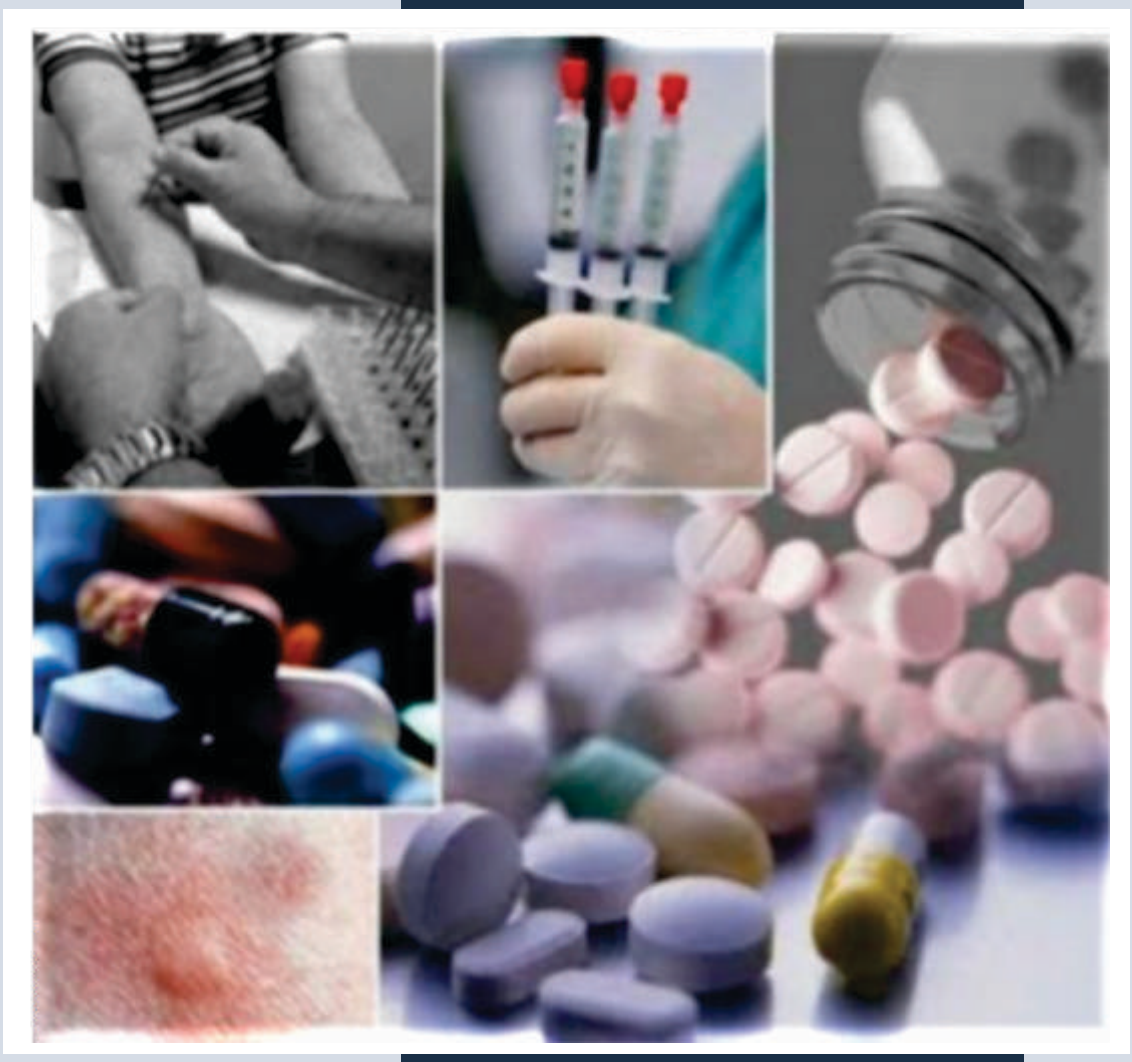
AUGUST 2019 / VOLUME 9 / ISSUE 2

BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL



DEPARTMENT OF PHARMACOLOGY,

LTMMC & LTMGH, Sion, Mumbai – 22.

Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

INDEX

From the Editor's Desk . . . . ✍

Dear friends and colleagues,

I am extremely pleased to release the second issue of Bulletin on Adverse Drug Reaction for the year 2019.

The first article deals with the adverse effects of drug causing hematological disorders affecting red blood cells. The effect of these drugs on RBCs can manifest in the form of various types of anemias including megaloblastic anemia, aplastic anemia, hemolytic anemia, methemoglobinemia and sideroblastic anemia. This review attempts to emphasize on drugs causing this condition and also some of the preventive and therapeutic measures described in literature.

The second article briefs us on a very important condition of Metabolic syndrome which constitutes high blood pressure, hyperglycemia, obesity, and dyslipidemia. Even though the awareness is increasing about this condition, paradoxically the incidence of Metabolic syndrome is also continuously rising. Apart from the changing lifestyle which involves high calorie diet and sedentary life, the use of certain drugs for the management of other diseases may also increase the risk for the development of metabolic syndrome. This article gives an overview of various drugs causing Metabolic syndrome and some preventive and therapeutic strategies for the same.

Other features in this issue include an interesting case report on ethambutol induced optic nerve damage seen in a pediatric patient, analysis of the ADRs from our institute, current news related to drug regulatory and puzzles.

I sincerely hope that this issue enlightens the readers regarding adverse drug reactions.

Finally, I would like to thank all the clinical departments of 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 hard work in unfolding our current issue of the bulletin.

Thank you,

Dr. Sudhir Pawar

DRUG INDUCED ANEMIA

Dr. Kinnera Putrevu

Specialty Medical Officer, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Introduction

Modern pharmacotherapy has been credited with significant advances in the field of human healthcare over the last few decades. However, these drugs are also capable of causing adverse effects such as drug-induced hematological disorders that can extend along the entire spectrum of hematology, affecting red cells, white cells, platelets, and the coagulation system. The effect of these drugs on red blood cells (RBCs) specifically can manifest in the form of various anemias which include megaloblastic anemia, aplastic anemia, hemolytic anemia, methemoglobinemia and sideroblastic anemia. Data obtained from the Berlin Case Control Surveillance Study for Serious Blood dyscrasias conducted from 2000 to 2009, also suggests that a substantial number of blood cytopenias can be attributed to drug therapy.[1,2] This article reviews the condition of drug induced anemia and briefs on the preventive and therapeutic measures.

Drug induced megaloblastic anemia [3,4]

Megaloblastic anemia is a condition characterized by the presence of a hypercellular bone marrow with large, abnormal hematopoetic progenitor cells called as megaloblasts. Megaloblastic anemia can be congenital or acquired and can most commonly arise from vitamin B12 (cobalamin) and folic acid deficiency. While malnutrition or defective absorption are the usual causes, megaloblastic anemia can also be drug induced.

Drugs can cause megaloblastosis via the following mechanisms;

- Reduced absorption, transport or delivery of folate
- Reduced absorption, transport or delivery of vitamin B12
- Physical destruction of the vitamins
- Competing for the reducing enzymes

The enzyme dihydrofolate reductase (DHFR) is required to convert dihydrofolate into tetrahydrofolate which functions as a methyl group shuttle. Tetrahydrofolate and its derivatives are essential for purine and thymidylate synthesis, which are vital for cell proliferation and cell growth. Thus, a deficiency of DHFR deprives the cell of thymidylate and interferes with DNA synthesis. Besides, tetrahydrofolate which is formed in this reaction is the active form of folate in humans. Hence, inhibition of DHFR can cause functional folate deficiency manifesting as megaloblastic anemia.

This fundamental role of dihydrofolate reductase is targeted by antineoplastic therapy and some antibacterial drugs (mainly sulfa drugs).[4] Thus, drugs that act by interfering with DNA synthesis, such

as antimetabolites and alkylating agents, some antinucleosides used against HIV and other viruses, can all induce megaloblastic anemia. Examples of such drugs include gemcitabine, capecitabine, hydroxyurea, permetrexed, cladiribine. Cotrimoxazole has been reported to cause megaloblastic anemia with both low and high doses with a more prominent effect in patients with folate or vitamin B12 deficiency. Antibiotics such as sulfasalazine may induce megaloblastic anemia probably by interfering with their absorption. Methotrexate can cause megaloblastic anemia in nearly 3-9% of patients as it acts by irreversibly inhibiting dihydrofolate reductase.[5] Phenobarbital, primidone, and phenytoin can cause megaloblastosis by inhibiting folate absorption or by increasing folate catabolism.

The anemia, usually, develops gradually, and symptoms may be present only in severely anemic patients. Common symptoms include weakness, shortness of breath primarily during exercise, palpitation, and lightheadedness. Some minor differences exist between the clinical manifestations caused by cobalamin deficiency and folic acid deficiency. Neurological manifestations are observable in vitamin B12 deficiency which include paresthesia and balance disorders. These patients may present with lancinating pain affecting mainly the lower limbs caused by peripheral neuropathy. Rarely, visual disturbances resulting from optic atrophy and autonomic disturbances such as bladder or erectile dysfunction may be observed.[6,7]

The drugs causing megaloblastic anemia with their possible mechanism of action are enlisted in Table 1.

