbonic anhydrase, is seen in about 1% of individuals during treatment of this sulfonamide antiepileptic.
8. About 17% patients receiving this monoclonal antibody experience an infusion reaction characterized by fever, urticaria, hypotension & dyspnea within 1-2 hours of its administration.
9. Gall bladder stones occur frequently with chronic use of somatostatin analogs when used in conditions like _____.
10. The principal therapeutic use of _____ factor (5 formyl-tetrahydrofolic acid) is to circumvent the inhibition of dihydrofolate reductase (DHFR) in high dose methotrexate therapy and also as an antidote to counteract the toxicity of folate antagonists.

ALPHABET 'M' PUZZLE:

ANSWERS : 1. Mefloquine 2.Amiodarone 3.Fomivirsen 4.Inamrinone 5.Mitomycin c 6.Vancomycin 7.Zonisamide 8.Daclizumab 9.Insulinoma 10.Citrovorum

NOTES

NOTES

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

Please feel free to contact us for the same.

Names	Phone No.	E-mail
Dr Sudhir Pawar	2406 3162	dr.sudhirpawar@gmail.com
Dr Neha Kadhe	2406 3206	nehakadhe@yahoo.com
Dr Manjari Advani	2406 3205	manjari.advani@gmail.com
Dr Jaisen Lokhande	2406 3164	dr_jaisen@yahoo.co.in
Dr Swati Patil	2406 3161	drswati246@gmail.com
Dr Swapnil Meshram	2406 3161	swapmd4@gmail.com
Dr Swapnil Jamdade	2406 3161	drswapniljamdade@gmail.com
Dr Trupti Jadhao	2406 3161	truptijadhao90@gmail.com

Address for correspondence :

Dr. Sudhir Pawar

Department of Pharmacology,

College Building, LTMMC & LTMGH,

Sion, Mumbai-400022.

Tel.: 022-2406 3160 • E-mail: ltmghbulletin@yahoo.com

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