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BULLETIN ON ADVERSE DRUG REACTIONS

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Committee Members for Bulletin on Adverse Drug Reactions

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From the Editor's Desk . . . . ✍

Dear friends and colleagues,

Hypoglycemia is one of the most common conditions seen in patients presenting to the emergency department. Although hypoglycemia is less common in patients who are not diabetic, it may cause serious problems in few patients especially elderly. Since there is ample information on hypoglycemia in diabetic patients, our first article deals with the hypoglycemia induced by drugs other than anti-diabetic agents. It gives an overview of the incidence, mechanism and preventive aspects related to this adverse drug reaction.

The second article is a review on adverse reactions due to angiotensin receptor blockers. Though this group of drugs is considered to be safe for long term use, their utility has been associated with few controversies. The article gives an overview on the current status of understanding on these aspects.

Other features in this issue include analysis of the ADRs from our institute for your quick review, an interesting case report of anaphylactic reaction due to platelets transfusion and other topics including crossword and puzzle.

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

Finally, I would like to urge all the readers to share medical documents for publication in this bulletin and contribute to the activities of Pharmacovigilance.

Thank you.

Dr. Sudhir Pawar

DRUG INDUCED HYPOGLYCEMIA

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Introduction: Many pharmacological agents commonly used in clinical practice affect glucose homeostasis, interfering with the body's balance between insulin, glucagon, catecholamines, growth hormone, and cortisol. Multiple mechanisms of action on glucose metabolism exist through pancreatic, hepatic, and peripheral effects. Based on circumstances at the time of use, a drug may cause both hyperglycemia and hypoglycemia in a patient.

Drug-induced hypoglycemia is a significant adverse effect that should be included in the differential diagnosis of hypoglycemia and considered whenever patients present with altered mental status. It is important to consider that hypoglycemia affects patients both physically, psychologically, can increase hospital stay and even lead to death in severe form.

Diagnosis of hypoglycemia:

It is widely accepted that most patients will begin to experience symptoms when their blood glucose level is less than 3.3 mmol/l (60 mg/dL).[1]

The symptoms patients commonly experience are listed in Table 1 below and can be manifestations of the response by the autonomic nervous system as well as the brain's response to being deprived of glucose. [1,2]

Table 1: Signs and symptoms of hypoglycemia.

Neurogenic symptoms of hypoglycemia	Neuroglycopenic symptoms of hypoglycemia	Physical signs of hypoglycemia
Anxiety/arousal Hunger Tremors /trembling Sweating Paresthesias	Blurry vision Changes in behavior - irritability is often noted Confusion/difficulty thinking Difficulty speaking Dizziness Emotional lability Fatigue Loss of consciousness Seizures Warmth Weakness	Increased systolic blood pressure Pallor Sweating Tachycardia

The American Diabetes Association (ADA) Workgroup on Hypoglycemia has defined and classified hypoglycemia based on the severity of symptoms in patients diagnosed with diabetes.

Table 2. ADA Workgroup on Hypoglycemia - definition and classification of hypoglycemia in people with diabetes [3, 4]

Type of Hypoglycemia	Presentation of Symptoms
Severe hypoglycemia	An event requiring assistance of another person to actively administer resuscitative actions
Documented symptomatic hypoglycemia	An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration 70 mg/dl
Asymptomatic hypoglycemia	An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration 70 mg/dl
Probable symptomatic hypoglycemia	An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration of 70 mg/dl)
Relative hypoglycemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration > 70 mg/dl but approaching the hypoglycemic level

It is important to note that monitoring blood glucose levels is the best way to monitor hypoglycemia since hemoglobin A1C (A1C) does not adequately depict hypoglycemia given that A1C provides a measure of average control of blood glucose over the past 2 to 3 months.[5]

Aetiology: Drug-induced hypoglycemia may be a result of direct changes due to glucose homeostasis on different organ system or indirect effects on a patient's ability to recognize onset of hypoglycemia.

Changes that affect glucose homeostasis include: [6]

1. Direct increase in insulin secretion from the pancreas,
2. Indirect increase in insulin secretion through decreased degradation of incretin hormones (GLP-1 and GIP),
3. Cytotoxic effects on pancreatic cells leading to increase insulin release,
4. Decrease in gluconeogenesis,
5. Increase in glucose utilization and storage, decrease in glucagon release from the pancreatic cells and
6. Decreased gastric emptying.

Risk factors: It should be noted that the risk factors associated with drug-induced hypoglycemia are similar to the risk factors associated with the development of hypoglycemia in patients with DM.

Table 3. Risk factors for drug-induced hypoglycemia

Risk Factors	Mechanism
Advancing age	Decreased symptoms/decreased awareness, decreased counter regulatory response to low blood glucose
Renal insufficiency	Decreased insulin clearance
Hepatic insufficiency	Decreased gluconeogenesis
Decreased food intake (skipping meals)	Insufficient glucose intake
Excessive alcohol intake	Decreased gluconeogenesis
Polypharmacy	Increased risk of drug interactions resulting in hypoglycemia

Causative agents:

There are a number of agents implicated in causing hypoglycemia; however, the level of evidence available varies significantly amongst agents. The most highly documented drug induced hypoglycemia occurs with antidiabetic agents. Of potentially greater concern are the agents which are used for indications other than hyperglycemia because the hypoglycaemic episodes are often less predictable and/or unexpected. These agents often have very little or no quality evidence to document the frequency and severity of their hypoglycemic effects. Medications commonly used for diabetes treatment are not discussed in detail in this review because hypoglycemia has been well established with the use of insulin, sulfonylureas (SUs), and meglitinides as monotherapy or in combination with other agents such as metformin, thiazolidinediones (TZDs), exenatide, or dipeptidyl peptidase-4 (DPP-4) inhibitors. Out of these, metformin, TZDs, and α-glucosidase inhibitors such as acarbose and miglitol, when administered as monotherapy at usual doses, should have little to no risk of hypoglycemia based on their mechanisms of action.[7]

Hence, the present article emphasizes on the non anti-diabetic agents causing hypoglycemia which are more likely to be missed by treating physician as a potential causative agent.