Table 1: Drugs causing megaloblastic anemia [3,4]

Mechanism	Drugs
Drugs that decrease absorption of folic acid	Erythromycin, aminosalicylic acid, oral contraceptive pills, tetracycline, cotrimoxazole, sulfadoxine-pyrimethamine, phenobarbital, phenytoin
Drugs that have folate analogue activity	Trimethoprim, raltitrexed, permetrexed, methotrexate, proguanil, pyrimethamine
Drugs that interfere with pyrimidine synthesis	Capecitabine, gemcitabine, hydroxyurea, teriflunomide, leflunomide, cytosine arabinoside, mercaptopurine
Drugs that modulate purine metabolism	Azathioprine, mycophenolate mofetil, fludaribine, cladiribine
Drugs that decrease absorption of vitamin B12	Isoniazid, metformin, proton pump inhibitors
Drugs that increase excretion of vitamin B12	Sodium nitroprusside

In order to manage drug-induced megaloblastic anemia, the cause of megaloblastosis should be determined initially. If an alternative drug is available, the causative agent might be discontinued and

replaced by the alternative agent. More importantly, adequate intake of Vitamin B12 and folic acid should be ensured. Toxicity from the use of folate antagonists is treated with folinic acid (N5-formyl tetrahydrofolate) 3 to 6 mg/d intramuscularly. This treatment is known as folinic acid rescue and is often used in chemotherapy to rescue patients receiving high doses of methotrexate. In patients suffering from phenytoin and phenobarbital induced megaloblastic anemia, 1 mg/day of folic acid can correct the anemia but may also interfere with the effectiveness of these medications.[8]

Drug induced aplastic anemia [3, 4]

Aplastic anemia (AA), characterized by pancytopenia with a hypocellular bone marrow, can be inherited or acquired. Though acquired aplastic anemia is most commonly idiopathic by nature, it can also occur following exposure to toxins, irradiation, viruses, and drugs. The number of circulating neutrophils, platelets, and erythrocytes is reduced in drug induced aplastic anemia. This is because the multipotent hematopoietic stem cells undergo damage before their differentiation to committed stem cells.[9]

Young and Maciejewski have postulated that drug induced aplastic anemia is mediated through intermediate metabolites that bind covalently to protein and DNA. These reactive metabolites are both formed and degraded by complex metabolic pathways. The idiosyncratic nature of drug-induced aplastic anemia can be explained by the genetic variation in the presence of these metabolites and the enzymes responsible for the pathways. It is characterized by dose independence, a latent period before the onset of anemia and continuing marrow damage even after drug discontinuation.[10]

Several drugs have been implicated in causing AA which include anti-inflammatory drugs such as indomethacin, diclofenac, naproxen, piroxicam, phenylbutazone and Disease Modifying Anti-Rheumatic Drugs (DMARDs) like gold, penicillamine, sulfasalazine, etc. Antibiotics like chloramphenicol, sulfonamides, cotrimoxazole and linezolid and anti convulsants including phenytoin, carbamazepine and valproic acid have also been implicated.

Table 2: Drugs reported to have a rare association with Aplastic anemia[4,10]

Class of drugs	Causative drugs
Anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs (NSAIDs) - indomethacin, diclofenac, naproxen, piroxicam, phenylbutazone
	Disease Modifying Anti-Rheumatic Drugs (DMARD) - gold, penicillamine, sulphasalazine
Antibiotics	Chloramphenicol, sulphonamides, cotrimoxazole, linezolid
Diuretics	Furosemide, thiazides
Anti-convulsants	Phenytoin, carbamazepine and valproic acid

Anti-thyroid drugs	Carbimazole, propylthiouracil
Anti-depressants	Dothiepin, phenothiazines, amphetamines
Anti-diabetics	Chlorpropamide, tolbutamide
Anti-malarial agents	Chloroquine
Others	Mebendazole, thiazides, allopurinol, mesalazine, ticlopidine

Drug induced aplastic anemia is associated with a mortality as high as 50% and is therefore one of the most serious acquired blood dyscrasias. While the frequency of aplastic anemia seen in hospitals of Asian countries is much higher than that reported from the West, the precise incidence of this disorder in India is not known. The estimated incidence of aplastic anemia in India and other Asian countries is said to be about 2-3 times higher than the Western countries and nearly 6 to 8 per million population per year.[9]

Symptoms of drug-induced aplastic anemia may develop days to months following initiation of therapy with the causative drug. These include signs of anemia like fatigue, pallor, and weakness; as well as signs of neutropenia like pharyngitis, fever and chills. Because anemia may develop slowly due to the longer life span of erythrocytes, the presenting symptoms may initially be those indicating neutropenia and thrombocytopenia (bruising, bleeding). In view of the high mortality in this condition, treatment of drug-induced aplastic anemia should be initiated immediately after the anemia is diagnosed. The treatment of aplastic anemia is decided by the severity of the disease and should primarily aim to limit the requirement for transfusions, improve peripheral blood counts, and minimize the risk for infections. The first step in the treatment is removal or withdrawal of the causative agent which may also help in the disease reversal. Treatment of moderate disease cases is decided by the degree of cytopenia and usually ranges from no clinical intervention to immunosuppressive therapy.[11]

Fundamentally, allogeneic hematopoietic stem cell transplantation and immunosuppressive therapy are the two major options for patients with drug-induced aplastic anemia. The therapy of choice depends on several factors, including disease severity, age and availability of a human leukocyte antigen-matched donor. Presently, the standard immunosuppressive therapy for aplastic anemia is a combination of cyclosporine and anti-thymocyte globulin (ATG). Cyclosporin is administered at a dose of 5 mg/kg/day to achieve trough blood levels of 100-200 µg/L. It is continued while the blood count continues to rise. The drug is then tapered slowly (25 mg every 2-3 months) to prevent the risk of relapse subsequently. The dose of horse ATG is 40 mg/kg/day for 4 days. It is given as an intravenous infusion over 12-18 h. Cyclosporine exerts its action by inhibiting the activation of resting T cells via suppression of interleukin (IL)-2 production and release. Addition of cyclosporine to anti-thymocyte globulin was found to improve failure-free survival, reduce the number of immunosuppressive courses required, and also increase the response rate. This regimen has been demonstrated to achieve 5-year survival rates, with a lower response in older patients.[12]

Drug induced hemolytic anemia [3,4]

Snapper in 1953 described a patient who developed pancytopenia with hemolytic anemia (HA), associated with a positive direct antiglobulin test (DAT), following ingestion of mephenytoin. This was the first instance when drugs were suspected as a cause of immune hemolytic anemia (IHA). Subsequently, in 1980, it was reported that nearly 12% of 347 immune hemolytic anemia cases were drug-induced.[13] Hemolysis is the process of premature destruction of RBCs and can occur because of abnormal changes in the intravascular environment or defective RBCs. Drug induced immune hemolytic anemia (DIIHA) commonly presents as malaise, pallor, fatigue and shortness of breath. The incidence of DIIHA is estimated to be approximately 1 in 1 million individuals.[14]

One of the earliest drugs to be implicated in the causation of drug induced immune hemolytic anemia was methyldopa. It is commonly used in the treatment of hypertension and was reported to cause a high incidence of positive DATs and even DIIHA in 1966. Four possible mechanisms of immune hemolytic anemia have been postulated. These include:

- Immune complex mechanism: Ackroyd suggested that drugs may act as a hapten, combining loosely with the cell membrane and stimulating antibody production to the combined antigen.[15] This "immune complex" theory was initially suggested for drug induced thrombocytopenia which was subsequently extended to RBCs to explain drug induced IHA due to drugs other than methyldopa and penicillin. Therefore, when the drug is received again, drug-anti-drug immune complexes form and get attached to RBCs nonspecifically, activating complement and leading to anemia.

- Drug adsorption: This mechanism was suggested by Garratty and Petz in view of hemolytic anemia occurring in patients receiving large doses of penicillins. It was postulated that RBCs became coated with penicillin in vivo, and that if IgG penicillin antibodies were present, they would react with the RBC bound penicillin, leading to IgG sensitized RBCs. This situation would lead to a positive DAT and possible destruction of the IgG-coated RBCs by macrophages. Complement is not usually involved in this reaction and intravascular hemolysis rarely occurs.

- Drug induced autoantibodies: In 1966, it was shown that some drugs (eg. Methyl dopa, L-dopa) could cause the production of true RBC autoantibodies. These could subsequently lead to autoimmune hemolytic anemia (AIHA).[16]

- Membrane modification: This mechanism was suggested by Garratty and Petz, when it was shown that cephalothin, and later some other drugs, can affect the RBC membrane so that proteins become bound to the RBCs nonimmunologically. This mechanism was first thought to lead only to positive antiglobulin tests, but more recently it was proven it could cause DIIHA.[17]

It has been reported that nearly 127 drugs have demonstrated sound evidence that they caused DIIHA. The three most common drugs currently causing DIIHA are piperacillin, cefotetan, and ceftriaxone.

The drug most commonly associated with fatal HA was cefotetan (8%), closely followed by ceftriaxone (6%), particularly in young children.[14]

First generation drugs like cephalexin, cephalothin, and cefazolin have caused positive DATs but have rarely resulted in DIIHA.[18] Reports of DIIHA due to the fourth generation cephalosporins have not been encountered until now. Following cefotetan and ceftriaxone, piperacillin is the third most common drug associated with DIIHA. Piperacillin is marketed in combination with tazobactam, a β-lactamase inhibitor for treating serious infections. RBCs coated with this drug combination can be reactive for either due to antibodies to piperacillin or because of nonimmunologic protein adsorption owing to the tazobactam component. Antibodies to tazobactam must also be considered even though they have not been reported yet. Piperacillin antibodies are usually IgM + IgG, activate complement, and cause intravascular lysis.

Besides these drugs, cases of immune hemolytic anemia in patients receiving immunosuppressive therapy with alemtuzumab (anti-CD52), mycophenolate mofetil (MMF) and daclizumab (anti-Tac/CD25) following pancreas transplant have been reported by Elimelakh et al.[19] A case of hemolytic anemia was reported by Sukhal et al which was likely due to the induction of drug-independent antibodies (which are indistinguishable from RBC autoantibodies in AIHA) by levofloxacin. The case satisfied the clinical and serological diagnostic criteria of hemolysis (indirect hyperbilirubinemia, decreasing haemoglobin level, elevated lactate dehydrogenase level, low haptoglobin level, and peripheral blood smear consistent with hemolysis) along with a positive Coombs test and an autoantibody screen showing IgG autoantibodies (warm antibodies).[20]

Oxidative hemolytic anemia is a hereditary condition that can occur most commonly as a result of glucose-6-phosphate dehydrogenase (G6PD) deficiency and also because of deficiencies of other enzymes like methemoglobin reductase, or nicotinamide adenine dinucleotide phosphate (NADPH). G6PD is required in RBCs for the production of NADPH to keep glutathione in its reduced form which is essential in order to protect RBCs from oxidative damage. RBCs deficient in G6PD are therefore vulnerable to hemolysis resulting from oxidation of the sulfhydryl groups of hemoglobin mediated by oxidative drugs. In cases of drug-induced oxidative hemolytic anemia, the only available treatment is removal of the offending drug. Hence, it is prudent to avoid drugs capable of inducing oxidative hemolytic anemia in patients with enzyme deficiencies. Some of these drugs are sulfanilamide, primaquine, phenazopyridine, sulfamethoxazole, metformin, dapsone, nitrofurantoin and rasburicase among others.

