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BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

Department of Pharmacology

LTMMC & LTMGH, Sion, Mumbai - 22

Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

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From the Editor's Desk . . . . ✍

Dear Friends and Colleagues,

It gives me great pleasure to present to you yet another issue of Bulletin on Adverse Drug Reactions.

The first article deals with the topic of drug induced hyperglycemia which is in continuity of the previous issue article of drug induced hypoglycemia. The chances of frank diabetes induced due to drugs in very rare however drugs aggravate the hyperglycemic state of diabetes and cause adjustment in diabetic therapeutic regimens. The article gives an overview of the pathology and therapeutic measures for this condition.

The second article reviews the adverse effects of corticosteroids which are a very important group of drugs. The article deals with the monitoring, prevention and management of this important drug group.

Other features in this issue include analysis of the ADRs from our institute for your quick review, an interesting case report of chloroquine induces extra-pyramidal adverse drug reaction.

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

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

Thank you.

Dr. Sudhir Pawar

DRUG INDUCED HYPERGLYCEMIA

Dr Jaisen Lokhande* and Dr Swati Patil*

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

Introduction

A large number of drugs affect glucose homeostasis resulting in either hypo- or hyperglycemia. However, the risk of drug induced hypoglycemia is more than the risk of drug induced hyperglycemia. Unlike hypoglycemia, acute hyperglycemia is often benign and may persist without any clinically significant signs or symptoms. Fewer drugs have been reported to cause new diabetes in previously nondiabetic individuals. There are reports indicating aggravation of the hyperglycemic state of diabetes leading to diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) which are hyperglycemic emergencies.[1] Drug-induced or drug-associated hyperglycemia, irrespective of previous diabetes diagnosis, should be suspected in patients newly started or maintained on any of the drug categories or drugs and further investigations should be done to elucidate the relationship. Drug-induced diabetes is defined as the new development of a hyperglycemic state that meets the definition of diabetes and that is due to the ingestion of a drug.[2] Drugs induced hyperglycemia occurs either by interfering with the production or secretion of insulin or by reducing the effectiveness (insulin resistance) of insulin.

In this review article we have depicted the common offending agents causing hyperglycemia. Apparently there are no studies available which evaluated the cumulative incidence of hyperglycemia and hence the incidence has been mentioned with the individual topics.

Glucocorticoids

The most common group of drugs implicated for causing hyperglycemia are the Glucocorticoids[3] implicated in 2% of newly diagnosed cases of diabetes mellitus (DM)[4] Hyperglycemia due to glucocorticoids is more frequent with continuous doses with a higher incidence of fasting hyperglycemia. One study found that in patients with high dose of prednisone (>1 mg/kg/day) for 6 to 12 weeks, the DM incidence of 40.6%.[5] Glucocorticoids can lead to transiently or permanently induced hyperglycemia in non diabetic individual or can cause worsening of glycemic control in already diabetic patients.[6]

Patients on corticosteroid should be monitored regularly which includes eliciting for the classical symptoms of polyuria, polydipsia and weight loss on every visit and blood glucose estimation about 48 hours after GC initiation and then every 3 - 6 months for the first year and annually thereafter.[7] The hyperglycemia ascribed to corticosteroids is due to increased insulin resistance while some data also indicated rise in blood glucose levels through various other mechanisms.[8]

The clinician should also be careful while selecting drugs to be given in combination with glucocorticoids to prevent the drug interactions. Drugs like antifungal agents (itraconazole, ketoconazole), antibiotics (clarithromycin), antiviral agents (atazanavir, indinavir, ritonavir, saquinavir), etc are known to cause hyperglycemia in a significant number of cases.[7]

Beta-2 agonist

Hyperglycemia one of the most important adverse responses of beta-2 agonist, primarily seen in pregnant females and patients already diagnosed with insulin dependent diabetes mellitus where beta-2 agonist have been seen to cause diabetic ketoacidosis.[8] A review of 3,804 patients on antihypertensive agents indicated that the risk for diabetes was 28% greater in those using a beta-blocker than those using other medications.[9] Ironically both beta agonist and antagonists have been implicated in causing diabetes, though through different mechanisms. Multiple mechanisms for this are involved including, stimulation of release of glucose by liver and skeletal muscles, induction of peripheral insulin resistance and increase in the plasma glucagon level.[10]

Growth hormone (GH)

Recombinant human growth hormone (r-hGH) is given as substitution therapy to growth hormone-deficient children. Higher doses are used for short stature due to Turner's syndrome and for idiopathic short stature and for metabolic indications such as AIDS-associated wasting and severe burns.[11] Patients with active acromegaly are insulin-resistant and glucose-intolerant, whereas children with growth hormone (GH) deficiency (GHD) are insulin-sensitive and may develop fasting hypoglycaemia. Surprisingly, however, hypopituitary adults with unsubstituted GHD tend to be insulin-resistant, which may worsen during GH substitution.[12]

Insulin therapy may cause hypoglycaemia and GH substitution may cause hyperglycaemia. Such untoward effects should be minimized by carefully monitoring the individual patient.[12]

Oral contraceptives

Although large epidemiologic studies indicated no difference in the frequency of diabetes mellitus in nonusers and ever users of high-dose combination oral contraceptives, other studies had shown an increased risk of impaired glucose tolerance in current users, which is estimated to be roughly twice as frequent as that in nonusers.[13] Women who developed impaired glucose tolerance while receiving high-dose oral contraceptives either had previous gestational diabetes mellitus or were older, obese, or had a positive family history of diabetes mellitus.[13]

Lower-dose progestogen-only methods have milder or no effects on blood glucose parameters.[14] The mechanism of decreased glucose tolerance in oral contraceptive seems to be related partially to increased peripheral resistance that is potentially caused by a post-receptor defect in insulin action.[13]

Diabetes screening should be offered to patients with symptoms of diabetes and those with family history or clinical risk factors for diabetes mellitus. The use of low-dose oral contraceptives, particularly with reduced progestogen content can be recommended in suitable patients as it is accompanied by a low risk of impaired glucose tolerance, even in previous gestational diabetes mellitus.[13]

Beta adrenergic blockers

Antagonists to beta adrenergic receptor are commonly used medications known to impair insulin secretion, especially agents that are not selective for the beta 1- receptor subtype. Regarding cardioselective beta-blockers it can be said that the potentially adverse results are all reported with atenolol; newer and more beta-1 selective agents may be more metabolically neutral.[15]