1. Quinine:

Quinine is an anti-malarial agent used for treatment of acute systemic and cerebral disease. More than 300 cases of hypoglycemia have been reported with quinine therapy and 30 clinical studies have demonstrated similar findings.[8]

Mechanism of ADR: The crux of the hypoglycaemic effects of quinine appears to be the result of increased insulin secretion from beta cells. Though this is most common in patients infected with malaria, there are reports of quinine-induced hypoglycemia in patients without malaria. Patients with malaria often exhibit more severe or sustained hypoglycemia since the organism responsible for malaria, Plasmodium falciparum, independently lowers glucose levels. There is also an increased risk of hypoglycemia with higher doses of quinine and with infusion times of intravenous doses of less than one hour. Manufacturers recommend intravenous infusions over four hours to minimize risk of hypoglycemia. Quinine-induced hypoglycemia can be resistant to traditional therapy with glucose and glucagon; however, treatment with octreotide 40-100 micro gm every 6-8 hour has been shown to be beneficial.[6]

2. Fluoroquinolones:

Fluoroquinolones are antibiotics which exhibit their antimicrobial activity through inhibition of DNA gyrase and topoisomerase IV, enzymes involved in bacterial cell division. The class includes the following agents: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, and rofloxacin. Though there are reports of hypoglycemia with most agents in this class, a majority of the evidence with fluoroquinolone-induced hypoglycemia (dysglycemia) is with gatifloxacin. [8,9,10]

Mechanism of ADR: The exact mechanism of this hypoglycaemic effect is not clear; however, quinolones indirectly cause hypoglycemia through blockade of adenosine 5-triphosphate (ATP)-sensitive potassium channels in the pancreatic β-cells that regulate calcium influx. This enhances insulin release in a dose dependent manner.[11]

The adverse effect does not appear to be dose-related and presents typically within the first three days of therapy for less severe hypoglycemia.[12,13,14] Incidences of quinolone-induced hypoglycemia in the literature vary within the class, but gatifloxacin has been associated with having a greater effect on increasing insulin levels and reducing blood glucose compared to other quinolones.[3] More severe episodes, specifically those requiring hospitalization or prolonged hospitalization, are more common after three days of therapy. Hypoglycemia has been reported with intravenous and oral therapies in both outpatient and inpatient settings and discontinuation of the medication is often required to resolve the glucose abnormalities.[8] Though new onset diabetes has been reported, risk factors for patients who are more likely to experience hypoglycemic episodes are: pre-existing diabetes, concomitant use of hypoglycemic medications, advanced age, and decreased renal function.[12, 15, 16]

3. NSAIDS:

Non-steroidal anti-inflammatory drugs (NSAIDs) are all thought to increase risk of hypoglycemia, with indomethacin having the greatest evidence, likely due to the large population being treated. Though often used for osteoarthritis and other inflammatory conditions, indomethacin may also be used to close a patent ductus arteriosus in neonates, often in those born prematurely.

Mechanism of ADR: Salicylate induced hypoglycemia is thought to be caused by several mechanisms: increased in insulin secretion in those with type 2 diabetes, increasing insulin sensitivity, displacing sulfonylureas from protein-binding sites and inhibiting renal excretion.[17, 18, 19]

Less than three per cent of neonates exposed to therapeutic levels of intravenous indomethacin for patent ductus arteriosus experience hypoglycemia. Whether this effect is dose-related is unclear; however, the risk may be significantly decreased by use of a concomitant infusion of intravenous glucose.[20] Other studies have shown high-dose aspirin therapy (e.g., 4-7 g/day) to indirectly enhance insulin sensitivity in liver and muscle through reduced rates of lipolysis and lowered levels of plasma fatty acid.[21]

4. Pentamidine:

Pentamidine is an anti-protozoal agent which exhibits its effects through inhibition of protozoal nuclear metabolism.

Mechanism of ADR: Direct cytotoxic effects on beta cells of the pancreas results in increased secretion of insulin. This early release of insulin is due to the lytic effects on the cell which result in cell death. This can ultimately result in insulin-dependent diabetes as a result of this cell loss.[6]

Hypoglycemia is the most common metabolic abnormality observed within 5-14 days of initiating therapy and occurs in about 6-40% of patients[17, 18] receiving intravenous or intramuscular pentamidine. Hypoglycemia is most commonly seen in patients with acquired immune deficiency syndrome (AIDS) treated for Pneumocystis jiroveci.[8] The risk of hypoglycemia and resultant pancreatic damage associated with pentamidine is greater with higher doses, higher cumulative doses, and prolonged use.[6] There also appears to be increased risk with use of pentamidine mesylate compared to pentamidine isothionate.[22]

5. Beta blockers:

Non-selective beta-adrenergic antagonists often used to treat hypertension and cardiac disease. Agents under this class are following: alprenolol, bucindolol, carteolol, nadolol, penbutolol, pindolol, propranolol, sotalol and timolol. These agents have been linked with hypoglycemic effects in patients with and without diabetes.[8] Oral formulations are most commonly the culprit; however, hypoglycemia associated with topical formulations is also documented.[6]

Mechanism of ADR: There are two proposed mechanisms for this hypoglycemic effect of beta blockers. First, there is a blunting of the signs and symptoms of hypoglycemia.[2] The exception to this blunting effect is sweating, an important educational point for all patients. The second mechanism is a direct potentiation of the effects of insulin. This heightened insulin effect increases glucose utilization in

the periphery and inhibits lipolysis. Further, there is a diminished physiologic response to hypoglycemia in patient receiving beta blockers, specifically a decrease in glycogenolysis and gluconeogenesis.[2, 8,23]

Patients at greatest risk for hypoglycemia with beta blockers include patients with hepatic disease, patients on haemodialysis, neonates, and patients with type 1 diabetes. Use of selective beta blockers, such as atenolol, metoprolol, and bisoprolol are thought to have a decreased risk of hypoglycemia and may be a reasonable alternative to patients unable to tolerate non-selective agents.[8] Non-cardio selective β-blockers such as propranolol are more likely to cause hypoglycemia than cardio selective ones such as atenolol and metoprolol. Nevertheless, patients on the latter should still be cautioned about the potential for drug-induced hypoglycemia.[24]

6. ACE inhibitors:

Angiotensin converting enzyme (ACE) inhibitors are a class of drugs that are typically used for hypertension and cardiovascular disease. Studies document the potential for ACE inhibitor-associated hypoglycemia, and a majority of these are with the use of captopril.[8, 25]

Mechanism of ADR: Though the mechanism for this drug-induced hypoglycemia is not well defined, it is proposed that the increase in bradykinins associated with ACE inhibitor use may cause an increase in insulin sensitivity.[26] One study suggests that captopril increases glucose utilization in the periphery compared to use of hydrochlorothiazide[27]; however, one study demonstrates that ACE inhibitors have no impact on hepatic or peripheral insulin sensitivity.[28] Because of the contradicting information available, the actual impact of ACE inhibitors on blood glucose is not clear.

Bradykinin may also have a contributory role in down regulating hepatic glucose production. Suppression of peripheral sympathomimetic over activity may also be involved in blood glucose-lowering effects of ACE inhibitors.[29]

ACE inhibitor therapy is a mainstay of hypertension, diabetes, and cardiovascular disease management. To date, there is insufficient evidence available to warrant discontinuation of this therapy in patients at risk for hypoglycemia with these disease states; however, in patients with suspected captopril-induced hypoglycemia, switching to another ACE inhibitor is a reasonable recommendation.

Treatment of hypoglycemia:

While it is important to determine the cause of a patient's hypoglycemia, once signs and symptoms of hypoglycemia are recognized it is imperative to quickly treat the patient's hypoglycemia. Since there are no guidelines that are specific to managing drug-induced hypoglycemia, the current recommendations for managing hypoglycemia in patients with diabetes mellitus should be followed.