Drug induced Methemoglobinemia[4, 21]

Methemoglobinemia is a condition characterized by excess production of methemoglobin which can result in impaired oxygen transport, thus leading to tissue hypoxemia and in severe cases, death. Methemoglobin (MetHb) is formed when the ferrous iron (Fe2+) of hemoglobin is oxidized to the

ferric (Fe3+) form due to oxidizing chemical or drugs. The level of MetHb, under normal conditions, is accommodated under <1% of the total Hb in blood. This is due to the presence of the MetHb reductase enzyme system comprising of cytochrome B5 reductase, flavin reductases, NADPH-MetHb reductase, and NADPH-MetHb-diaphorase which are required to convert the MetHb back to Hb in the red blood cells. The NADPH pathway is directly dependent on both, the activity of glutathione and glucose-6-phosphate dehydrogenase. However hereditary deficiencies in the activity of this enzyme may lead to chronic methemoglobin levels of 40% to 50%.

Methemoglobinemia can be congenital (due to defects in enzymatic reduction of hemoglobin) or acquired. These patients present with symptoms of anoxia, cyanosis, reduced oxygen saturation, and chocolate-brown arterial blood. The diagnosis is confirmed by measuring the methemoglobin level on arterial blood gas sampling. Drugs that induce methemoglobinemia can either directly oxidize hemoglobin or are metabolically activated to oxidizing species. Dapsone, used to treat leprosy, dermatitis herpetiformis, and prophylaxis for pneumocystis carinii, is metabolized to a hydroxylamine derivative and can lead to methemoglobinemia. Primaquine and local anesthetics (topical or spray benzocaine and prilocaine) have also been reported to cause methemoglobinemia. Amyl nitrite and isobutyl nitrite have also been implicated.

The treatment of methemoglobinemia includes cessation of the inducing agent, oxygen, and methylene blue.[22] The use of supplementary O2 increases plasma levels of dissolved O2 and increases diffusion and oxygen delivery. Methylene blue is started as an antidote in patients with significant clinical manifestations. It is administered intravenously in a dose of 1 to 2 mg/kg over five minutes. During its use, the alternative enzymatic system (NADPH methemoglobin reductase) becomes essential in the reduction of methemoglobin. Methylene blue activates NADPH methemoglobin reductase which reduces methylene blue to methylene leucoblue, which then transforms methemoglobin to reduced hemoglobin by a non-enzymatic mechanism. Additional doses can be administered every hour, if necessary, up to a maximum total dose of 7 mg/kg.[23]

Drug induced sideroblastic anemia[4]

Sideroblastic anemia is a condition in which ring sideroblasts (erythroblasts containing iron-positive granules arranged around the nucleus) are present on the bone marrow aspirate smear stained for iron with Prussian blue. Sideroblastic anemia is characterized by impaired heme biosynthesis in erythroid progenitors, the etiology of which can be inherited or acquired. Acquired sideroblastic anemia may arise from primary or secondary causes. Primary causes comprise of clonal hematologic disorders which include myelodysplastic syndrome with ring sideroblast (MDS-RS) and refractory anemia with ring sideroblasts RARS. Secondary causes include drugs, toxins, copper deficiency or chronic neoplastic disease. Various drugs such as antibiotics, hormones, copper-chelating agents and chemotherapeutic agents have been associated with causing sideroblastic anemia. Moreover, ringed sideroblasts may also be found in malnourished patients who abuse alcohol.[24]

Drug-induced sideroblastic anemia has been associated with isoniazid in multiple reports.[25, 26] Piso et al reported a case of a 45 year old woman who developed severe anemia (Hb- 4.7g/dL) four months after introducing isoniazid as part of her treatment for tuberculosis. The anemia rapidly resolved following cessation of isoniazid. Piso et al postulated that isoniazid inhibits the enzyme amino-levulinate synthase thus, resulting in marked depletion of heme synthesis. This anemia may also be reversed by the administration of pyridoxine.[27]

Chloramphenicol and chelating agents such as penicillamine and triethylene tetramine dihydrochloride (used in Wilson's disease) are known to induce reversible Sideroblastic anemia. Linezolid, an effective oxazolidinone antibiotic used in the treatment of respiratory tract and skin infection caused by Gram-positive pathogens, has been implicated in causing sideroblastic anemia following prolonged therapy. The toxicity with linezolid appears to be due to inhibition of mitochondrial translation leading to reversible sideroblastic anemia following a median exposure of 2 weeks, similar to that observed with chloramphenicol.[28]

The management of drug induced sideroblastic anemia includes packed cell transfusion and discontinuation of the offending drug. Besides, substitution of pyridoxine has been recommended during treatment with isoniazid in patients suffering from tuberculosis.

Conclusion:

The most commonly occurring drug induced anemias include megaloblastic anemia, aplastic anemia, and hemolytic anemia. Direct immune reaction or toxicity due to drug or metabolite are the possible mechanisms by which these reactions can occur. Determining the exact cause of a drug induced blood abnormality and establishing the incidence of these reactions is challenging due to the large number of drugs implicated. Withdrawal of the causative drug and providing symptomatic support to the patient remain the initial steps in the treatment of drug-induced anemia and possibly, disease reversal. Due to the potentially dangerous nature of this condition, care should be taken before prescribing agents which are prone to causing drug induced anemias.

References:

1. Andersohn F, Bronder E, Klimpel A, Garbe E. Proportion of drug-related serious rare blood dyscrasias: Estimates from the Berlin Case-Control Surveillance Study. American journal of hematology. 2004;77(3):316-318.
2. Rao KV. eChapter 24. Drug-Induced Hematologic Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 9e New York, NY:McGraw-Hill;2014.http://accesspharmacy.mhmedical.com/content.aspx?bookid= 689&sectionid=48811451. Accessed August 16, 2019.
3. Al Qahtani SA. Drug-induced megaloblastic, aplastic, and hemolytic anemias: current concepts of pathophysiology and treatment. Int. J. Clin. Exp. Med. 2018;11(6):5501-12.
4. Mintzer DM, Billet SN, Chmielewski L. Drug-induced hematologic syndromes. Advances in hematology. 2009;2009:1-11.

5. Weinblatt ME. Toxicity of low dose methotrexate in rheumatoid arthritis. J Rheumatol 1985;12(Suppl 12): 35-39.
6. Nagao T, Hirokawa M. Diagnosis and treatment of macrocytic anemias in adults. Journal of General and Family Medicine. 2017;18(5):200-204.
7. Hesdorffer C, Longo D. Drug-Induced Megaloblastic Anemia. New England Journal of Medicine. 2015;373(17):1649-1658.
8. Green R, Datta Mitra A. Megaloblastic Anemias. Medical Clinics of North America. 2017;101(2):297-317.
9. Melinkeri SR. Epidemiology, pathogenesis and diagnosis of aplastic anaemia. J Assoc Physicians India. 2015;63(3 Suppl):8-12.
10. Young NS, Maciejewski J. The pathophysiology of acquired aplastic anemia. New England Journal of Medicine. 1997;336(19):1365-72.
11. Malkin D, Koren G, Saunders E. Drug-Induced Aplastic Anemia: Pathogenesis and Clinical Aspects. Journal of Pediatric Hematology/Oncology. 1990;12(4):402-410.
12. Young N. Aplastic Anemia. New England Journal of Medicine. 2018;379(17):1643-1656.
13. Petz LD, Garratty G. Immune hemolytic anemias. 2nd ed. Philadelphia: Churchill Livingstone; 2004
14. Garratty G. Immune hemolytic anemia associated with drug therapy. Blood reviews. 2010;24(4-5):143-50.
15. Ackroyd JF. The immunological basis of purpura due to drug hypersensitivity. Proc R Soc Med 1962;55:30-6.
16. Worlledge SM, Carstairs KC, Dacie JV. Autoimmune haemolytic anaemia associated with alpha-methyldopa therapy. Lancet 1966;2:135-9.
17. Spath P, Garratty G, Petz L. Studies on the immune response to penicillin and cephalothin in humans. II. Immunohematologic reactions to cephalothin administration. J Immunol 1971;107:860-9.
18. Lim K, Tran H, Hirai-Yang A, Vakil N, Marks G, Klapper E. Cefotetan-Induced Hemolytic Anemia: Case Series and Review. Journal of Pharmacy Practice. 2018;1-4.
19. Elimelakh M, Dayton V, Park KS, Gruessner AC, Sutherland D, Howe RB, Reding MT, Eastlund T, van Burik JA, Singleton TP, Gruessner RW. Red cell aplasia and autoimmune hemolytic anemia following immunosuppression with alemtuzumab, mycophenolate, and daclizumab in pancreas transplant recipients. Haematologica. 2007;92(8):1029-36.
20. Sukhal S, Gupta S. Drug-induced immune haemolytic anaemia caused by levofloxacin. Singapore medical journal. 2014;55(8):e136-e138.
21. David SR, Sawal NS, Hamzah MN, Rajabalaya R. The blood blues: A review on methemoglobinemia. Journal of Pharmacology and Pharmacotherapeutics. 2018;9(1):1-5.
22. Alanazi MQ. Drugs may be induced methemoglobinemia. J Hematol Thrombo Dis. 2017;5(3):1-5.
23. Zedan A, Omar S, Fenire M. Drug-induced methemoglobinemia: a case report and review of literature. The Southwest Respiratory and Critical Care Chronicles. 2014;2(5):34-8.
24. Ashorobi D, Chhabra A. Sideroblastic Anemia. [Updated 2019 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538287
25. Haden HT. Pyridoxine-responsive sideroblastic anemia due to antituberculous drugs. Archives of internal medicine. 1967;120(5):602-6.
26. Verwilghen R, Reybrouck G, Callens L, Cosemans J. Antituberculous Drugs and Sideroblastic Anaemia. British Journal of Haematology. 1965;11(1):92-98.
27. Piso R, Kriz K, Desax M. Severe isoniazid related sideroblastic anemia. Hematology Reports. 2011;3(1):2.
28. Willekens C, Dumezy F, Boyer T, Renneville A, Rossignol J, Berthon C, Cotteau-Leroy A, Mehiaoui L, Quesnel B, Preudhomme C. Linezolid induces ring sideroblasts. Haematologica. 2013;98(11):e138-e140.