In a recent study, atenolol was also shown to contribute to new-onset diabetes and to worsen hyperglycemia in people with abdominal obesity within 9 weeks of therapy initiation.[16] Potential mechanisms by which beta-blockers may contribute to the development of diabetes include weight gain, attenuation of the beta-receptor-mediated release of insulin from pancreatic beta-cells, and decreased blood flow through the microcirculation in skeletal-muscle tissue, leading to decreased insulin sensitivity. Blockage of other beta-receptor-mediated effects, such as glycogenolysis in muscle, may also influence plasma glucose levels.[3] Interestingly, carvedilol and nebivolol are not associated with the development of hyperglycemia or new-onset diabetes.[17, 18] Carvedilol's metabolic neutrality can be possibly explained by the alpha-blocking effects, resulting in increased peripheral blood flow and facilitation of glucose uptake by skeletal muscle.[19]

Thiazide and Thiazide-Like Diuretics

Thiazide antihypertensive drugs (e.g., hydrochlorothiazide) and thiazide-like drugs (e.g., metolazone) are often prescribed to control blood pressure in people with diabetes. Thiazide diuretics are known to promote hyperglycemia and in some cases contribute to the new onset of diabetes. Hydrochlorothiazide has been implicated in contributing to new-onset diabetes in as few as 9-18 weeks of therapy initiation.[16] Patients on hydrochlorothiazide may not experience altered blood glucose levels for weeks or longer (or not at all) if doses are kept low (12.5-25 mg).[20]

Diuretic-induced hyperglycaemia may be due to decreased insulin secretion as a result of hypokalaemia. The reduction in total body potassium correlates with a reduction in insulin secretion. Furthermore, correction of hypokalaemia by replacement with potassium salts can prevent the deterioration in glucose tolerance and may restore insulin sensitivity or drug discontinuation. Another possible contributor to elevated glucose levels may be enhanced free fatty acid and lipid exposure of tissues subsequent to thiazide use. Other mechanisms that may result in hyperglycaemia include decreased insulin sensitivity, increased hepatic glucose production, a direct inhibitory effect on insulin secretion, enhanced catecholamine secretion and action, and phosphodiesterase inhibition.[3, 21, 22, 23]

Even with new-onset diabetes, thiazide diuretics are commonly found to be safe, reducing risk of stroke, heart attack, and renal failure characteristic of uncontrolled hypertension. Therefore, risks of new-onset diabetes, induced by diuretic therapy, will be difficult to ascertain because of hypertension for which thiazide diuretic is widely used.[24] Potassium-sparing diuretics, such as spironolactone or triamterene, have minimal or no effects on glucose tolerance can be preferred.[3]

Second-Generation Antipsychotics (SGAs)

Newer SGAs, also known as "atypical antipsychotics," may increase the risk of hyperglycemia or type 2 diabetes. In particular, olanzapine and clozapine are most likely to increase the risk of diabetes when used in people with schizophrenia.[23]

The mechanisms for this remain unclear, but are probably multifactorial. The suggested reasons include drug-induced weight gain and adiposity, development of the metabolic syndrome, antagonism of serotonin (5-hydroxytryptamine) receptors, drug-induced leptin resistance, dyslipidaemia mediated pancreatic beta-cell damage and hepatocyte transcription factor dysregulation. Patients with schizophrenia are known to be at a higher genetic risk of developing diabetes mellitus and cardiovascular disease.[25]

One possible mechanism for hyperglycaemia is the impairment of cholinergic-regulated insulin secretion. Clozapine and olanzapine are potent anticholinergics and could interfere with these processes, but their effects on cholinergic activation of the beta-cell have not been investigated in detail.[3]

With regards to SGAs, a consensus statement developed by the ADA in conjunction with other medical professional organizations recommends monitoring fasting blood glucose for 12 weeks after initiation of therapy and annually thereafter in those without diabetes. However, cases involving hyperglycemic crises have been reported within weeks of starting SGAs.[26, 27] Furthermore, the panel recommends that consideration be given to switching a patient with blood glucose abnormalities to an SGA that is not associated with contributing to the development of diabetes (e.g., aripiprazole or ziprasidone). For patients with diabetes who are on SGAs, specific treatment guidelines are not available.[23]

There are also pharmacologic options for preventing type 2 diabetes; recent studies have shown that metformin can be added to a patient's drug regimen to not only prevent metabolic changes, but also to treat atypical antipsychotic-induced type 2 diabetes.[29]

Protease Inhibitors

Combination therapy with various drug groups used for the management of HIV infection have been associated with the development of significant metabolic adverse effects such as hyperlipidemia, peripheral fat wasting, central adiposity, hyperglycemia, insulin resistance, and new-onset diabetes.

This spectrum of changes is now thought to be part of a new syndrome associated predominantly with Protease inhibitors (PIs) use.[29] Up to 60% of HIV-infected patients treated with these agents develop either impaired glucose tolerance (IGT) or type 2 diabetes, and it now appears to be well established that regimens including protease inhibitors are associated with insulin resistance.[30]

A recent cohort study, which followed up patients already treated with PIs for 21 months, revealed that hyperlipidemia and impaired glucose tolerance were common in PI-treated patients.[31] It has been observed that the PI effects on blood glucose were not abolished by controlling for virological suppression, CD4 cell count, and increase in weight.[29] Management include dietary modification, regular physical activity and periodic screening for impaired glucose tolerance especially for patients receiving long-term PI therapy.[32]

NRTIs:

Several antiretroviral drugs and drug combinations are related to the development of DM; in particular, these include indinavir, lamivudine-stavudine, didanosine-stavudine and didanosine-tenofovir. Among the currently used NRTIs, the strongest association with mitochondrial toxicity, measured as inhibition of the mitochondrial DNA polymerase-gamma, is found for didanosine and stavudine (known as the d-drugs); notably, these 2 drugs were strongly associated with DM.[33]

The acquired alterations in mitochondrial number and function may contribute to worsening insulin sensitivity. Furthermore, larger studies are needed to understand the time course and mechanisms by which mitochondrial dysfunction and insulin resistance may be linked.[34]