Regardless of the cause of hypoglycemia, patients that are conscious should be given 15 - 20 g of glucose or any carbohydrate that contains glucose.[5] The patient's blood glucose should be monitored in 15 minutes and they should continue to receive 15 - 20 g of glucose until their blood glucose level is greater than 70 mg/dl (3.9 mmol/l). Once the patient's blood glucose is above 70 mg/dl (3.9 mmol/l), the patient should eat something more substantial (a meal or snack) to maintain their blood glucose in a normal range, usually 70 -130 mg/dl (3.9 - 7.2 mmol/l).[5]

Hypoglycemia is defined as severe when a patient cannot treat their hypoglycemia on their own due to loss of consciousness. In cases of severe hypoglycemia, caregivers should administer glucagon.[5] It should be noted that glucagon is a prescription medication, available as a glucagon kit, whereas the glucose products routinely used for mild to moderate hypoglycemia are available without a prescription. Dose of glucagon is 1 mg (1 unit) IM/SC/IV. Repeat at 20min once or twice; give dextrose if no response. Administer supplemental carbohydrate to replete glycogen stores.[5]

Although there are number of studies which have described the occurrence of drug induced hypoglycemia, it is unclear how often drug-induced hypoglycemia is severe. Therefore, it will be up to the healthcare provider to determine the patient's risk for severe hypoglycemia. If the patient's hypoglycemia is severe enough to warrant attention of emergency personnel, then additional measures to raise their blood glucose may include the administration of intravenous dextrose sources.

Prevention:

One easy way to prevent drug-induced hypoglycemia is to avoid the medication that poses the potential for drug-induced hypoglycemia in patients that are at high risk for drug-induced hypoglycemia. Unfortunately, it may not be practical to avoid certain medications that may cause drug-induced hypoglycemia. Hence whenever deciding to use any medication, weigh the benefit of using the medication versus risk, in this case drug-induced hypoglycemia. If avoiding the agent is not possible, attempt to minimize the risk of hypoglycemia by keeping in mind the following restrictions.[3, 6]

1. Reinforce with patients the need to avoid alcohol intake
2. Minimizing the length of time and dose of an offending agent may also be beneficial.
3. Since hypoglycemia awareness is largely reliant on patient perception of the signs and symptoms of hypoglycemia, education is important. Therefore, it is important to review the signs and symptoms of hypoglycemia with patients and caregivers.
4. One way to monitor patients for evidence of hypoglycemia is to monitor their blood glucose concentrations, which is especially important in patients with pre-existing diabetes. Blood glucose should be carefully monitored with initiation, dose changes, or discontinuation of any medication in patients with diabetes.

5. When at all possible, patients should not be taking multiple agents that may cause drug-induced hypoglycemia. Healthcare providers should also be diligent to review a patient's medication profile for drug interactions, pharmacokinetics and pharmacodynamic, with potentially offending hypoglycemic agents.

Conclusion:

Very low quality evidence supports the association between numerous drugs and hypoglycemia. Drug-induced hypoglycemia can be severe and may cause significant morbidity. Prescribers should strive to avoid these adverse events particularly in elderly patients, patients with sepsis, renal or hepatic disease, or in patients on insulin and sulfonylureas.

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ANGIOTENSIN RECEPTOR BLOCKERS - ADVERSE REACTION AND MANAGEMENTS

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Introduction:

The angiotensin receptor blockers (ARBs) were originally approved by the US Food and Drug Administration (FDA) for the treatment of hypertension, and although they were very effective and safe drugs, they were used initially as alternatives to angiotensin-converting enzyme (ACE) inhibitors for patients intolerant to ACE inhibitors. The examples of ARBs include candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, azilsartan, etc. Specific adverse effects are associated with ACE inhibitor due to effects on the enzyme; and ARBs may offer more complete angiotensin II inhibition by interacting selectively with the receptor site.[1] Recent studies have also shown that ARBs are quite effective for the treatment of heart failure (HF)[2] and nephropathy in patients with or without diabetes mellitus.[3] Another significant benefit that has emerged from large clinical outcome trials in hypertensive patients treated with ARBs is protection from new or recurrent stroke. In addition, certain unique effects of ARBs, such as their antiatherogenic, antioxidant, antidiabetic, hypouricemic, antiplatelet aggregating, and atrial antifibrillatory actions have shown that ARBs are truly a pleiotropic class of drugs.

Angiotensin II Receptor Subtypes:

The discovery of specific angiotensin II receptor antagonists has confirmed the existence of various subtypes of angiotensin II receptors.[4] Angiotensin II type 1 (AT1) receptors are selectively inhibited by losartan and are sensitive to dithiothreitol, whereas type 2 (AT2) receptors are inhibited by PD 123177 and related compounds but are insensitive to dithiothreitol. Both the AT1 and the AT2 receptors have been cloned.[5] They belong to the superfamily of G-protein coupled receptors that contain 7 transmembrane regions.

Table 1: Angiotensin II Receptors and Their Functions and Location.[1]

Receptor	Actions	Location
AT1	Vasoconstriction, increase sodium retention, suppress rennin secretion, increase endothelin secretion, increase vasopressin release, activate sympathetic activity, promote myocyte hypertrophy, stimulate vascular and cardiac fibrosis, increase myocardial contractility, induce arrhythmias, stimulate plasminogen activator inhibitor 1, and stimulate superanoxide formation	Vessels, brain, heart, kidney, adrenal gland, and nerves
AT2	Antiproliferation/inhibition of cell growth, cell differentiation, tissue repair, apoptosis, vasodilation (NO mediated), kidney and urinary tract development, control of pressure/natriuresis, stimulate renal prostaglandins, and stimulate renal bradykinin and NO	Adrenal gland, heart, brain, myometrium, fetus, and injured tissues

Receptor	Actions	Location
AT3	Unknown	Neuroblastoma cells in amphibians
AT4	Renal vasodilator; stimulate plasminogen activator inhibitor 1	Brain, heart, vessels, lungs, prostate, adrenal gland, and kidney

AT-II-receptor antagonists were developed as agents that would more completely block the RAS and thus decrease the adverse effects seen with Angiotensin Converting Enzyme (ACE inhibitors). The ARBs' mechanism of action, selective inhibition of angiotensin II by competitive antagonism of the angiotensin II receptors, has been speculated to reduce adverse effects and possibly improve clinical efficacy.[6]

Adverse Reactions of ARBs

In general, the ARBs are well tolerated. None of the drugs reviewed has a specific, dose-dependent adverse effect. Because cough is seen as a class effect of ACE inhibitors, studies with ARBs have specifically addressed this concern. The frequency of cough has been significantly lower in patients taking ARBs than in patients taking ACE inhibitors. All of the ARBs are pregnancy category C for the first trimester and category D for the second and third trimesters.

Table 4: Common adverse reactions of ARBs include [6,7]

Central nervous system	Headache, dizziness, fatigue, insomnia
Gastrointestinal	Diarrhea, dyspepsia, abdominal pain
Musculoskeletal	Muscle cramp, myalgia, back pain
Respiratory	URTI, cough, sinusitis, viral infection
Miscellaneous	Rash, hyperkalemia, orthostatic hypotension, abnormal liver function, renal impairment, decreased hemoglobin level

Adverse Effects Of Combination Of ARBs & ACE Inhibitors[8]

Combination of ARB & ACE inhibitor was accompanied by marked increases in the risk of medication discontinuation because of adverse effects like symptomatic hypotension, worsening of renal function, and hyperkalemia in subjects with chronic heart failure or acute myocardial infarction with symptomatic LV dysfunction. These adverse effects are more common in older patients. Additionally, baseline creatinine, potassium and systolic blood pressure are predictors of kidney impairment, hyperkalemia,

and hypotension, respectively in patients taking combination therapy. Diabetes, lower baseline haemoglobin level and diuretic use are also significant predictors of kidney impairment and hyperkalemia. Furthermore, the frequency of these events continue to rise over time and is not limited to the period surrounding initiation of therapy. These events are associated with a higher risk of death. At-risk patients should be carefully monitored for the development of progressive kidney impairment and hyperkalemia as long as ARB therapy continues.