DRUGS CAUSING METABOLIC SYNDROME

Dr. Roshini Panchal

Specialty Medical Officer, Department of Pharmacology, LTMMC & GH, Sion, Mumbai

Introduction

Metabolic syndrome (MS) is a condition which constitutes of high blood pressure, hyperglycemia, obesity, and dyslipidemia.[1] In India, prevalence of metabolic syndrome is continuously increasing due to changed lifestyle which involves high calorie diet associated with sedentary life. In a study, it was found that the overall prevalence of metabolic syndrome was 40.9%.[1] Co-existence of multiple metabolic abnormalities like hypertension, hyperglycemia, and hyperuricemia, was observed in few patients as early as 1923.[2] After five decades , Reaven coined the term 'syndrome X' which constitutes of glucose intolerance , hypertension, increased very-low-density lipoproteins (VLDL), triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C), with insulin resistance.[2] The American Association of Clinical Endocrinologists (AACE) have preferred using the term insulin resistance syndrome over Metabolic Syndrome.[2] There are various terminologies used for MS and various parameters used to assess MS. Indian diabetes risk score (IDRS) is one such parameter which is useful for predicting MS. It constitutes of simple clinical information like age, waist circumference, family history of diabetes, and physical activity. IDRS > 60 predicts the chances of developing MS and cardiovascular disease.[2] Apart from the causes mentioned above, the use of certain drugs while management of a particular disease may also increase the risk for the development of the MS by either increasing weight or altering metabolism of lipid or glucose.[3]

Drug induced metabolic syndrome[3]

Drug induced metabolic syndrome is a significant issue which clinicians have to be watchful while treatment of patients. There are numerous adverse drug reaction reports regarding metabolic effects such as glucose intolerance and lipid abnormalities with the use of diuretics and β blockers. These are among the most prescribed drugs which increase the susceptibility to metabolic syndrome hence weighing risks versus benefits is very important while prescribing such drugs.[3]

Following are the drugs which gives rise to parameters which constitute **Metabolic Syndrome**

Drugs	**Parameters**
Thiazides	Dyslipidemia, hyperglycemia
Beta Blockers	Dyslipidemia, hyperglycemia
Niacin	Hyperglycemia
Thiazolidindiones	Dyslipidemia, obesity

Oral Contraceptives	Dyslipidemia, hyperglycemia
Protease Inhibitors	Dyslipidemia, obesity
Antipsycotics	Dyslipidemia, hyperglycemia, obesity
Antidepressants	Obesity
Anticonvulsants	Obesity
Glucocorticoids	Dyslipidemia, hyperglycemia, obesity, elevated blood pressure

Thiazides[3]

There were clinical trials conducted from 1966 to 1993 which found that thiazides increase total cholesterol, low-density lipoprotein cholesterol (LDL C), and triglyceride levels, particularly when given at high doses.[4] In another analysis, cholesterol levels returned to normal after 1 year of treatment with diuretics.[5] Thiazides are reported to contribute to insulin resistance and uncontrolled diabetes. Mechanisms hypothesized include the effect of hypokalemia on insulin secretion, changes in hepatic gluconeogenesis, and a direct toxic effect on the pancreas.[6]

In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[7] post hoc analysis, the incidence of new diabetes was highest for subjects randomized to a diuretic based regimen. But despite the increase in new onset diabetes with the diuretic based regimen in ALLHAT, the chlorthalidone, amlodipine, and lisinopril based regimens provided similar protection from coronary heart disease and non -fatal myocardial infarction. Despite the potential adverse effects, numerous long term clinical trials have demonstrated a reduction in morbidity and mortality with diuretic base therapy. Health care providers should be aware of potential insulin resistance and diabetes among patients utilizing thiazides.

Beta Blockers[3]

Beta blockers are also among the agents recommended in the treatment of primary hypertension. Nonselective and selective β_1 blockers have mild effect on total cholesterol and LDL C levels but lead to a reduction in HDL C and increased triglycerides. In contrast, plasma lipid levels are relatively stable with labetalol (combined α and β blockers) and β blockers with intrinsic sympathomimetic activity. Carvedilol, a combined nonselective β and α_1 blocker, actually has a favorable effect on lipids and is associated with an 8% increase in HDL-C and a 20% reduction in triglycerides.[8]

The use of β blockers may enhance the risk of developing insulin resistance and type 2 diabetes. The Atherosclerosis Risk in Communities Study (ARIC)[9] demonstrated that among hypertensive patients, β-blocker therapy was associated with a 28% increased risk of developing type 2 diabetes compared with no antihypertensive therapy. It is controversial whether the addition of β-blocker therapy for patients with existing diabetes and hypertension has an adverse effect on glucose metabolism or whether

combination therapy consisting of a β blocker and another antihypertensive agent (such as an ACE inhibitor) given to patients without diabetes results in a similar increased risk.[10]

In spite of the potential for metabolic abnormalities induced by β blockers, clinical trials have demonstrated morbidity and mortality benefits in the treatment of hypertension, myocardial infarction, and heart failure.[11]

Niacin[3]

Earlier research demonstrated that niacin may precipitate hyperglycemia in people at risk for diabetes and worsen glycemic control in patients with type 2 diabetes.

More recently, the Arterial Disease Multiple Intervention Trial (ADMIT) demonstrated that niacin can safely be given to type 2 diabetes patients, but careful monitoring of blood glucose levels should be done. The mechanisms for hyperglycemia are unknown but may be related to hepatic parenchymal damage, induction of insulin resistance, or decreased ability to respond to hyperglycemic stimuli.

Thiazolidinedione[3]

Pioglitazone and Rosiglitazone increase insulin sensitization and decrease circulating free fatty acids. Retrospective analyses have demonstrated an increase in LDL-C and total cholesterol concentrations with rosiglitazone, and a lesser improvement in HDL-C concentration than with pioglitazone. Furthermore, pioglitazone had a better reduction in triglycerides and no significant effects in either LDL-C or total cholesterol concentrations. Both of these thiazolidinedione agents may cause similar weight gain.[12]

Oral Contraceptives (OCs)[3]

Progestin has the greatest impact on carbohydrate metabolism. High-dose OCs often result in abnormal glucose tolerance tests.[13] The use of low-dose combination OCs, however, results in minimal change in glucose tolerance or insulin resistance.[14] In general, estrogen increases serum triglycerides and HDL-C but lowers the levels of LDL-C. The androgenic progestins in OCs usually increase serum LDL-C and decrease HDL-C.[13] Women taking OCs should be advised to have evaluations of lipid profiles. This is of particular significance for women who have other risk factors for the development of the metabolic syndrome.

Protease Inhibitors[3]

Protease inhibitors are widely used in the antiretroviral treatment of acquired immunodeficiency syndrome. A common adverse effect of these agents is acquired lipodystrophy, a syndrome similar to the very rare inherited forms. The cause of protease inhibitor-induced lipodystrophy is unknown.

Mechanism hypothesized include impaired differentiation on apoptosis of adipocytes. There is evidence that messenger RNA of key transcription factors regulating adipogenesis is involved in the development of acquired lipodystrophy.[15][16] Recent studies also point to changes in the signaling pathway regulating the peroxisome proliferator-activated receptor-γ.[17] Patients with lipodystrophy develop criteria for the metabolic syndrome and are at increased risk for CV disease and type 2 diabetes. Lipodystrophy is characterized by subcutaneous fat wasting in the face, arms, and legs, with central adiposity. Patients may develop excess fat in the neck and upper back. Dyslipidemia and insulin resistance are also typically associated with the syndrome. Lipodystrophy is associated with all of the protease inhibitors following long-term use. They may increase total cholesterol 40% and triglyceride levels may increase by 200-300 mg/dL.[18]

Antipsychotics[3]

Antipsychotic medications are widely used to treat a variety of psychiatric disorders including schizophrenia, depression, bipolar, and developmental disorders. Since the introduction of the atypical or "second generation" antipsychotics, the older "first generation" medications are used less frequently because of potential adverse effects, which include affective and cognitive impairment and extrapyramidal effects. Weight gain and associated morbidities, however, are common and significant with atypical antipsychotic drug use. The prevalence of obesity and diabetes in patients with psychiatric illness is 1.5-2.0-fold greater than in the general population.[19] Average weight gain varies from 0.5 kg to 5 kg, depending on the specific antipsychotic treatment. Clozapine and olanzapine are associated with the greatest weight gain, followed by risperidone and quetiapine. Ziprasidone and aripiprazole[20][21] are associated with the least amount of weight gain. Changes in appetite and satiety leading to increased caloric intake and altered glucose metabolism are proposed associations. Increased leptin secretion may be related to increased adiposity, although it is unclear whether this is related to medication use or a consequence of increased adipose tissue. Drugs with the highest affinity for histamine H1 (e.g., clozapine, olanzapine) are associated with more weight gain than with those agents that have a lower histamine-H_1 affinity (e.g., ziprasidone, aripiprazole). This dose-dependent effect occurs despite body weight changes and may be related to drug effects on pancreatic insulin secretion. While much of the literature on cardiovascular risk and antipsychotic use is related to body weight and glucose metabolism, recent guidelines for the management of patients treated with these medications also include monitoring recommendations for hyperlipidemia.[3]

Appropriate selection of an antipsychotic is one of the important steps in prevention of metabolic complications for psychiatric patients. Baseline screening should be considered when making the antipsychotic choice. When initiating an antipsychotic, the patient, caregivers and family should be informed regarding drug-induced metabolic risks and symptoms of emergent diabetes and diabetic ketoacidosis so they would know what to expect and for what they should watch. It is essential that appropriate ongoing metabolic monitoring should be included in the patient's care plan.[22]

Antidepressants[3]

Tricyclic antidepressants, particularly amitriptyline, and monoamine oxidase inhibitors, are associated with the greatest weight gain. These agents are no longer widely used. Among the selective serotonin reuptake inhibitors, paroxetine is most likely to cause weight gain. Data are limited on other selective serotonin reuptake inhibitors and their effect on weight. The atypical antidepressants bupropion and nefazodone are considered to have a neutral effect on body weight.[23]

Antiepileptics[3]

Valproate is associated with significant long-term weight gain. In patients treated with valproate, there is evidence that a low resting metabolic rate, contributes to increased body weight. Weight gain has also been reported in patients treated with high doses of gabapentin. Compared with valproate treatment, lamotrigine-treated patients are less likely to have significant weight increase.

Immunosuppressive[3]

Cyclosporine and tacrolimus are immunosuppressive agents used to prevent post-transplant organ rejection. Cyclosporine may cause hyperglycemia through toxic effects on β cells or by the development of insulin resistance. Its effect on carbohydrate metabolism appears to be dose dependent.[24] The mechanism underlying the development of diabetes with tacrolimus is unclear. The multicenter FK506 Kidney Transplant Study[25] reported that compared with cyclosporine-treated individuals, there was a relatively high incidence of insulin-dependent diabetes mellitus in tacrolimus-treated patients. Glucocorticoids are well recognized for their diabetogenic potential, risk of elevated blood pressure with long-term use, and effect on lipid changes.[26]

Cancer treatment induced metabolic syndrome[27]

Even though anticancer agents have shown to cause weight reduction, these drugs have shown to cause insulin resistance and increased blood glucose which can be due to the direct toxic effects on the beta cells of pancreas. The following table gives in the list of drugs and mechanisms involved.