Strong predictors for DM are non modifiable characteristics, such as age and ethnicity, but, importantly, the strong predictors also include obesity, which should become a major target for prevention. Furthermore, there are risks for DM associated with antiretroviral therapy, especially with PIs and some NRTI combinations. Because of their association with other metabolic disorders, regimens containing stavudine and didanosine are avoided as long as possible in developed countries, but they belong to first-line regimens in resource-limited areas. Together with the probably genetically determined elevated DM risk associated with Asian and African ethnicity, this may have an important impact on the long-term tolerability of anti-HIV treatment in the regions that are most affected.[33]

Calcineurin Inhibitors (CNIs)

The CNIs cyclosporine, sirolimus, and tarcrolimus are often used to avoid allograft rejection in transplantation therapy. The sustained use of these agents results in post-transplantation diabetes. Risk factors for the development of hyperglycemia and a diagnosis of post-transplantation diabetes (PTDM) include age, non-white ethnicity, glucocorticoid therapy for rejection, and the use of cyclosporine or tacrolimus.[35, 36] However, comparative incidence of PTDM is twofold higher with

tacrolimus as compared to cyclosporin.[3] In transplant patients, while potentiating the hyperglycaemic effects of corticosteroids, calcineurin inhibitors have a more complex mechanism of action, which may include islet toxicity, diminished insulin synthesis or release and decreased peripheral insulin sensitivity.[37]

Tacrolimus decreases glucose-stimulated insulin release due to reduced ATP production and glycolysis in beta-cells derived from reduced glucokinase activity. On the other hand, tacrolimus impairs glucose-stimulated insulin secretion and that protein kinase C-mediated (Ca2+-dependent and -independent) and Ca2+-independent GTP signalling pathways may be involved. However, tacrolimus-induced impaired insulin secretion was reversed three days after removal of the drug. Similarly, diabetogenic effect of cyclosporin appears to be dose-dependent and has been ascribed to a direct beta-cell toxic effect.[3]

Transplantation patients with new-onset or concurrent diabetes often remain on the most effective post-transplant drug regimens with management of blood glucose following current recommendations. However, modification of the immunosuppressive regimen could be considered and consists of reduction or split-dosing of corticosteroids, reduction or alteration of CNI therapy, and consideration of instituting steroid-sparing immunosuppressive therapies.[23]

Fluoroquinolones

Fluoroquinolones are one of the most commonly prescribed classes of antibiotics worldwide. Fluoroquinolones can cause dysglycemia as an adverse effect in diabetic and non diabetic patients.[38] The most commonly implicated fluoroquinolone is gatifloxacin, whereas levofloxacin is weakly implicated.[23] The mechanism of hyperglycemia is unclear. It may be due to a direct drug effect on glucose metabolism, or it may be a result of multiple confounding factors.[39] In addition, some recent findings imply that disturbed cellular glucose transport and GLUT1 function may underlie the dysglycemic effects of ciprofloxacin and levofloxacin.[40] This adverse effect has important clinical implications, especially for diabetic patients.[41]

Nicotinic acid (Niacin)

Niacin is an important agent for increasing the high-density lipoprotein cholesterol and second line agent for reducing cholesterol levels in blood. The severity and type of underlying lipid abnormality determines the extent of response to niacin treatment.[42] A meta-analysis of published and unpublished data from randomised controlled trials of niacin demonstrated that niacin therapy led to a 34% increase in the risk of developing diabetes compared with placebo or standard care.[43] These results are consistent regardless of the presence or absence of background statin therapy.[43]

The mechanism that explains niacin's detrimental effect on glycaemic control and diabetes risk remains unclear.[43] Niacin therapy is infrequently associated with incident diabetes or the need for new insulin

prescriptions.[44] Guidelines recommend monitoring glycemic control after initiating niacin treatment or increasing its dosage.[44]

Statin:

The effect of statin treatment on glucose metabolism and the risk of diabetes remains an issue of controversy. Given the success of statins in both primary and secondary prevention of cardiovascular morbidity and mortality, their use is progressively increasing. One emerging risk is an increased incidence of diabetes mellitus (DM). There is evidence that incident DM associated with statin use may be more common in the elderly, in women, and in Asians. Statin medication use in postmenopausal women is associated with an increased risk for DM. This may be a medication class effect.[45] Comparison trials suggest that the hydrophilic statins pravastatin, rosuvastatin and pitavastatin as compared to lipophilic components of the class, including atorvastatin and simvastatin have favourable effects on glucose homeostasis.[46]

Overall, although statins slightly increase the risk for New Onset Diabets Mellitus (NODM), no change is recommended to current practice because the benefits of statin therapy for the reduction of cardiovascular events in patients at risk for diabetes (including prediabetic patients) outweigh this risk. However, prediabetic patients should be counseled regarding lifestyle modification, particularly weight loss if overweight or obese, and engaging in adequate physical activity. Last, in very high risk prediabetic patients, antidiabetic treatment, mainly metformin, may also be considered.[47]

Total parenteral nutrition

The beneficial effect of total parenteral nutrition (TPN) in improving the nutrition status of hospitalized malnourished patients is well established. Recent randomized trials and meta analyses, however have shown the development of hyperglycemia in 10-88% of hospitalized patients receiving TPN therapy.[48] Observational studies have reported a 33% mortality rate in TPN patients who developed hyperglycemia, as well as an increased risk of cardiac complications, infections, systemic sepsis, and acute renal failure.[48]

Currently, as recommended by American College of Endocrinology (ACE) and the American Diabetes Association (ADA), insulin is the most appropriate agent for management of hyperglycemia. The American College of Endocrinology (ACE) and the American Diabetes Association (ADA) recommends less stringent blood glucose targets between 7.8-10.0 mmol/L for critically ill patients to prevent hypoglycemia, while controlling for hyperglycemia. They also recommend intravenous insulin infusions for critically ill patients and subcutaneous basal-bolus, prandial and correctional dosing for all non critically ill patients. One study recommended insulin infusion for all patients irrespective of their inpatient location if during TPN treatment blood sugars were persistently above 10 mmol/L. Treatment of hyperglycemia with insulin infusion was associated with an increased rate of complications, although not statistically significant for death.[49]

Other Drugs

L-asparaginase is a valuable chemotherapeutic agent used in the induction of remission and improvement of long term survival in patients with acute lymphoblastic leukemia Hyperglycemia was observed after a mean of five doses of L-asparaginase (range 2-10).[50] Phenytoin induces hyperglycaemia by inhibition of insulin release which is reversible on stoppage of the drug.[51]

Conclusion

In cases of drug induced hyperglycaemia there is a perturbation in glucose metabolism that exceeds the patient's adaptive capacity. Hence, sulfonylureas which act primarily by enhancing endogenous insulin secretion would not be expected to be effective therapy. In such cases where causative drug must be continued, insulin therapy is the most efficacious approach.[15] Thus careful monitoring is imperative in diabetic, prediabetic and non diabetic individuals receiving any of the above drugs. In most of the clinical scenario discontinuation of the drug reverses the adverse effect but such step must be wisely taken keeping in mind the risk benefit profile of the drug for that condition.