Myocardial Infarction: The Controversy

The issue of whether angiotensin II receptor antagonists slightly increase the risk of myocardial infarction (MI or heart attack) is currently being investigated. Some studies suggest ARBs can increase the risk of MI.[9] However, other studies have found ARBs do not increase the risk of MI.[10] To date, there is no consensus on whether ARBs have a tendency to increase the risk of myocardial infarction and further investigations are underway.

Indeed, as a consequence of AT1 blockade, ARBs increase angiotensin II levels several-fold above baseline by uncoupling a negative-feedback loop. Increased levels of circulating angiotensin II result in unopposed stimulation of the AT2 receptors, which are in addition, upregulated. However, recent data suggest AT2 receptor stimulation may be less beneficial than previously proposed, and may even be harmful under certain circumstances through mediation of growth promotion, fibrosis, and hypertrophy, as well as eliciting proatherogenic and proinflammatory effects.[11]

Cancer Risk Factors

The mechanism of the occasional increase in the incidence of newly developed cancer during ARB therapy has not been fully elucidated. While the well-known effects of angiotensin II (e.g., vasoconstriction and aldosterone synthesis) are mediated primarily by the AT1R, the function of the AT2R is not as well clarified.[12] The role of angiotensin II in cell proliferation, cell migration, and angiogenesis suggests a role in certain steps of tumor genesis and tumor progression.[13] ARBs exert their main clinical effects by inhibiting AT1R, and they have an inhibitory effect on tumor growth. However, some studies have demonstrated continuing tumor growth despite AT1R blockade. Results of experimental studies have shown that increased stimulation of free AT2R during ARB therapy results in increased tumor progression. Therefore, evidence has shown in vivo enhancement of tumor vascularisation by inhibition of AT1R by ARBs (accompanied by stimulation of AT2R, which remain with no counterbalance) and direct stimulation of AT2R.[14] Because of the incomplete information available, varying follow-up periods, and other differences, the effects of individual ARB active substances on the risk of cancer cannot be accurately determined.

Drug Interactions of ARBs

Comparison of the class as a whole reveals that losartan has the highest potential for drug interactions due to its involvement with the hepatic cytochrome P450 enzyme system.[15] No significant drug interactions involving valsartan, irbesartan, or candesartan have been reported. Olmesartan is not metabolized by the cytochrome P450 enzyme system reducing the risk of interactions with drugs metabolized by these enzymes.[6]

Table 5: Interactions of ARBs with other drugs

Precipitant drug	Object drug	CYP 450 Substrates	Effect
Cimetidine	Losartan	-	Increase losartan no effect EXP3174
Fluconazole	Losartan	3A4, 2C9	Increase losartan
Indomethacin	Losartan	-	Decrease hypotensive effect
Phenobarbital	Losartan	-	Decrease losartan
Rifampin	Losartan	3A4, 2C9	Decrease losartan
Telmisartan	Digoxin	-	Increase digoxin

Special Patient Considerations

The Elderly and Patients with Renal or Hepatic Impairment

There are no specific considerations for the ARBs in the elderly or patients with renal or hepatic impairment. As with ACE inhibitors, acute renal failure may occur if these agents are given to patients with renal artery stenosis. In patients with mild to moderate hypertension who took part in the clinical trials, kidney function was not adversely affected; even in the presence of chronic renal insufficiency, ARBs are generally well tolerated, presumably because they are largely cleared in the bile.[1]

Patients with Heart Failure

Several large ongoing trials have been designed to evaluate the effects that ARBs have on morbidity and mortality in cardiac disease, including heart failure. The goal is to define the role of ARBs in therapy and compare it to that of ACE inhibitors. The results from the ELITE II trial suggest that treatment with losartan (50 mg daily) is not superior to treatment with captopril (50 mg 3 times daily) but is significantly better tolerated.[16] Because the differences in morbidity or mortality rates associated with losartan and captopril are insignificant, losartan would be an appropriate choice for patients who are unable to tolerate ACE inhibitors.

Conclusion

The ARBs have very similar clinical profiles. They do, however, have different pharmacokinetic profiles, which may lead to some differences in efficacy. The newer agents have longer half-lives and durations

of action than the older agents. Combination of ARB & ACE inhibitor was accompanied by marked increases in the risk of medication discontinuation because of adverse effects, symptomatic hypotension, worsening renal function, and hyperkalemia in subjects with chronic HF or AMI with symptomatic LV dysfunction. Many of the randomized trials do not provide adequate definitions of the key adverse effects, such as hypotension, decreased kidney function, and hyperkalemia. Data concerning the allergic reactions and fetal abnormalities are derived primarily from observational studies. It is unclear whether substitution of one agent from a different class will attenuate an adverse effect. Risk factors for adverse effects need clarification.

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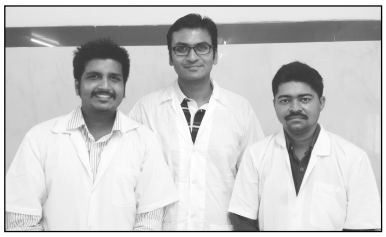
ANALYSIS OF ADVERSE DRUG REACTION REPORTED IN LTMGH

(March 2014 - June 2015)