Pharmacological cancer Treatment	Mechanism	Associated with
Cisplatin Alkylators, anthracyclines, camptothecins, epipodophyllotoxins	Possibly damage to vascular endothelium, possibly through damage to mitochondria and production of ROS	Insulin resistance
Androgen-deprivation therapy	Hypogonadism	Dyslipidaemia and insulin resistance

Non Pharmacological cancer treatment	Mechanism	Associated with
Brain surgery with damage to pituitary and hypothalamus.	Hormonal disturbance: deficiency of growth hormone, thyroidtropin, gonadotropin, adenocorticotropin	Obesity
Cranial radiotherapy	Hormonal disturbance: deficiency of growth hormone by damage to the hypothalamus-pituitary axis	Obesity, dyslipidaemia, insulin resistance

Pharmacological and Non Pharmacological Interventions in cancer, both contribute towards developing risk factors to produce metabolic syndrome.

Treatment of Drug-Induced Metabolic Syndrome

The choice of medications for a variety of conditions may affect one or more components of the metabolic syndrome. The association of medication use and development of the metabolic syndrome is increasingly being recognized with many common medications[3] Targeted health education strategies, needs to be systematically implemented in clinical practice.[28]

All the components of the metabolic syndrome are improved by even modest amounts of weight loss achieved with diet and exercise. Pharmacological intervention recommended are statins for dyslipidemia, renin-angiotensin-aldosterone system inhibitors for arterial hypertension, metformin or sodium/glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1RAs) for glucose intolerance, and the GLP-1RA liraglutide for achieving body weight and waist circumference reduction.[29]

Liraglutide 3.0 mg daily subcutaneous injection is the FDA approved drug for chronic weight management in patients with obesity or who are overweight with a BMI ≥27 kg/m2 and have a weight related comorbid condition.[30]

Conclusion

Research needs to be done on the triggering events that lead to metabolic syndrome and the commonality that leads to associated diseases. Nowadays each disease is treated as a separate entity leading to polypharmacy and a high risk of adverse drug reactions. With more knowledge, it may be easier to prevent and treat this syndrome that is leading to mortality.

References

1. Khadanga S, Khan Y, Lalchandani A, Gupta A, Kumar S. Prevalence of metabolic syndrome crossing 40% in Northern India: Time to act fast before it runs out of proportions. Journal of Family Medicine and Primary Care. 2018;7(1):118.

2. Parikh R, Mohan V. Changing definitions of metabolic syndrome. Indian Journal of Endocrinology and Metabolism. 2012;16 (1):7.
3. Wofford MR, King DS, Harrell TK. Drug Induced Metabolic Syndrome. The Journal of Clinical Hypertension. 2006;8(2):114-9.
4. Kasiske, BL, Ma, JZ, Kalil, RS, et al. Effects of antihypertensive therapy on serum lipids. Ann Intern Med. 1995;122: 133- 141.
5. Lakshman, MR, Reda, DJ, Materson, BJ, et al. Diuretics and β blockers do not have adverse effects at 1 year on plasma lipid and lipoprotein profiles in men with hypertension. Arch Intern Med. 1999;159: 551- 558.
6. Harper, R, Ennis, CN, Heane, AP, et al. A comparison of the effects of low and conventional-dose thiazide diuretic on insulin action in hypertensive patients with NIDDM. Diabetologia. 1995;38: 853-859.
7. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288: 2981- 2997.
8. Giugliano, D, Acampora, R, Marfella, R, et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. Ann Intern Med. 1997;126: 955- 959.
9. Gress, TW, Nieto, FJ, Shahar, E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med. 2000;342: 905-912.
10. Sowers, JR, Bakris, GL. Antihypertensive therapy and the risk of type 2 diabetes mellitus [editorial;comment]. N Engl J Med. 2000;342: 969- 970.
11. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42: 1206- 1252.
12. Peters Harmel, AL, Kendall, DM, Buse, JB, et al. Impact of adjunctive thiazolidinedione therapy on blood lipid levels and glycemic control in patients with type 2 diabetes. Curr Med Res Opin.2004;20: 215- 223.
13. Krauss, RM, Burkman, RT. The metabolic impact of oral contraceptives. Am J Obstet Gynecol.1992;167: 1177- 1184.
14. Lewis, UJ, Singh, RN, Tutwiler, GF, et al. Human growth hormone: a complex of proteins.Recent Prog Horm Res. 1980;36: 477- 508.
15. Bastard, JP, Caron, M, Vidal, H, et al. Association between altered expression of adipogenic factor SREP1 in lipotrophic adipose tissue from HIV-1 infected patients and abnormal adipocyte differentiation and insulin resistance. Lancet. 2002;359: 1026- 1032.
16. Garg, A. Acquired and inherited lipodystrophies. N Engl J Med. 2004;350: 1220- 1234.
17. Hadigan, C, Yawetz, S, Thomas, A, et al. Metabolic effects of rosiglitazone in HIV lipodystrophy.Ann Intern Med. 2004;140: 786- 794.
18. Mantel Teeuwisse, AK, Kloosterman, JM, Zee, AH, et al. Drug induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. Drug Saf. 2001;24:443- 456.
19. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004;27: 596- 601.
20. Kroeze, WK, Hufeisen, SJ, Popadak, BA, et al. H1 histamine receptor affinity predicts short term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology. 2003;28:519-526

21. Melkersson, KI, Dahl, ML, Hulting, AL. Guidelines for prevention and treatment of adverse effects of antipsychotic drugs on glucose insulin homeostasis and lipid metabolism.Psychopharmacology. 2004;175: 1- 6.
22. Marvanova M. Strategies for prevention and management of second generation antipsychotic-induced metabolic side effects. Mental Health Clinician. 2013;3(3):154-61.
23. Aronne, LJ, Segal, KR. Weight gain in the treatment of mood disorders. J Clin Psychiatry. 2003;64(suppl 8): 22- 29.
24. Pandit, MK, Burke, J, Gustafson, AB, et al. Drug induced disorders of glucose tolerance. Ann Intern Med. 1993;118: 529- 539.
25. Pirsch, JD, Miller, J, Deierhoi, MH, et al., For the FK506 Kidney Transplant Study Group. A comparison of tacrolimus. (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation. 1997;63: 977- 983.
26. Delaunay, F, Khan, A, Cintra, A, et al. Pancreatic cells are important targets for the diabetogenic effects of glucocorticoids. J Clin Invest. 1997;100: 2094- 2098.
27. Westerink N, Nuver J, Lefrandt J, Vrieling A, Gietema J, Walenkamp A. Cancer treatment induced metabolic syndrome: Improving outcome with lifestyle. Critical Reviews in Oncology/Hematology. 2016;108:128-36.
28. Wang Q, Chair SY, Wong EM-L, Taylor-Piliae RE, Qiu XCH, Li XM. Metabolic Syndrome Knowledge among Adults with Cardiometabolic Risk Factors: A Cross-Sectional Study. International Journal of Environmental Research and Public Health. 2019;16(1):159.
29. Larsen JR, Dima L, Correll CU, Manu P. The pharmacological management of metabolic syndrome. Expert Review of Clinical Pharmacology. 2018;11(4):397-410.
30. Mehta A, Marso S, Neeland I. Liraglutide for weight management: a critical review of the evidence. Obesity Science & Practice. 2016;3(1):3-14.

ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(March 2019 to June 2019)

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

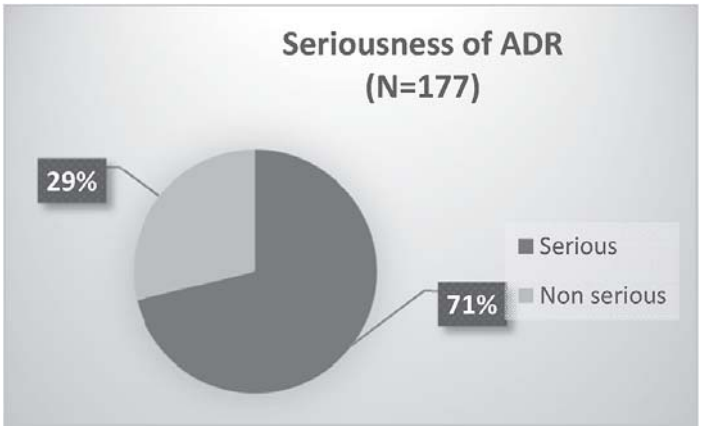
Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Total No. of cases: N = 177

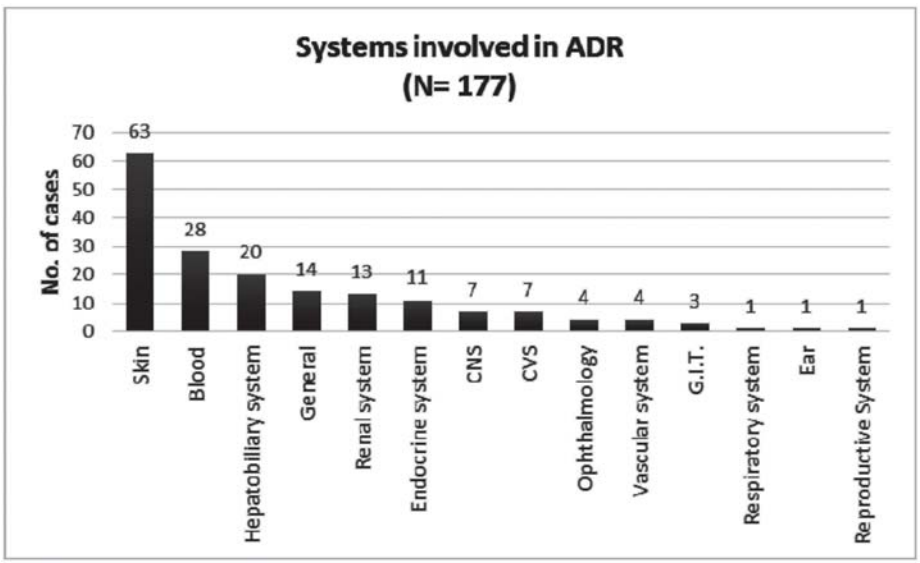
1. Age and Gender distribution

Age group (years)	No. of patients	Males	Females
<3	11	7	4
3 to 17	32	14	18
18-44	77	48	29
45-60	37	23	14
>60	20	13	7
Total	177	105	72