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SYSTEMIC CORTICOSTEROIDS – ADVERSE EFFECTS AND THEIR MONITORING

Dr. Nishikant N. Mankar

Assistant Professor, Dept. of Pharmacology, Dr. V. M. Government Medical College, Solapur

Corticosteroids are synthetic analogues of the natural steroid hormones produced by the adrenal cortex. Like the natural hormones, these synthetic compounds have glucocorticoid (GC) and/or mineralocorticoid properties.[1] Since their discovery in the 1940s, corticosteroids have become one of the most widely used and effective treatments for various inflammatory and autoimmune disorders.[1] The following table gives different corticosteroid available.

Corticosteroid		**Potency relative to Hydrocortisone**		**Half-Life**	
	Equivalent Glucocorticoid Dose (mg)	**Anti-Inflam-matory**	**Mineral Corticoid**	**Plasma (minutes)**	**Duration of Action (hours)**
Short Acting					
Hydrocortisone	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	0.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400 +	20	- -

These drugs have become important agents for use in the treatment of many inflammatory, immunologic, hematologic, and otherdisorders.[2]Although systemic corticosteroids provide an effective therapy for many inflammatory conditions, they also have associated adverse effects that have been well studied and described.[3,4] The objective of this article is to present a review of the physiology of systemic corticosteroids and the known side effects associated with their use.

Morphological changes

Redistribution of adipose tissue is a common effect associated with prolonged corticosteroid treatment. These changes are known as cushingoid changes, and include truncal obesity, facial adipose tissue referred to as moon face, and dorsocervical adipose tissue referred to as buffalo hump[5] which could be due to the difference of sensitivity to the glucocorticoid facilitated lipolytic effect-that is, the peripheral adipocytes are more sensitive to this effect than the central adipocytes.[6] It has been reported to occur in 15% of patients in less than 3 months 'time, with doses equivalent to 10 to 30 mg of prednisone per day.[7] Higher doses and longer duration of corticosteroid use seem to increase the frequency of adipose tissue redistribution. Patients taking daily prednisone demonstrated adipose redistribution or corticosteroid-induced lipodystrophy at incidences of 61%, 65%, and 69% at 3, 6,and 12 months, respectively, with mean doses of 32 mg, 19 mg, and 11 mg at the respective time points.[7] Weight gain, which can be enormous in some patients, can be minimised by the early use of a calorie controlled diet.[6]

Hyperglycemia

Corticosteroids increase blood sugar levels by increasing hepatic gluconeogenesis and by decreasing glucose uptake in peripheral tissues. Corticosteroids stimulate proteolysis, promote the release of gluconeogenesis-stimulating enzymes, and inhibit adipose and muscle tissue glucose uptake.[8] Furthermore, acute exposure to corticosteroids causes insulin resistance by decreasing the ability of adipocytes and hepatocytes to bind insulin. This effect can occur within 12 hours of beginning therapy, although it has been found to decrease with prolonged corticosteroid use. Synthetic corticosteroids such as prednisone and dexamethasone are 4 and 30 times more potent, respectively, than natural corticosteroids such as hydrocortisone at decreasing carbohydrate tolerance.[8]

Correlations have also been made to steroid dose and the development of diabetes, with daily and cumulative dose likely independent risk factors.[5, 8] On cessation of corticosteroids, the inhibition of glucose uptake and metabolism in peripheral tissues usually returns to normal.[8]

All patients should be educated about the classic signs and symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss) so that they are screened for steroid-induced diabetes if symptoms arise. In adults, monitoring of glycated hemoglobin (A1C), fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) (using a 75-g oral glucose tolerance test [OGTT]), or casual PG (any time of the day without regard to the interval since the last meal) are recommended.

In patients taking prednisolone, some experts have recommended that blood glucose be monitored within 8 hours of the first dose (i.e., in the afternoon if once-daily prednisolone is administered in the morning).[1]

Infection

Steroids decreases circulating lymphocytes, monocytes, basophils, and eosinophils, which is due to their migration from the vascular bed to lymphoid tissue.[2] Corticosteroids can affect neutrophils function by reducing their adherence to vascular endothelium as well as their bactericidal activity and thus enhance the chances of infection. The administration of corticosteroids on alternate days has been shown to reduce their negative impact on leukocyte function.[9]

Several studies have demonstrated that patients treated with glucocorticoids are at increased risk for developing invasive fungal infections, pneumocystosis, and viral infections, especially in patients who have undergone bone marrow transplantation.[5, 10, 11]

Wound healing

Corticosteroids inhibit the natural wound-healing process in several ways. First, they decrease the circulating monocytes, thus decreasing the influx of macrophages.[12, 13] Studies suggest that the reduced number of macrophages may decrease phagocytosis as well as growth factor/cytokine production. In addition, corticosteroids can delay reepithelialization, decrease the fibroblast response, slow capillary proliferation, and inhibit collagen synthesis and wound maturation,[12, 14] ultimately leading to delayed wound healing. Agents such as epidermal growth factor, transforming growth factor beta, platelet-derived growth factor, and tetrachlorodecaoxygen have been shown to counteract the effect of corticosteroids on wound healing.[12]

Bone metabolism

The role of steroids in bone loss is well described and may occur through several different mechanisms. These effects places bones, such as vertebral bodies, femoral necks, and distal radii, at increased risk for fracture.[15, 16]

Corticosteroids have been found to cause apoptosis of osteoblasts and osteocytes. This effect has been shown to occur within 1 month of use; however, it slows after 6 to12 months. A reduction in bone formation based on markers of bone metabolism has been demonstrated with as little as 5 mg of prednisone daily for as short as 2weeks.[17]