Compiled by Dr Chiranjeeve Bonda

3rd year resident, Department of Pharmacology, LTMMC & GH, Sion, Mumbai - 22

Total Case Reports: 60

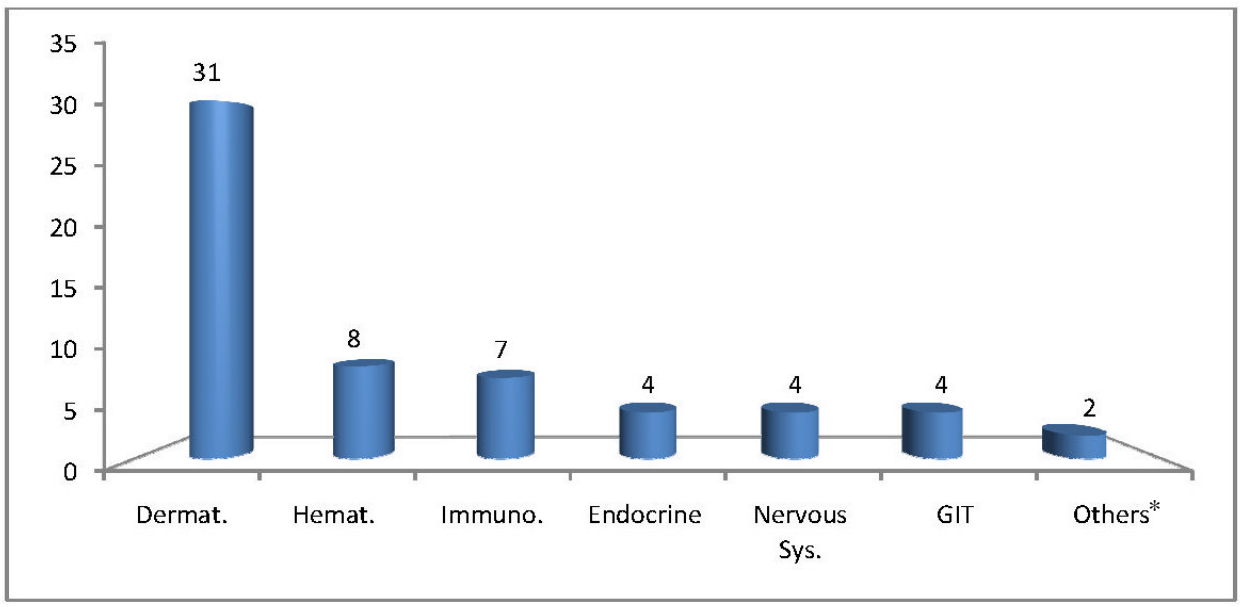
I. Age and Gender distribution:

Age groups	Number of patient	Males	Females
<3yrs	5	3	2
3-17yrs	14	12	2
18-44yrs	32	15	17
45-60yrs	6	1	5
>60yrs	3	1	2
Total	60	32	28

II. Seriousness of reactions reported:

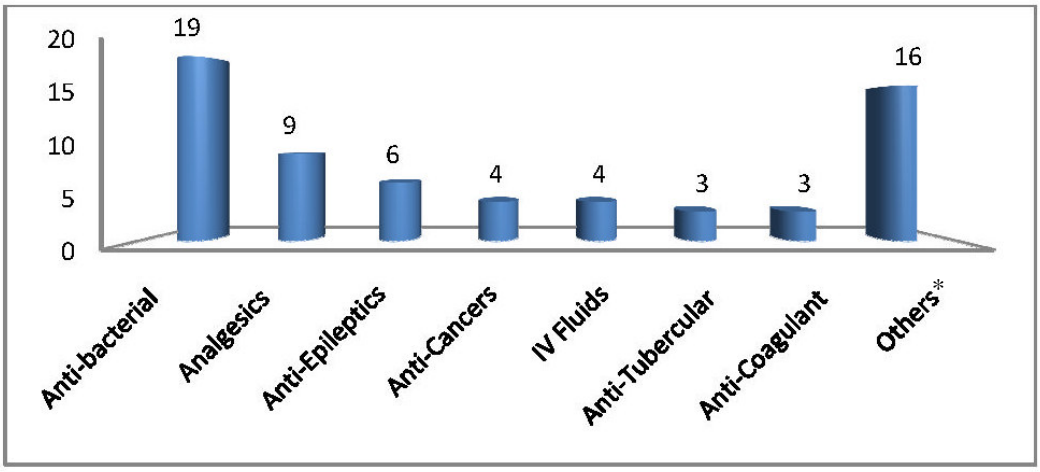
Seriousness of reactions reported	Number of cases
Yes	52
No	8

III. Systems involved in adverse drug reaction: (N = 60)



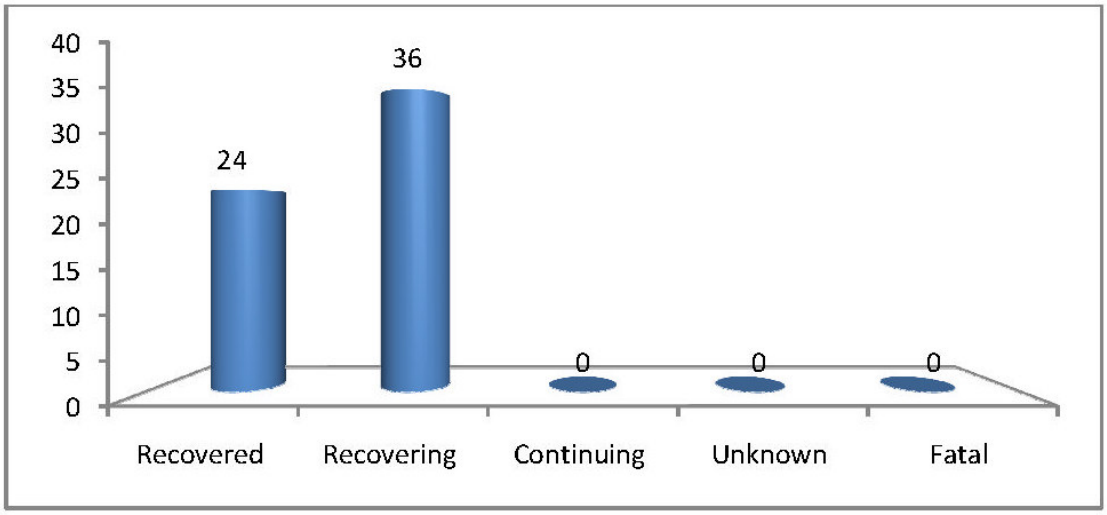
*Others include adverse reaction related to electrolyte imbalance and oncology

IV. Class of Suspected Drugs (N= 60)

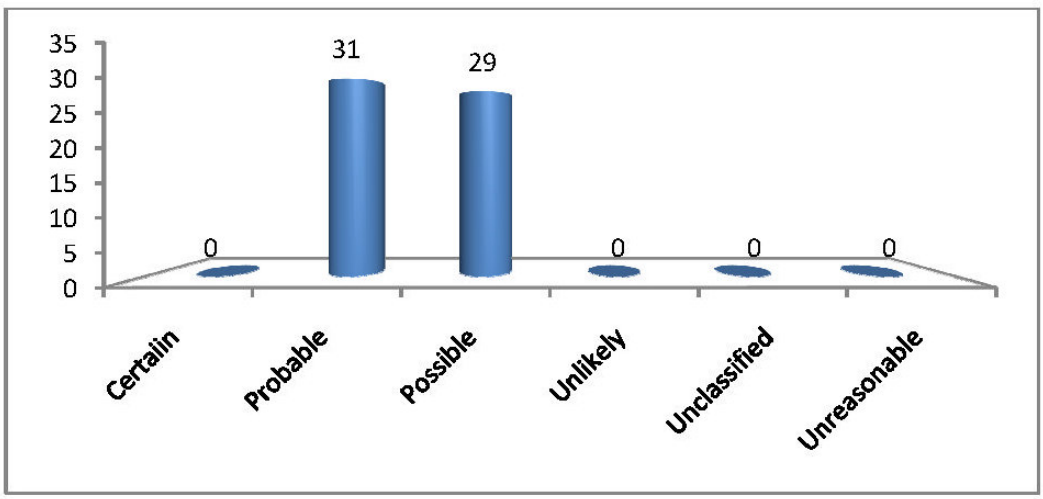


*Others include anti-viral, anti-leprosy, hypolipidemic, diuretic, anti-fungal, nutritional supplements, hormonal and vaccine.