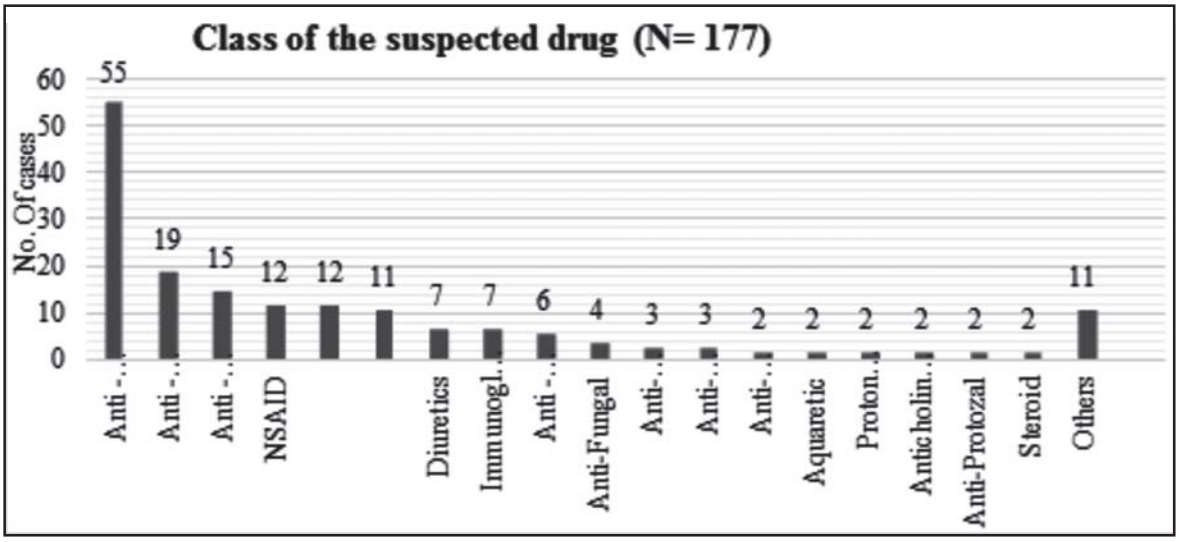
2. Seriousness of the ADR :



3. System involved in ADR = 177

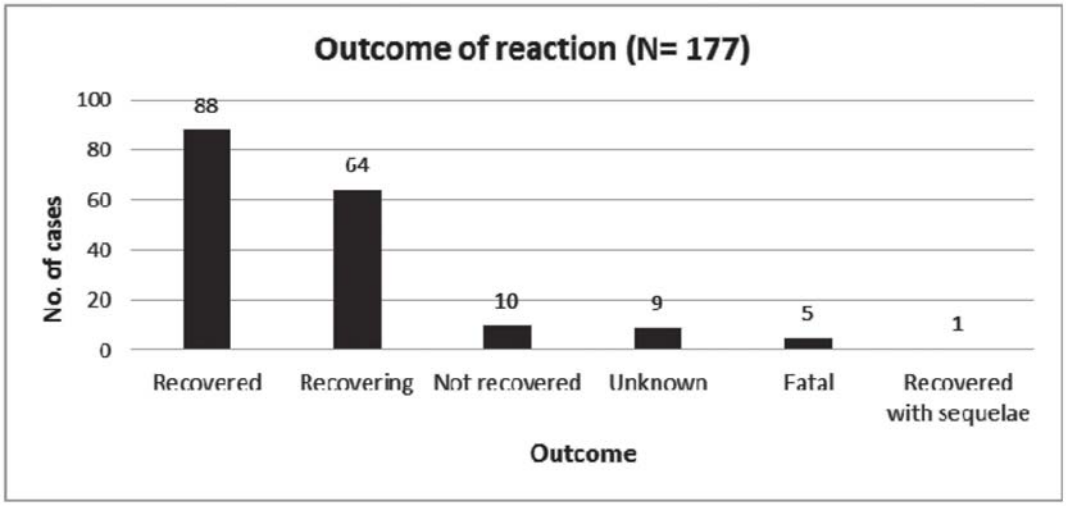


4. Class of the suspected drug:

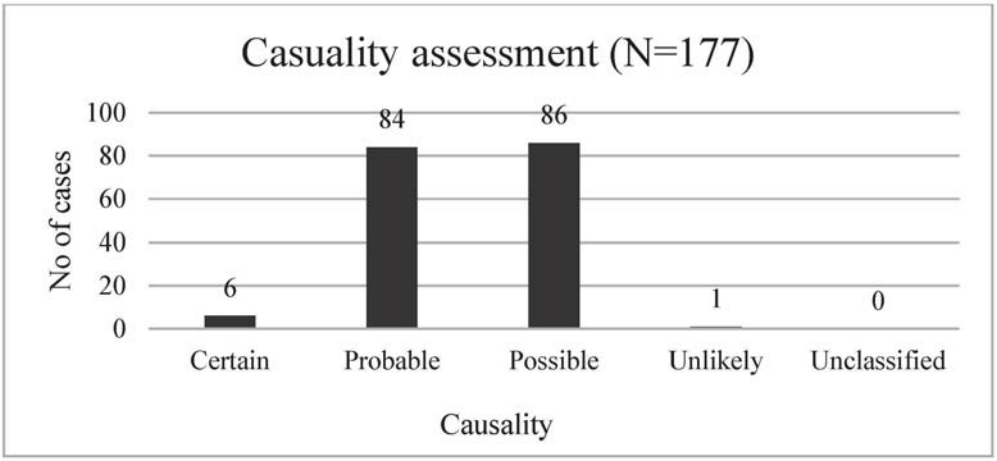


Others* class of drugs include ADR of Blood substitute, Vaccine, Anaesthesia, Nutritional supplements, Anti-Cancer, Antidote, Selective Estrogen Receptor Modulator, Anti- spasmodic, Dopamine Agonist.

5. Outcome of the reaction:



6. Causality assessment (WHO UMC Classification)



EVALUATION OF A CASE : ETHAMBUTOL INDUCED OCULAR TOXICITY

Dr. Shankhini S. Deshpande,* Dr. Prajakta Kude* and Dr Kejal Merani**

Department of Pharmacology; *

Department of Pediatric, LTMMC & GH, Sion, Mumbai.

Introduction

Ethambutol hydrochloride was introduced in 1961 as a chemotherapeutic agent for the treatment of tuberculosis.[1] Ethambutol is a bacteriostatic antimicrobial agent and one of the first-line drugs in the treatment regimen of tuberculosis. It has synergistic action when given with other first-line drugs such as isoniazid, rifampicin, and pyrazinamide.[2]

Ethambutol is a well-tolerated drug but can cause serious adverse reactions such as ocular toxicity manifesting as optic neuritis, which has been described since its first use in the treatment of tuberculosis. In majority of cases, the visual abnormalities resolve on cessation of ethambutol.[3] However, recent ophthalmologic experiences do not support this belief. In fact, several recent studies[4,5] showed that patients who experience ethambutol toxicity often have severe and persistent visual defects despite receiving appropriate dosages and monitored regularly for visual acuity and color vision.

Ethambutol toxicity is generally related to the dose administered to the patient.[6] Thus, dose calculation of ethambutol according to the weight of the patient is important. There are no cases of ocular toxicity due to ethambutol in children have been reported in the recent times. Here we present a case of severe visual impairment in an adolescent boy receiving ethambutol. The dose prescribed to the patient exceeded the required dose according to the patient's weight.

Case Report

An eleven-year-old boy with 14 kg body weight who was a known case of immunocompromised status receiving antiretroviral therapy (ART) since a year was diagnosed with pulmonary tuberculosis by a private practitioner. The same physician started him on antitubercular regime containing Isoniazid 300mg, Rifampicin 450mg, Pyrazinamide 750mg and Ethambutol 800mg orally once daily, since February 2019.

After taking these medications for one month, the patient started complaining of blurring of vision and difficulty in locating objects. Blurring of vision gradually increased and after 4 days, he had a complete loss of vision along with loss of perception of light. He was then brought to our hospital for his ophthalmic complaints.

On ophthalmological evaluation it was detected that his pupils were not reactive to light, the fundus was clear and optic disc had temporal pallor. In the view of immunocompromised status, the possibility of cytomegalovirus retinitis was ruled out. On reviewing the antitubercular regime it was discovered that he had received an adult dose of ethambutol i.e 800mg/day. The current recommendations for

ethambutol dosage state a dose of maximum 15mg /kg/day[6] hence for a patient with 14 kg body weight, the calculated dose is 210mg/day. This suggested prescription errors leading to an overdose of ethambutol in this patient. Ethambutol was then discontinued but vision recovery, in this case, seemed to be unlikely as per ophthalmologist's opinion. The patient died in few days thereafter due to septicaemia secondary to immunocompromised status. The "outcome" of this reaction hence remained "unknown".

As per the ICH E2 seriousness criteria, the reaction was serious as it led to hospitalization. According to the Modified Schumock & Thornton Preventability Scale, the occurrence of reaction in case of our patient was preventable because the dose given to the patient was inappropriate. The causality of this reaction as per WHO UMC causality assessment scale is "Possible" as the dechallenge is not applicable due to the irreversible nature of the reaction and the outcome was unknown.

Discussion:

Ethambutol hydrochloride is the drug included as the first-line agent in the treatment of TB. The daily dosage of ethambutol in patients who have not previously received this medication is usually 15 mg/kg of body weight, given as a single dose for adults and children. The daily dosage in patients who have previously received anti-TB therapy is 25 mg/kg of body weight, which is usually decreased after 60 days to 15 mg/kg/day.[7] Adverse effects caused due to the consumption of ethambutol are visual disturbances, hyperuricemia, thrombocytopenia, rash, pruritus, urticaria, peripheral neuropathy. The most commonly reported side-effect of ethambutol is optic neuritis; however, it is uncommon in patients prescribed standard doses.[8]

According to a study conducted on patients with suspected active TB, it was observed that 58% of patients had at least one error with a dose of medication. Of the total errors identified, the most common errors involved incorrect dose prescription of pyrazinamide [45%] followed by ethambutol [25%].[9] Ethambutol toxicity is related to the dose administered to the patient. Patients receiving 25 mg/kg per day have a 5% to 6% reported incidence of ocular toxicity, and the incidence with dosages of 15 mg/kg per day is reportedly less than 1%.[10] In the present case, dose optimization according to the weight of the patient would have reduced the risk to ocular side effects of ethambutol.