Data are conflicting as to whether daily dose or cumulative dose has a more significant clinical effect on bone density. A meta-analysis[18] demonstrated a stronger correlation between cumulative steroid dose on bone mineral density than daily dose. Fracture risks have also been shown to increase based on dose, duration, age, gender, and body weight.[5]

Corticosteroid use has also been associated with avascular necrosis or osteonecrosis. This complication has been correlated with cumulative dose, and has been seen primarily in the head of the femur,

although other weight-bearing and non- weight-bearing bones can be affected.[15] The exact cause is not fully understood, but is thought that several mechanisms may play a role which finally results in generation of bone edema of decreased blood flow leading to impaired perfusion of the bone.[15, 19]

Assessment of bone marrow density(BMD) at baseline and after 1 year of GC therapy in adults who are expected to be on prednisone ≥5 mg/day (or equivalent)for over 3 months is recommended. If BMD is stable at the 1-year follow-up and fracture risk is low, then subsequent BMD assessments can be performed every 2-3 years. However, if bone density has decreased at the initial 1-year follow-up, both BMD and fracture risk should be assessed annually.

Because early diagnosis and appropriate intervention can prevent or delay the progression of osteonecrosis and the need for joint replacement, patients using high-dose GC therapy or those treated with GCs for prolonged periods should be evaluated for joint pain and decreased range of motion at each visit. Magnetic resonance imaging should be considered in adult or pediatric patients presenting with these signs or symptoms.[1]

Therapeutic managements includes appropriate use of calcium and vitamin D3, bisphosphonates, calcitonin, hormonal replacement therapy, etc.

Ophthalmic

Corticosteroids can have extensive ophthalmic effects, depending on the route of administration. Systemic administration of corticosteroids can lead to cataract formation, increased intraocular pressure, myopia, exophthalmos, papilledema, central serous chorioretinopathy, and subconjunctival hemorrhages.[20] The most commonly encountered ophthalmologic side effects include cataract formation and increased intraocular pressure or glaucoma. Although studies have shown that doses as low as 5 mg of oral prednisone taken for as little as 2 months can lead to cataract, most report doses of 10 mg or more daily for at least 1 year before the onset of cataract formation.[20]

Increased intraocular pressure can lead to visual field loss, optic disk cupping, andoptic nerve atrophy. Corticosteroids cause significant increases in intraocular pressure in approximately 5% of patients within the first few weeks of therapy.[16] Eventually, between 18% and 36% of the population will develop at least a moderate (5 mm Hg or greater) increase in pressure with prolonged steroid treatment. Factors associated with a greater risk of increased intraocular pressure induced by corticosteroids include open-angle glaucoma, diabetes mellitus, high myopia, rheumatoid arthritis, hypertension, migraine headaches, and first-degree relatives with open-angle glaucoma.[16, 20]

The route of administration seems to play an important role; topical ophthalmic and systemic administration have a high correlation with the incidence of glaucoma. The exact mechanism by which corticosteroids cause glaucoma is unknown. One theory suggests that corticosteroids may have a

negative effect on the trabecular meshwork by causing the build up of proteins such as glycosaminoglycans, fibronectin, elastin, laminin, and collagens or by preventing the appropriate expression of prostaglandins, collagenase, plasminogen activator, and stromelysin, enzymes that help break down outflow obstructions.[16, 20]

Patients on low-to-moderate doses of systemic corticosteroids for more than 6-12 months should undergo annual examination by an ophthalmologist. An earlier examination is required in patients with symptoms of cataracts (namely blurred vision), however, this is generally not considered an ocular emergency that requires urgent treatment. Early referral for monitoring of intra-ocular pressure (glaucoma) is recommended in patients at higher risk of developing steroid-induced glaucoma, such as those with a personal or family history of open angle glaucoma, diabetes mellitus, high myopia, or connective tissue disease (especially rheumatoid arthritis).

Skin changes

Cutaneous complications caused by corticosteroids include Cushing syndrome, skin atrophy, striae, ecchymoses, and changes in mechanical properties of the skin. Less commonly, pustular acne, tinea incognito, and Stevens-Johnson syndrome may occur.[16] The frequency with which these complications occur seems to be more common with systemic corticosteroids than topical or inhaled corticosteroids.

Although treatment of red striae is often disappointing, some success has been noted with topical vitamin A 0.1% cream, flash lamp-pumped pulsed dye lasers, and a combination of pulsed dye laser and non ablative radiofrequency application. To help reduce the risk of striae, patients initiating systemic corticosteroid therapy should be advised to follow a low-calorie diet.[1]

Gastrointestinal

Despite the commonly held perception that steroid use increases the risk of peptic ulcer disease, several large meta-analyses of randomized, placebo-controlled trials have failed to show this association.[21] Conn and Poynard performed a follow-up meta-analysis of 93 randomized, double-blind, placebo-controlled trials and found no statistically significant association between ulcer development and prednisone use.[22] These studies did find that patients using prednisone complained of peptic ulcer-type symptoms more frequently than the control patients. The investigators suggested that this could be due to superficial ulcers that were not deep enough to be detected by barium studies in the pre-endoscopic era.[22]

In addition to gastric issues, pancreatitis has been reported with the use of corticosteroids.[5] The exact incidence and the mechanism by which the corticosteroids cause pancreatitis is unknown.

Consideration can be given to the use of proton pump inhibitors (PPIs) for GI protection in GC users at high-risk of GI bleeding or peptic ulcers, such as those using NSAIDS, patients with a history of ulcers or GI bleeding, and those with serious comorbidities (i.e., advanced cancer)

Adrenal suppression (AS)

In the normal, non stressed adult, the adrenal gland secretes 10 to 20 mg of cortisol per day, which translates to approximately 5 to 7 mg of prednisone per day.[2, 22] Exogenous steroids increase the circulating corticosteroid levels, which can lead to a negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis at the levels of the hypothalamus and the pituitary gland. This effect can lead to a decrease in production of corticotropin-releasing hormone from the hypothalamus and corticotrophin or adrenocorticotropic hormone from the pituitary gland.[23, 24] which leads to decreased cortisol secretion from the adrenal cortex.[25] Post mortem studies have shown atrophy of adrenal glands following as few as 5 days of corticosteroid therapy. Studies have demonstrated that short courses for less than 30 days, with doses ranging from 15 to 50 mg of prednisone per day, can result in significant adrenal suppression in patients.[5] This suppression can then last for many weeks after the course is completed. Longer-term, lower-dose synthetic corticosteroids can also lead to adrenal insufficiency, requiring months for adrenal recovery.[5]

Physicians should be aware of the risk of AS in patients receiving supraphysiological GC doses for >2 weeks, those who have received multiple courses of oral steroids totalling>3 weeks in the last 6 months, or in patients presenting with symptoms of AS (including growth failure in children) If AS is suspected, biochemical testing of the HPA axis should be considered after GC treatment has been reduced to a physiologic dose. Given the ease and practicality of a first morning cortisol measurement, it should be considered for the initial screening of patients at risk for AS.