V. Outcome of the reaction: (N=60)



VI. Causality assessment (WHO causality assessment scale): (N= 60)



EVALUATION OF A CASE

Transfusion Reaction To Platelets: A Case Report

Dr Swapnil Meshram and Dr Swapnil Jamdade

1st year Residents, Department of Pharmacology, LTMMC & GH, Sion, Mumbai - 22.

INTRODUCTION

Platelet transfusions play a crucial role in the prevention of bleeding in patients with thrombocytopenia due to various causes.[1] Platelet transfusions are a clinical necessity and do save lives every day worldwide. Majority of the platelet transfusions are administered for prophylaxis to prevent hemorrhage in case of thrombocytopenia. Platelet transfusions are a relatively safe form of therapy as far as transmission of infections is concerned. However, platelet transfusion is still accompanied by febrile and anaphylactoid reactions.The mechanism for reactions related to transfusion of platelet concentrates include IgE and IgG antibodies in the recipient against plasma proteins in the transfused blood component or transfusion of cytokines, chemokines, and histamine generated in the platelet product during preparation and storage.

We are reporting a case of platelet induced anaphylactic reaction and discussing the diagnosis and management of the same.

CASE REPORT

A 25-year-old male patient came to the emergency department in our tertiary care hospital with complaints of high grade fever with loose stools since 3 days. The patient was admitted and diagnosed with dengue. His platelet count was 25,000/mm^3.Other investigations included Hb -15.8gm%,WBC-8500/mm^3. Chest X-ray and renal function tests were normal. In view of the reduced platelet, it was decided to start prophylactic platelet transfusion for which 4 units were ordered. The patient was administered 3 units without any untoward event. However, when the 4th unit was given, immediately the patient developed chest pain generalized itching, difficulty in breathing and vomiting. Following the reaction, the transfusion was stopped. The patient was immediately treated with inj. chlorpheniramine maleate 2cc and inj. hydrocortisone sodium succinate 100cc given as single dose by intravenous injection. The reaction stopped 30 minutes after the treatment and the patient recovered subsequently. In view of the above findings a diagnosis of platelet induced anaphylactic reaction was made.

DISCUSSION

The incidence for transfusion reactions is 0.4% (of products transfused) in patients receiving platelet concentrates.[1]

The risk of allergic reactions is between 0.09 and 21% in patients who receive platelet transfusions.[1] Allergic reactions are highly variable in severity. They can present as isolated pruritus and urticaria as the only dermal manifestations. Systemic reactions may include bronchoconstriction, hypotensive reactions and shock.

In the present case the signs and symptoms of transfusion reaction such as rashes all over the body, breathlessness and chest pain developed immediately after the platelet transfusion. The reaction may be due to an antibody in the recipient reacting with a plasma protein in a blood component like IgA or Haptoglobin. As the reaction was rapid in onset and there were no signs of fever, we suspected platelet induced anaphylactic reaction.

Anaphylaxis is an acute, potentially life threatening systemic reaction with various mechanisms, clinical presentations, and severity that result from the sudden systemic release of mediators from mast cells and basophils.[2] Allergy is a hypersensitivity reaction mediated through immunological mechanisms in a predisposed individual.[3] The first allergic transfusion reaction was described in 1919.[4] Ever since, the possible mechanisms that produce the allergic transfusion reactions are pre-existing IgE or IgG antibody in the recipient which reacts with allergens or proteins in the transfused blood [e.g., drugs or chemicals (ethylene oxide), plastics, albumin, haptoglobin, and complement components], class or subclass specific anti IgA antibody in the recipient reacting against IgA in the transfused blood, passive transfer of IgE antibodies from the donor to the recipient, transfusion of complement derived anaphylatoxins (C3a and C5a) produced during blood storage.[5]

Other transfusion related reactions include acute hemolytic reaction which could be due to human error such as mislabeled pre-transfusion specimen or clerical errors occurring within the Blood Bank. Delayed Hemolytic Reactions occur in patients who have developed antibodies from previous transfusion. Febrile Reactions occur due to cytokines and antibodies to leukocyte antigens reacting with leukocytes or leukocyte fragments. Allergic or anaphylactic Reactions are due to anti-IgA or foreign plasma proteins. Septic reactions occur due to bacterial contamination of donor blood.

Patients who have previously been transfused, multiparous women and patients receiving emergency uncross-matched transfusion are at increased risk of immediate and delayed hemolytic transfusion reactions. Febrile, allergic and anaphylactic reactions occur more commonly in multiparous women and in patients with IgA deficiency and anti-IgA antibodies. Volume overload is a particular risk in the very young, the elderly and in patients with cardiovascular disease.[6]

In the present case, the patient did not have any such risk factors however the patient showed improvement on stopping the transfusion. Based on the above and according to WHO scale of Causality assessment, the association of platelet transfusion with the ADR can be considered to be "Probable" because of temporal relation with platelet transfusion, having a "dechallenge response" positive and the ADR was unlikely to be caused by other drugs or the underlying disease.

Treatment of platelet induced reactions

In case of first sign of anaphylactic reaction due to platelet or any other blood product, the first step of management is always to stop the transfusion immediately. The label of the transfusion pack and the information of the identity of the recipient showed be confirmed to be matching. The patient should be kept on continuous close monitoring and started on symptomatic treatment including intravenous fluids, oxygen and antihistamine, e.g. Promethazine 25-50 mg IV (max rate-25 mg/min) or Loratadine 10mg or Cetirizine 10mg oral. In the presence of wheezing, the patient may be started with Aminophylline at a dose of 125-250 mg intravenously slowly over a period of about five minutes. In case of severe reaction including laryngeal edema or bronchospasm, Epinephrine should be considered in a dose of 0.1-0.5 mg (0.1-0.5 mL of a 1:1000 solution) subcutaneously. The subcutaneous dose of epinephrine may be repeated at 10-15 minute intervals. A maximum dose of 5mg epinephrine can be given in one setting. A Haemovigilance notification should be sent to the blood bank.[1,7,8,9]

Other reactions should be managed accordingly, including paracetamol 500-1000mg oral for febrile reaction, replacement of intravenous infusion set and infusion of normal saline in case of hypotensive reaction, diuretic therapy with furosemide 1-2mg/kg intravenously for acute hemolytic reaction.[11,12]

Prevention of platelet induced anaphylactic reactions

Platelets can be stored at 22°C for 3-5 days in plastic containers.[11] The risk of reaction depends on the days of storage of platelets, so it is recommended that the component should be used as soon as possible. One of the easy ways of prevention is to elicit about the history of previous similar reactions. In some cases, pre-transfusion antipyretic agent paracetamol can be given, especially to patients with minor reactions and in those in whom large transfusions are required.

For recurrent mild reactions prophylaxis use of antihistamine to alleviate symptoms, e.g. Loratadine 10mg or Cetirizine 10mg oral can be considered. IgA deficient blood/blood products may be appropriate if recipient is known to have absolute IgA deficiency or to have anti-IgA.[8] Meticulous checking of recipient's ID and labelling of pre-transfusion blood sample should be to be done at recipient's side.