Symptoms of ethambutol induced ocular toxicity generally appear after about two months of consumption. Presenting complaint of toxicity is a progressive painless blurring of vision. The loss of visual acuity usually starts with a blur at the point of fixation [a relative scotoma] and is followed by a progressive, bilateral and painless decline.[11] Papillomacular bundle loss and optic atrophy may develop as temporal pallor of the optic disc. In the present case the symptoms occurred much earlier. Though the reaction is described as reversible after withdrawal of ethambutol, permanent visual impairment without recovery has also been reported. Even if patients show visual improvement after therapy discontinuation, complete recovery is not always achieved.

The exact mechanism of reaction is not clear yet, but hypotheses are made to understand that pathway of occurrence of the reaction. It is postulated that mitochondrial disturbance is the possible underlying mechanism. Ethambutol disrupts oxidative phosphorylation and mitochondrial function by interfering with iron-containing complex I and copper-containing complex IV. The resultant effect is the generation of reactive oxygen species and a cascade of events, resulting in tissue injury and cellular apoptosis. Another theory is the zinc-chelating effect and its metabolite [ethylenediiminodibutyric acid] in the retinal ganglion. Anti-mycobacterial properties of ethambutol are related to the inhibition of arabinosyltransferase, which is an important enzyme for mycobacterial cell-wall synthesis.

The metabolite of ethambutol is a strong chelator of copper which is required as a cofactor for cytochrome C oxidase in the electron transport chain and cellular oxidative metabolism. It is possible that ethambutol decreases the levels of copper available for cytochrome C oxidase, and hence, the required energy for axonal transport around the optic nerve.[12]

In optic neuritis, the central fibres of the optic nerve are most commonly affected which causes blurring of vision, decreased visual acuity, central scotoma. In rare cases, it involves the peripheral fibres of the optic nerve so that visual acuity and color vision may not be affected, but the peripheral constriction of the visual fields occurs. Because the neuritis is retrobulbar in both forms, the fundus appears normal on ophthalmoscopic examination. In the majority of cases, the visual abnormalities resolve on cessation of ethambutol.[3]

On literature search, 2 cases of ethambutol induced ocular toxicity in children were reported in 1983, who developed subjective and transient visual symptoms after 4 months. Recently, no such case has been reported. Estlin KAT, et.al reported cases of ethambutol induced ocular toxicity in patients more than 70 years of age.[13,14]

Risk factors for ethambutol toxicity include, dose and duration of ethambutol therapy. People receiving 2 months or less of ethambutol therapy are at less risk for optic toxicity than those taking the drug for a longer period of time and the risk of optic neuropathy continues to rise as the duration of ethambutol therapy increases. To reduce the risk, the dose should be maintained close to 15 mg/kg as possible. Older patients who require prolonged ethambutol therapy or a middle-aged patient with other renal risk factors such as diabetes who requires prolonged ethambutol therapy are at higher risk of developing toxicity. [13]

In this case, the patient was HIV positive but details regarding ART treatment were not available. Mustak H, et.al performed a study in HIV patient receiving ethambutol in which they found that there is no statistically significant difference in mean dose, duration of therapy, age or CD4 count between those who showed visual improvement and those who did not.[15]

Currently, discontinuation of ethambutol is the only management strategy that can stop the progression of vision loss and allow recovery of vision. Recommendation of various preventive strategies for the prevention of ethambutol toxicity is difficult. Patients with risk factors but in need, the drug should be prescribed ethambutol only after careful thought is given to the pros and cons. As abnormal color perception may be an early and sensitive indicator of toxicity, prescribing ethambutol, for those with

baseline color vision abnormality will need more careful monitoring. A high degree of awareness of this potential ocular side effect of ethambutol is crucial for both the healthcare staff as well as the patient.

Conclusion

Ocular toxicity is the most commonly reported adverse drug reaction with ethambutol. Hence, it is important to follow up with the patient prescribed by this drug. Regular ophthalmological evaluation should be conducted in order to prevent ocular damage, especially in patients with risk factors. If any visual signs and symptoms are observed, the drug must be immediately withdrawn and the patient should be prescribed with another antitubercular drug. The patients should be explained about the risk of visual impairment and should be asked to approach the doctor as early as possible.

References

1. Kahana LM. Toxic ocular effects of ethambutol. CMAJ: Canadian Medical Association Journal. 1987;137(3):213.
2. Makunyane P, Mathebula S. Update on ocular toxicity of ethambutol. African Vision and Eye Health. 2016;75(1):1-4.
3. Alvarez KL,Krop LC. Ethambutol-induced ocular toxicity revisited. Ann Pharmacother 1993;27(1):102-103
4. Kumar A, Sandramouli S, Verma L, Tewari HK, Khosla PK. Ocular ethambutol toxicity: is it reversible, J Clin Neuroophthalmol. 1993;13:15-17.
5. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther. 1997;13:473-477.
6. Sivakumaran P, Harrison AC, Marschner J, Martin P. Ocular toxicity from ethambutol: a review of four cases and recommended precautions. N Z Med J. 1998;111:428-430.
7. Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. InMayo Clinic Proceedings. 2003;78(11):1409-1411
8. Garg P, Garg R, Prasad R, Misra AK. A prospective study of ocular toxicity in patients receiving ethambutol as a part of directly observed treatment strategy therapy. Lung India. 2015;32(1):16-19.
9. Buczynski P, Odenigbo C, Zucker J, Jen SP, Cennimo D, Patrawalla A. Evaluation of Anti-Tuberculosis Medication Errors at an Urban University Hospital. In Open forum infectious diseases 2014;1(1):S209
10. Petri WA Jr. Drugs used in the chemotherapy of tuberculosis, Mycobacterium avium complex disease, and leprosy. In: Hardman JS, Limbird LE, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw-Hill; 2001:1279-1280.
11. Makunyane P, Mathebula S. Update on ocular toxicity of ethambutol. African Vision and Eye Health. 2016;75(1):1-4.
12. Heng JE, Verwerk CK, Lessell E, Zurakowski D, Levin LA. Ethambutol is toxic to retinal ganglion cells via excitotoxic pathway. Invest Ophthalmol Vis Sci. 1999;40(1):190-195.
13. Estlin KA, Sadun AA. Risk factors for ethambutol optic toxicity. International ophthalmology. 2010;30(1): 63-72.
14. Junnanond C, Chotibut S, Lawtiantong T. Safety evaluation of ethambutol inchildren. J.Med.Assoc.Thai. 1983;66:75-80.
15. Mustak H, Rogers G, Cook C. Ethambutol induced toxic optic neuropathy in HIV positive patients. International journal of ophthalmology. 2013;6(4):542.

PUBLISHED LITERATURE ON ETHAMBUTOL INDUCED OPTIC TOXICITY

Dr. Prathamesh P. Avad
Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Is the Ethambutol Administration Triggering Factor for Onset of Leber's Hereditary Optic Neuropathy?: a Case Report

Masanori Nakazawa, Hitoshi Ishikawa, Toshiaki Goseki, Eiichi Nishimura, Nobuyuki Shoji

Neuro-Ophthalmology.2018;35(2):239-243

We report a case involving a 38-year-old woman who developed Leber's hereditary optic neuropathy (LHON) during treatment with orally administered ethambutol. Nine months after treatment initiation with oral ethambutol (52 kg body weight, 750 mg/day, 225 g in total), the patient exhibited decreased visual acuity. Although ethambutol-induced optic neuropathy was primarily suspected on the basis of her medical history and examination, optic disc swelling was significant, and the onset of the disease was rapid, which was atypical of ethambutol-induced optic neuropathy. Neuro-ophthalmological evaluations were performed, and mitochondrial DNA assessment confirmed the mitochondrial DNA11778 point mutation, leading to a diagnosis of LHON. Our findings suggest that ethambutol is a likely triggering factor for LHON, and it is important to consider LHON in cases of decreased visual acuity during the oral administration of ethambutol. Patients should be asked about their family history before the initiation of ethambutol treatment, and mitochondrial DNA assessments should be performed, particularly when the course of optic neuropathy is atypical.

Ethambutol-induced optic neuropathy linked to OPA1 mutation and mitochondrial toxicity

Virginie Guillet, Arnaud Chevrollier et al

Mitochondrion.2010;10:115–124

Ethambutol (EMB), widely used in the treatment of tuberculosis, has been reported to cause Leber's hereditary optic neuropathy in patients carrying mitochondrial DNA mutations. We study the effect of EMB on mitochondrial metabolism in fibroblasts from controls and from a man carrying an OPA1 mutation, in whom the drug induced the development of autosomal dominant optic atrophy (ADOA). EMB produced a mitochondrial coupling defect together with a 25% reduction in complex IV activity. EMB induced the formation of vacuoles associated with decreased mitochondrial membrane potential and increased fragmentation of the mitochondrial network. Mitochondrial genetic variations may therefore be predisposing factors in EMB-induced ocular injury.

Ethambutol Induced Optic Neuritis in Patients with End Stage Renal Disease on Hemodialysis: Two Case Reports and Literature Review

Fang TJ, Chen YC, Chang MY

Renal Failure.2004; 26(2):189-93

Ethambutol, a synthetic bacteriostatic agent, is a first line agent against Mycobacterium tuberculosis. Although optic neuritis is the most serious adverse effect of ethambutol, most cases in the literature are reversible. Renal failure prolongs the half-life of ethambutol and increases the risk of ethambutol-induced optic neuritis. We present two patients with end stage renal disease (ESRD), who were on maintenance dialysis and suffering ethambutol-induced optic neuritis. The first woman had been suffering ESRD on hemodialysis for 2 years. After tuberculosis was diagnosed, she was prescribed three-combined anti-tuberculosis medications, including ethambutol 800 mg/day. Bilateral blurred vision suddenly occurred 4 months after the start of treatment, and she became totally blind despite discontinuing ethambutol. The second woman had been on hemodialysis for 5 months. Tuberculosis was diagnosed by lung biopsy. After 3 weeks of three-combined anti-tuberculosis medications including ethambutol (1,200 mg/day), reduced visual acuity and color vision defects occurred. One year after the discontinuation of ethambutol, visual acuity remained little improved. Physicians should be aware of ethambutol-induced optic neuritis and ethambutol should be used cautiously in patients with renal failure.