If the 8:00 am cortisol value is below the normal laboratory reference range, AS is likely present and further GC withdrawal should occur only once testing has normalized. The insulin tolerance test (ITT) is the definitive test for evaluation of the HPA axis, but performing this test is complicated and risky for patients since insulin is administered to achieve hypoglycemia.

Therefore, in the setting of a normal morning cortisol result and the presence of AS symptoms, the low-dose adrenocorticotropic hormone (ACTH) stimulation test should be performed to confirm the diagnosis since it is a sensitive and specific test for AS.[1]

Myopathy

Muscle weakness associated with corticosteroid use is believed to be caused by type IIb muscle fiber atrophy.[5, 26] Corticosteroids interfere with skeletal muscle oxidative phosphorylation, protein synthesis, muscle membrane excitability, and carbohydrate metabolism.[5, 26] The onset is usually asymptomatic with the muscles of the proximal limbs affected first. Patients often notice difficulty with tasks such as climbing stairs which gradually resolves over 1 to 4 months after cessation of the corticosteroids and affected muscles regain their strength.[27] This effect has been shown to be dose dependent, with the corticosteroid effect lasting from days to months after the cessation of therapy.[5] Simple exercises are useful in the prevention and early recovery of steroid induced myopathy

Cardiovascular (CV)

Corticosteroids have been associated with increases in blood pressure, although the mechanisms have not been clearly elucidated. One debated theory is that mineralocorticoids increase plasma volume by binding to mineralocorticoid receptors in the renal distal tubular epithelial cells, resulting in increased sodium reabsorption and water retention with subsequent extracellular volume expansion.[5, 21, 28]

The incidence of secondary hypertension due to corticosteroids has not been adequately described. This risk was found to be associated with cumulative dose, and seemed to be higher in patients with increased baseline risk such as cardiac or pulmonary disease.

There are currently no evidence-based guidelines for the monitoring of dyslipidemia and CV risk in patients using corticosteroid therapy. The assessment of lipid profile at baseline, 1-month after initiating systemic GC therapy and then every 6-12 months thereafter is recommended. Ten-year CV risk should also be assessed using the Framingham Risk Score (FRS).[1]

Psychiatric

Corticosteroids cause cognitive as well as psychiatric disturbances. Cognitive deficits, such as memory disturbances, may emerge as early as 4 days after starting steroids, and appear to be dose dependent and reversible on termination of the medication.[29]

The most common psychiatric manifestations include agitation, anxiety, distractibility, fear, hypomania, indifference, insomnia, irritability, lethargy, mood liability, pressured speech, restlessness, and tearfulness. Most psychiatric side effects occur within the first week of therapy and the time of onset has not been correlated with dose.[30] Although these effects can cause significant detriment to an individual's daily quality of life, they are not considered severe reactions. Severe reactions include mania, depression, or a mixed state. Most individuals developing psychiatric manifestations on short courses report euphoria or hypomania, whereas those on long term therapy tend to develop depressive symptoms.[29] The association between corticosteroids and psychiatric side effects was supported by the meta-analysis of Conn and Poynard. They reported that with a mean daily dose of 35 mg of prednisone, psychiatric side effects occurred 2 times more often than in those receiving placebo (P<.02).[22]

Most of these reactions occurred early in the course of therapy, and most involved irritability and anxiety. Duration of the psychiatric disturbance is variable with delirium resolving within days, whereas severe symptoms such as depression or mania may take up to 6 weeks to resolve.[29] More than 90% of individuals with psychiatric reactions to corticosteroids recover from these symptoms.[30] Patient education about potential psychiatric side effects is crucial for early reporting and management.

GC-induced psychosis usually only occurs with the use of high doses (>20 mg of prednisone or

equivalent) for prolonged periods. For patients with persistent symptoms of psychosis, antipsychotic therapy may be required. Most patients with psychiatric reactions to corticosteroids usually recover from these symptoms with dose reductions or upon cessation of therapy. Lithium has also been found to be effective for both the prophylaxis and management of GC-related affective disorders.[1]

Summary

This article presents a comprehensive review of the side effects of exogenous corticosteroids and their relative frequencies. Corticosteroids are commonly prescribed to treat various inflammatory conditions and diseases. For this reason, it is essential that the specific effects of these drugs, including their relative frequencies, severities, and associated doses, are better understood.

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ANALYSIS OF ADVERSE DRUG REACTION REPORTED

(July 2015 to October 2015)

Compiled by Dr Mayur Gawde

2nd year Resident, Department of Pharmacology, LTMMC & GH, Sion, Mumbai-400022

Total Case Reports: 87

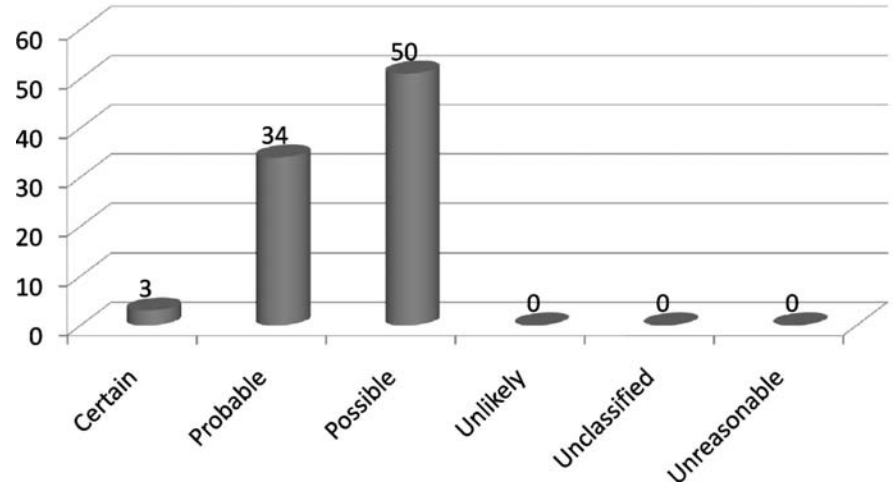
I. Age and Gender distribution:

Age groups	Number of patients	Males	Females
< 3 yrs	4	2	2
3 - 17 yrs	23	15	8
18 - 44 yrs	43	19	24
45 – 60 yrs	13	4	9
> 60 yrs	4	0	4
Total	**87**	**40**	**47**

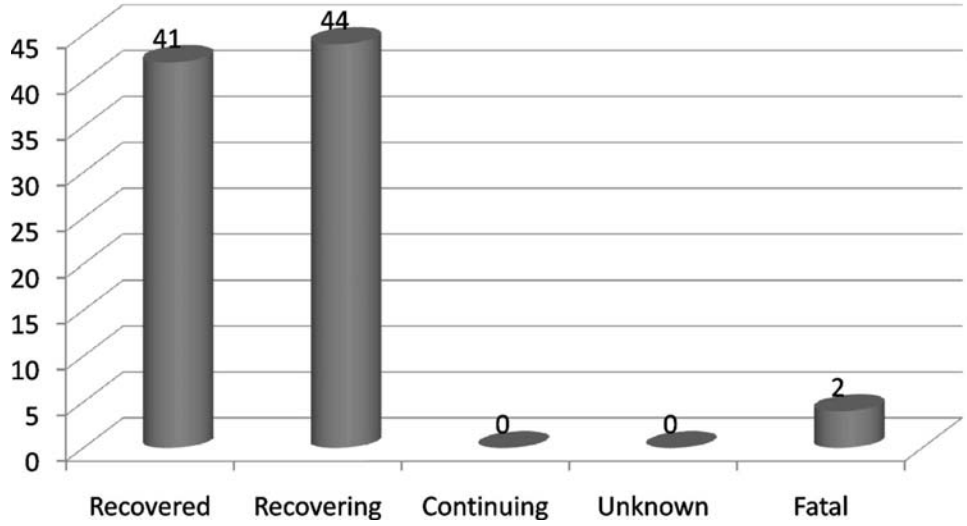
II. Seriousness of reactions reported:

Seriousness of reactions reported	Number of cases (N = 87)
Yes	**57**
No	**30**

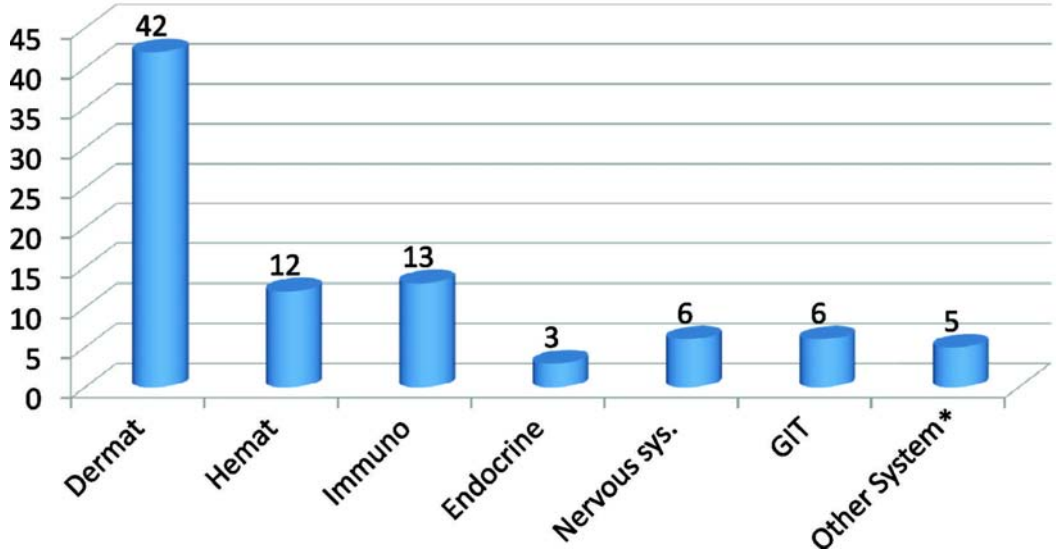
III. Causality assessment (WHO) causality assessment scale : N = 87



IV. Outcome of Reaction (N = 87)

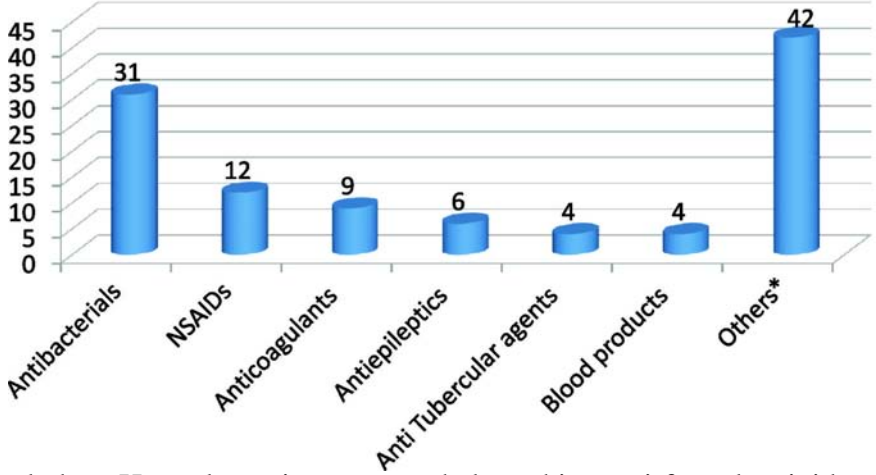


V. System involved in adverse drug reaction (N = 87)



* Other systems includes Hepatibiliary, electrolyte imbalance, Renal, CVS

VI. Class of drugs involved (N = 87)



* Other drugs includes – Hypoglycemic agents, anthelmenthics, anti-fungal, opioid, anti-retroviral, IV fliuds, diuretics, anti-cancer, anti-malarial, anti-depressant, vaccines.