Careful monitoring of recipient for first 15 min of each unit transfused. Storage of blood components has to be done within specifications. Pre-transfusion testing for serum IgE and IgG levels may help in planning preventive measures like premedication, washed blood products and anti IgE therapy to achieve safe transfusion.[1,7,8,9]

Conclusion

Platelet transfusions are highly effective in many clinical settings. On the other hand, the rate of transfusion reactions is rather high. Knowledge of the risk factors and pre-transfusion testing are essential to the effective diagnosis and management of this condition.

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PUBLISHED CASE REPORTS ON TRANSFUSION REACTIONS

Compiled by Dr Swati Patil

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Anaphylactic reaction to platelet transfusion as the initial symptom of an undiagnosed systemic mastocytosis: a case report and review of the literature.

J Med Case Rep. 2014 Nov 26;8:389.

Blieden CR1, Campuzano-Zuluaga G, Moul A, Chapman JR, Cioffi-Lavina M, Ikpatt OF, Byrne GE Jr, Vega F.

The association between anaphylactic reactions and systemic mastocytosis is well documented. However, platelet transfusion has not previously been reported as a potential elicitor of anaphylaxis in the context of systemic mastocytosis. We describe the clinicopathological findings of a 59-year-old Latin American man who presented to the emergency room with fatigue, leukocytosis, thrombocytopenia and mild hepatosplenomegaly. He developed two separate, temporally associated and severe anaphylactic reactions after receiving platelet transfusions. The result of a laboratory investigation for clerical errors and Coombs test was negative. Pre- and post-transfusion urine samples were negative for hemolysis. Bone marrow biopsy and aspirate smears performed demonstrated involvement by systemic mastocytosis, which had been previously undiagnosed. We posit the transfusion reaction to be an anaphylactic reaction to transfused products as a result of heightened allergic sensitivity due to the underlying systemic mastocytosis. To the best of our knowledge, this is the first reported case of a severe anaphylactic-type reaction to blood products occurring in the setting of a previously undiagnosed systemic mastocytosis. Furthermore, it seems there are no published studies closely examining the relationship between hematopoietic neoplasms and transfusion reactions in general.

IgE- and IgG mediated severe anaphylactic platelet transfusion reaction in a known case of cerebral malaria

Asian Journal of Transfusion Science. 2013;7 (1) :81-83.

Bhavanadhar, Priscilla Chandran, A Krishna Prasad, B Shanthi.

Allergic reactions occur commonly in transfusion practice. However, severe anaphylactic reactions are rare; anti-IgA (IgA: Immunoglobulin A) in IgA-deficient patients is one of the well-illustrated and reported causes for such reactions. However, IgE-mediated hypersensitivity reaction through blood component transfusion may be caused in parasitic hyperimmunization for IgG and IgE antibodies. We have evaluated here a severe anaphylactic transfusion reaction retrospectively in an 18 year-old male,

a known case of cerebral malaria, developed after platelet transfusions. The examination and investigations revealed classical signs and symptoms of anaphylaxis along with a significant rise in the serum IgE antibody level and IgG by hemagglutination method. Initial mild allergic reaction was followed by severe anaphylactic reaction after the second transfusion of platelets. Based on these results, screening of patients and donors with mild allergic reactions to IgE antibodies may help in understanding the pathogenesis as well as in planning for preventive desensitization and measures for safe transfusion.

Transfusion related acute lung injury presenting with acute dyspnoea: a case report.

Journal of Medical Case Reports. 2008;2:336.

Haji AG, Sharma S, Vijaykumar D, Paul J.

Transfusion-related acute lung injury is emerging as a common cause of transfusion-related adverse events. We report a case of a 46-year old woman who developed acute respiratory and hemodynamic instability following a single unit blood transfusion in the postoperative period. Investigation results were non-specific and a diagnosis of transfusion-related acute lung injury was made after excluding other possible causes of acute lung injury. She responded to symptomatic management with ventilatory and vasopressor support and recovered completely over the next 72 hours. The diagnosis of transfusion-related acute lung injury relies on excluding other causes of acute pulmonary edema following transfusion, such as sepsis, volume overload, and cardiogenic pulmonary edema. All plasma containing blood products have been implicated in transfusion-related acute lung injury, with the majority being linked to whole blood, packed red blood cells, platelets, and fresh-frozen plasma. The pathogenesis of transfusion-related acute lung injury may be explained by a "two-hit" hypothesis, involving priming of the inflammatory machinery and then activation of this primed mechanism. Treatment is supportive, with prognosis being substantially better than for most other causes of acute lung injury.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr Swati Patil

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

FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin to include updates on bone fracture risk and new information on decreased bone mineral density.

The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin related to the increased risk of bone fractures and added new information about decreased bone mineral density. Bone mineral density relates to the strength of a person's bones. To address these safety concerns, a new Warning and Precaution was added and Adverse Reactions section of the drug labels was revised.

Health care professionals should consider factors that contribute to the risk of fractures prior to starting patients on canagliflozin. Patients should talk to their health care professionals about factors that may increase their risk for bone fracture. Patients should not stop or change their diabetes medicines without first talking to their health care professional.

Information about the risk of bone fractures was already in the Adverse Reactions section of the drug label at the time of canagliflozin's approval. The additional data confirm the finding that fractures occur more frequently with canagliflozin than placebo. Fractures can occur as early as 12 weeks after starting the drug. In the clinical trials, when trauma occurred prior to a fracture, it was usually minor, such as falling from no more than standing height. In addition, we have added new information about the risk of decreased bone mineral density to the canagliflozin label. A clinical trial that we required the manufacturer of canagliflozin to conduct evaluated changes to bone mineral density over two years in 714 elderly individuals and showed that canagliflozin caused greater loss of bone mineral density at the hip and lower spine than a placebo. This new safety information has been added to the Adverse Reactions section of the drug label.

FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density.[Internet].[Cited 2015 October 30]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm

FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain.

DPP-4 inhibitors are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling. We have added a new Warning and Precaution about this risk to the labels of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors. Patients should not stop taking their DPP-4 inhibitor medicine, but should contact their health care professional if they experience severe and persistent joint pain. Health care professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.