A 37-year-old woman presenting with impaired visual function during antituberculosis drug therapy: a case report

Abdulkabir A Ayanniyi & Rashidat O Ayanniyi

Journal of Medical Case Reports volume 5, Article number: 317 (2011)

Case presentation: A 37-year-old Yoruba woman, weighing 48 kg, presented with impaired visual functions and mild sensory polyneuropathy in about fourth month of antituberculosis treatment. Her therapy comprised ethambutol 825 mg, isoniazid 225 mg, rifampicin 450 mg, and pyrazinamide 1200 mg. Her visual acuity was 6/60 in her right eye and 1/60 in her left eye. She had sluggish pupils, red-green dyschromatopsia, hyperemic optic discs and central visual field defects. Her intraocular pressure was 14 mmHg. Her liver and kidney functions were essentially normal. Screening for human immunodeficiency virus was not reactive. Her impaired visual function improved following prompt diagnosis and attention, including the discontinuation of medication. **Conclusions:** The ethambutol and isoniazid in antituberculosis medication are notorious for causing impaired visual function. The diagnosis of ocular toxicity from antituberculosis drugs should never be delayed, and should be possible with the patient's history and simple but basic eye examinations and tests. Tight weight-based antituberculosis therapy, routine peri-therapy visual function monitoring towards early detection of impaired function, and prompt attention will reduce avoidable ocular morbidity.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr. Hardik Thaker
Department of Pharmacology, LTMMC & GH, Sion, Mumbai.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors: Drug Safety Communication - Risk of necrotising fasciitis of the perineum (Fournier's gangrene)

Background: SGLT2 inhibitors are oral glucose lowering agents that increase the renal excretion of glucose (i.e. glycosuria) by inhibiting the SGLT2 mediated renal glucose reabsorption. Three SGLT2 inhibitors including canagliflozin, dapagliflozin and empagliflozin are available in India since 2014. These drugs are indicated as monotherapy or as add-on combination therapy with other glucose lowering agents including insulin along with diet and exercise.

Issue: Food and Drug Administration (FDA) issued a drug safety communication warning that cases of Fournier's gangrene have been reported in SGLT2 inhibitor treated patients. Fournier's gangrene usually presents as a polymicrobial infection with common clinical features of swelling of the external genitalia, fever and pain which can progress to skin necrosis if not treated promptly. Adverse event reporting system database (FAERS) from March 2013 to February 2018 as well as the medical literature through 2018, identified a total of 12 cases of Fournier's gangrene associated with SGLT2 inhibitors. Whereas only six cases of Fournier's gangrene associated with other antidiabetic drug classes (insulins, biguanides, sulfonylureas, and dipeptidyl peptidase-4 inhibitors) were identified over a period of 34 years. The average time from the initiation of a SGLT2 inhibitor to the onset of Fournier's gangrene was 9.2 months (range 7 days to 25 months).

Recommendation: The US FDA and the European Medicines Agency (EMA) had requested for updating the package inserts of SGLT2 inhibitor products for warning the risk of Fournier's gangrene. Healthcare professionals are encouraged to consider the possibility of Fournier's gangrene in SGLT2 inhibitor treated patients who present with pain, tenderness, erythema, or swelling in the genital or perineal area, associated with fever or malaise. If Fournier's gangrene is suspected, discontinuation of SGLT2 inhibitor with the initiation of prompt treatment should be done.

Reference: *Sodium glucose cotransporter 2 (SGLT2) inhibitors: Drug Safety Communication - Risk of necrotising fasciitis of the perineum (Fournier's gangrene) [Internet], [cited in July 2019], Available from Product Safety Alerts, HSA, 8 March 2019 https://www.hsa.gov.sg/content/hsa/en.html*

Hydrochlorothiazide: Drug Safety Communication risk of non-melanoma skin cancer (NMSC) with prolonged use.

Background: Hydrochlorothiazide is a diuretic that is commonly used alone or in combination with other antihypertensives for the treatment of hypertension.

Issue: Two recent studies using data from Danish registries found a cumulative dose dependent association between hydrochlorothiazide and NMSC. According to these studies, high cumulative usage of hydrochlorothiazide (i.e. e"50,000mg, corresponding to 12.5mg daily for 11 years) was

associated with an increased risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The possible mechanism of NMSC attributed by hydrochlorothiazide was presumed to be due to the photosensitising actions of hydrochlorothiazide, which might influence cancer risk at sun exposed sites, as well as induce a chronic inflammatory reaction.

Recommendation: Healthcare professionals should consider the findings from the two Danish pharmacoepidemiological studies when prescribing hydrochlorothiazide and are advocated to report any suspected cases of NMSC to the concerned drug regulatory authorities. Patients taking hydrochlorothiazide should be advised to limit the exposure to sunlight and ultraviolet (UV) rays to minimise risk of skin cancer. It is also recommended that the package inserts (PIs) of hydrochlorothiazide-containing products be changed to provide warning on risk of NMSC.

Reference: *Hydrochlorothiazide: Drug Safety Communication - risk of non-melanoma skin cancer (NMSC) with prolonged use. Summary Safety Review, Health Canada, 30 January 2019 [Internet], [cited in July 2019] Available from http://hpr-rps.hres.ca/reg-content/summary-safety-review/detail.php?lang=en&linkID=SSR00215*

Fluoroquinolones: Drug Safety Communication - risk of aortic aneurysm and dissection on systemic use

Background: Fluoroquinolones are a class of broad-spectrum antibiotics including ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, levofloxacin, moxifloxacin and pefloxacin, etc.

Issue: Multiple epidemiological studies published between 2015 to 2018, appears to indicate approximately two-fold increased risk of aortic aneurysm or dissection with fluoroquinolone compared to the baseline risk. Fluoroquinolones upregulate multiple matrix metalloprotinases which can destroy collagen and connective tissue along the aortic wall (similar to their adverse effect on Achilles tendon) and lead to degenerative changes in tenocyte cells, resulting in reduction in the diameter and amount of certain type of collagen fibrils, which can ultimately lead to aortic aneurysm. As such, they may contribute acutely to aneurysm progression and rupture.

Risk: Risk of aortic aneurysm or dissection varies depending on population, ranging from 9 aortic aneurysm events per 100,000 people per year in general population to 300 aortic aneurysm events per 100,000 people per year in highest risk, like those over age of 85 years. Other risk factors include family history of aneurysm disease, pre-existing aortic aneurysm or dissection, genetic predisposition (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome), atherosclerosis and hypertension.

Recommendation: Healthcare professionals are advised to take into consideration of the above safety information when prescribing fluoroquinolones, especially in patients who are at high risk of aortic aneurysm and dissection. They should also counsel their patients on other adverse effects associated with fluoroquinolones which involve the tendons, muscles and joints, and the nervous system.

Reference*: Fluoroquinolones: Drug Safety Communication - risk of aortic aneurysm and dissection on systemic use [Internet], [cited in July 2019], Available from Product Safety Alerts, HSA, 8 March 2019 https://www.hsa.gov.sg/content/hsa/en.html*

MATCH THE ADVERSE EFFECT WITH THE DRUG

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

1	Pentamidine	A	Hemolysis
2	Isoniazid	B	Cardiotoxicity
3	Artesunate	C	Fetopathy
4	Muromonab – CD3	D	Severe Headache
5	Ketoprofen	E	Bronchospasm
6	Fumagillin	F	Symptomatic Hypotension
7	Alfamethyldopa	G	Uveitis
8	Quetiapine	H	Drug induced lupus erythematosis
9	ACE Inhibitors	I	Aseptic meningitis
10	Epirubicin	J	Pancreatitis
11	Aspirin	K	Increased Transaminase level
12	Fomivirsen	L	Peripheral neuropathy
13	Ulipristal	M	Galactorrhea
14	Cinaciguat	N	Thrombocytopenia
15	Hydralazine	O	Unusual tiredness

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

ALPHABET 'V' PUZZLE

Dr. Abhilasha Rashmi*, Dr. Sharmada Nerlekar*

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

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

1. This first "hedgehog signaling pathway" inhibitor approved for treatment of basal cell carcinoma in adults can cause embryo-fetal death and severe birth defects if prescribed in pregnancy.
2. A small (<1%) risk of neurocognitive effects is seen with this PCSK9 inhibitor which is approved for once monthly subcutaneous injection in a dyslipidemic patient as an adjunct to diet and maximally tolerated statin therapy.
3. This specific muscarinic agonist on M1 and M2 receptors, indicated for treatment of xerostomia associated with Sjogren syndrome, is associated with lesser side effects & better patient compliance than Pilocarpine.
4. Hypertension, thrombotic & hemorrhagic events, hepatotoxicity, GI perforation and QT prolongation are the major adverse reactions seen with this antiangiogenic protein kinase inhibitor approved for treatment of metastatic thyroid cancer.
5. The most dangerous adverse effect of Vasopressin V2 receptor antagonist like _____ is "osmotic demyelination syndrome" which occurs due to rapid correction of hyponatremia resulting in fatal consequences.
6. The major complications of subcutaneous therapy of recombinant human IL-11 named _____ are fluid retention and associated cardiac symptoms like tachycardia, palpitation, edema and shortness of breath.
7. In case of insecticide & nerve gas poisoning, drugs like Pralidoxime & Obidoxime _____ the organophosphate-AchE conjugate and regenerate the active enzyme.
8. Due to its sulfonamide moiety, photosensitivity (5%), rash (16%) and itching (14%) are commonly seen with this drug used in combination with Sofosbuvir for treatment of HCV.
9. Because of presence of side effects like concentric visual field constriction, use of Vigabatrin is restricted only to _____ therapy of refractory focal seizures with impaired awareness in adults.
10. The risk of nonmelanoma skin cancer is present with chronic use of _____-A therapy approved for treatment of psoriasis & vitiligo.

ALPHABET 'V' PUZZLE: ANSWERS :

1. Vismodegib
2. Evolocumab
3. Cevimeline
4. Lenvatinib
5. Conivaptan
6. Oprelvekin
7. Reactivate
8. Simeprevir
9. Adjunctive
10. Psoralen UV

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	0222406 3162	dr.sudhirpawar@gmail.com
Dr. Neha Kadhe	02224063206	drkadhe@gmail.com
Dr. Manjari Advani	02224063205	manjari.advani@gmail.com
Dr. Jaisen Lokhande	02224063165	dr_jaisen@yahoo.co.in,
Dr. Swati Patil	02224063165	drswati246@gmail.com
Dr. Hardik Thaker	02224063160	drhardikthaker@gmail.com
Dr. Prajakta Kude	0222406 3160	prajakta.kude13@gmail.com
Dr. Shankhini Deshpande	0222406 3160	shankhinid@gmail.com
Dr. Shariva Ranadive	0222406 3160	ranadiveshariva@gmail.com
Dr. Prathamesh Avhad	0222406 3160	prathiavhad@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@gmail.com

Printing and distribution of this bulletin is sponsored by

ALKEM LABORATORIES LIMITED

BOEHRINGER - INGELHEIM

GLAXOSMITHKLINE

A new way for a new world

GLENMARK PHARMACEUTICALS LIMITED

NOVARTIS INDIA LTD.