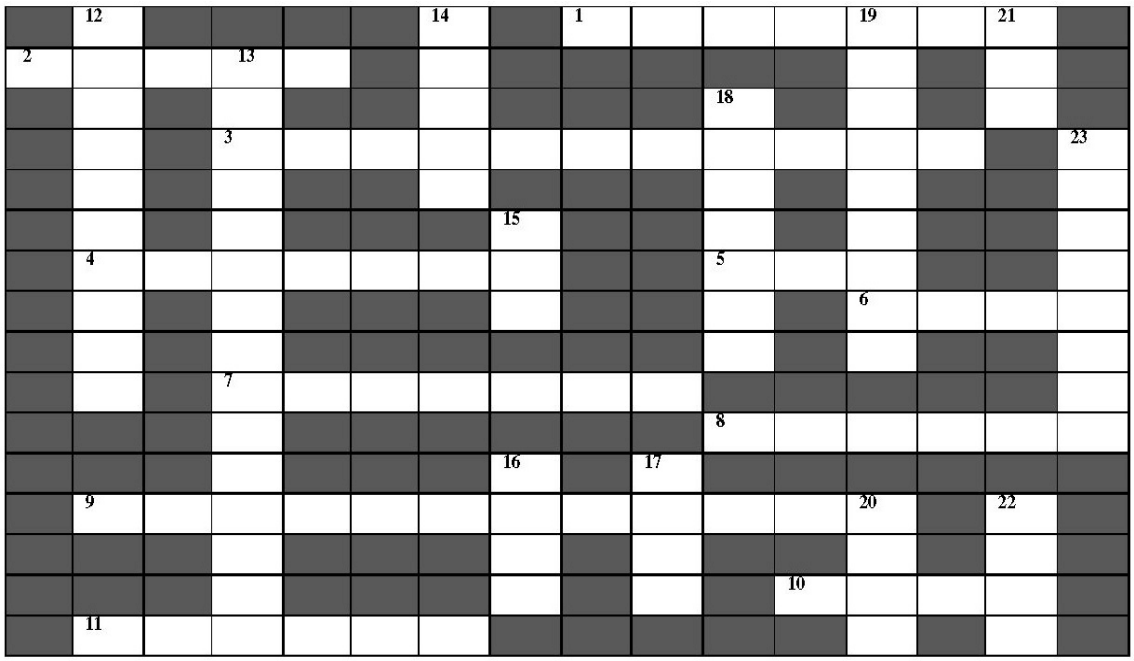
These medicines are available as single-ingredient products and in combination with other diabetes medicines such as metformin. In a search of the FDA Adverse Event Reporting System (FAERS) database and the medical literature, cases of severe joint pain associated with the use of DPP-4 inhibitors were identified. Patients started having symptoms from 1 day to years after they started taking a DPP-4 inhibitor. After the patients discontinued the DPP-4 inhibitor medicine, their symptoms were relieved, usually in less than a month. Some patients developed severe joint pain again when they restarted the same medicine or another DPP-4 inhibitor.

FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. [Internet]. [Cited 2015 October 30]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm

CROSSWORD PUZZLE

Dr. Sharmada Nerlekar *, Dr Abhilasha Rashmi**

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



ACROSS

Q1. ---------- is the only serious complication of long term use of Minocycline (7)

Q2. The dose limiting toxicity of Tacrolimus is --------- (5)

Q3. Miltefosine is -------- and it is contraindicated in pregnant women.(11)

Q4. The most important dose related toxicity of Primaquine that includes haemolysis, methaemoglobinemia, tachypnoea and cyanosis is due to its --------- property.(7)

Q5. Cidofovir which inhibits most DNA viruses including HSV, Pox, adenoviruses and ----- is known to produce dose related kidney damage.(3)

Q6. Blurring of vision,-------- pigmentation, thickening of eyelashes have occurred in some cases after using latanoprost.(4)

Q7. Avoidance of--------- is advised when patient is on Abacavir.(7)

Q8. Alcohol ingestion can precipitate---------acidosis in a patient taking metformin.(6)

Q9. L-Asparginase produces adverse effects like hyperglycaemia, liver damage, clotting defects and---------- due to defective protein synthesis .(12).

Q1O. Pyrazinamide can precipitate ------(4)

Q11. QTc prolongation, an acute reaction on iv injection and ---------- disturbances are the significant adverse effects due to voriconazole.(6)

DOWN

Q12. Amifostine is particularly used for prophylaxis of radiotherapy related --------(10)

Q13. Infusion reactions due to Rituximab can be dampened by pretreatment with---------(15)

Q14. Dose reduction of Vancomycin is needed in ------ insufficiency (5)

Q15. Ceftriaxone used to treat abdominal sepsis, septicaemias and complicated ------can cause bleeding due to hypoprothrombinaemia (3)

Q16. Cotrimoxazole can produce adverse effects like nausea, vomiting, stomatitis headache and --------in the patient.(4)

Q17. Ampicillin produces a high incidence of rashes especially in patients with -------, EB virus infections or lymphatic leukaemia (4)

Q18. ----------cycline antagonizes ADH action thereby causing Diabetes insipidus(7)

Q19. Excess fluids must be consumed to avoid nephrolithiasis while taking the retroviral protease inhibitor---------(9)

Q20. Prolonged or repeated use of relatively high doses of Quiniodochlor can cause a neuropathic syndrome called ---------- (4)

Q21. Streptomycin is contraindicated in pregnancy due to risk of foetal ------- toxicity (3)

Q22. ------floxacin, a second generation fluoroquinolone, has been banned in India since March 2011 due to Q-T prolongation, arrhythmias and unpredictable hypoglycemia (4)

Q23. ---------anaemia is the most common manifestation of non dose related idiosyncratic bone marrow depression due to chloramphenicol (8)

ALPHABET 'I' PUZZLE

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

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

1 I									
2	I								
3		I							
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1. Clinically significant thrombocytopenia occurs in about a 10% of patients receiving this Phosphodiesterase- III inhibitor for treatment of Congestive Heart Failure.
2. Since hypocalcemia is the principal adverse effect of this calcimimetic drug, it should not be used if the initial serum calcium concentration is less than8.4 mg/dl.
3. This thiophosphate cytoprotective agent is used to control nephrotoxicity due to Cisplatin & xerostomia due to irradiation for head & neck cancer.
4. Approximately 1% of patients develop renal calculi during treatment with this antiepileptic drug, probably due to its ability to inhibit carbonic anhydrase enzyme.
5. Progressive Multifocal Leukoencephalopathy is a very serious neurological complication reported after prolonged use of this humanized monoclonal antibody used for treatment of severe plaque type psoriasis.
6. Iritis is seen in up to 25% of HIV infected patients receiving intra-vitreal injection of this first FDA approved antisense oligonucleotide drug for treatment of refractory cytomegalovirus retinitis.
7. Administration of this luminal amoebicide in high doses in children has been found to be associated with optic atrophy and permanent loss of vision.
8. Because of its unique property to cause methemoglobinemia, and because neonates are prone to have methemoglobinemia, the use of this local anesthetic is very limited in obstetrical anaesthesia.
9. As serious nephrotoxicity results from systemic use of this polypeptide antibiotic, its use is restricted to topical applications only.
10. This hydrocarbon ointment base, obtained from the head of sperm whale, and used as an emollient, is so greasy that once applied, it is very difficult to remove it from the skin.

ALPHABET 'H' PUZZLE:

1. Inamrinone 2. Cinacalcet 3. Amifostine 4. Zonisamide 5. Efalizumab 6. Fomivirsen 7. Iodoquinol 8. Prilocaine 9. Bacitracin 10. Spermaceti

---

CROSSWORD ANSWERS

CROSS : 1. VERTIGO 2. RENAL 3. TERATOGENIC 4. OXIDANT 5. CMV 6. IRIS 7. ALCOHOL 8. LACTIC 9. PANCREATITIS 10. GOUT 11. VISUAL

DOWN : 12. XEROSTOMIA 13. ANTIHISTAMINICS 14. RENAL 15. UTI 16. RASH 17. AIDS 18. DEMECLO 19. INDINAVIR 20. SMON 21. OTO 22. GATI 23. APLASTIC

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

Please feel free to contact us for the same.

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