EVALUATION OF A CASE

Case report - Chloroquine induced extrapyramidal adverse drug reaction

Dr. Smita Mali

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

Introduction

Chloroquine (CHQ) is one of the ancient antimalarial drugs and along with hydroxychloroquine has been used as secondary drug to treat a variety of chronic autoimmune diseases. These alkaloids concentrate in lysosomes and have anti-inflammatory properties.[1] Some of the novel uses of CHQ in the treatment of viral infections and cancer are also been discussed.[2] It is a safe drug when given in a therapeutic dose. In acute toxicity chloroquine affects cardiovascular system and the central nervous system (CNS), and may result in convulsion, coma and death.[1] Neuropsychiatric disturbances due to chloroquine have been reported earlier. These are commonly seen in paediatric population.[3,4] This case report narrates extrapyramidal adverse drug reaction seen in a middle-aged man with a single dose of 600 mg of base of chloroquine.

Case Report

A 32 year old man complained of fever with chills and after confirming parasitologically, uncomplicated malaria was treated with chloroquine 600 mg base. He was also given tablet paracetamol 500 mg, tablet pantoprazole 40 mg and tablet ondansetron 8 mg. Four hours after taking the single dose of chloroquine the patient developed involuntary movements of face and neck. The patient's relative also informed about his irrelevant talking. There was no altered consciousness or weakness in the limbs ruling out stroke as a diagnosis for the patient. The patient was known to be a chronic alcoholic without any past history of similar complaints or of any transient ischemic attack. He had neither a family history of dystonia nor had been indulged in use of illicit drugs. A general examination demonstrated twitching on the face and neck stiffness. The patient was talking excessively and irrelevant. Deep tendon reflexes and tones were normal. Other systemic examination was unremarkable.

The patient was diagnosed to have extrapyramidal symptoms (EPS) as an adverse drug reaction to chloroquine. Subsequent doses of chloroquine were withheld and injection promethazine 25 mg was given intramuscularly. Symptoms ameliorated in an hour and the patient felt better. Patient was started on injection artesunate 120 mg intravenous twice a day followed by same dose once a day along with tablet clindamycin 600mg twice a day on subsequent days, for two days to treat malaria.

Causality assessment

Definite temporal relation between CHQ intake and development of EPS was present and the reaction ameliorated with the withdrawal of chloroquine. Other drugs were continued without affecting recovery of the patient and underlying disease was not contributory towards ADR manifestation. With the fulfilment of these criteria causality for the EPS due to chloroquine in the reported case is 'probable' as per WHO-UMC causality categories scale.[5]

This patient also presented with the irrelevant and excessive talking which was considered as febrile delirium or alcohol withdrawal delirium by treating physicians. Though this could be attributed to the chloroquine as a drug induced psychosis, but causality would be possible in this regard. There are few reports published about the chloroquine induced psychosis in literature which would support this ADR possibility.[4,6,7] One study reported the psychosis due to chloroquine in a toxic dose as against this patient who had received only single loading dose of chloroquine.[7]

Discussion

Although therapeutic index of chloroquine is narrow (single fatal dose 30 mg/kg), in therapeutic dose for malaria, it is a safe drug. Doses given as oral therapy may cause gastrointestinal upset, visual disturbances, headache and urticaria. Acute toxicity may show hypotension, arrhythmias eventually cardiac arrest or CNS dysfunction. Cumulative toxicity may lead to irreversible retinopathy and ototoxicity, which is not seen with treatment of malaria.[1]

Dystonic reactions to chloroquine are uncommon though few reports have been published. Singh et al has described case series of children diagnosed to have malaria developing EPS after receiving chloroquine which is summarised in table 1.

Table 1 Extra-pyramidal syndromes following chloroquine therapy[3]

Age (year)	Gender	Dose	Onset of reaction	Recovery
2.5	Female	Therapeutic dose (oral)	1 day	Spontaneous within 48 hrs
12	Female	Therapeutic dose (oral)	4 days	Spontaneous within 8 hrs
6	Female	900 mg (base) oral	Immediate	Spontaneous within 48 hrs
7	Male	100 mg (Phosphate salt) intravenous	2 hours	Gradual over 48 hrs

Busari et al has reported a case of a 54 year old man who developed EPS after a single dose of chloroquine like the reported patient. He recovered from it after receiving diazepam 10 mg orally.[8] In this reported case the recovery drug was promethazine. The relief produced could be attributed to the anti-cholinergic property of the drug.

Risk factors for acute, drug induced dystonia include young age, male sex, use of cocaine, and a history of acute dystonia.[9] Out of these factors male gender and addiction of alcohol though not of cocaine is seen in the present case. Concomitant presence of metronidazole has been noted by Achumba JI et al as a contributory factor towards EPS development post chloroquine therapy.[10] Concomitant drugs given in our patient were paracetamol, pantoprazole and ondansetron which were continued afterwards and no association of these drugs with EPS has been reported.

The pathophysiological mechanism underlying chloroquine associated EPS, though not well understood, has been linked to a reduction in forebrain catecholamine levels and an inhibition of neuronal calcium uptake.[10] This could be correlated with the pro-inflammatory effect of chloroquine which depends upon the cellular context in central nervous system.[11] Extrapyramidal side effects due to neuroleptics

are thought to be because of imbalance between dopamine and acetylcholine in the basal ganglia which in normal conditions is balanced by gamma aminobutyric acid (GABA)-containing striatonigral neurons. GABA-ergic neurons are inhibitory and antagonise excitatory dopaminergic neurons. Also it is noted that in neuroleptic induced dystonia cholinergic limb is overactive and hence an anticholinrgic like biperidin resolves the condition.[12] The reported patient has responded to promethazine, an antihistaminic drug with high anticholinergic activity.

Conclusion

Chloroquine has a place in future with important special actions like antiviral, anticancer which are associated with its lysosomotropic and immunomodulatory mechanisms.[2] The possibility also exists that CHQ may be re-introduced into regular malaria treatment.[13,14] Hence attention should be paid to such an uncommon and reversible but morbid adverse reaction of chloroquine.

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PUBLISHED CASE REPORTS ON CHLOROQUINE INDUCED NEUROLOGICAL ADVERSE DRUG REACTION

Compiled by Dr Jaisen Lokhande

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

Chloroquine induced Acute Dystonic Reactions after a Standard Therapeutic Dose for Uncomplicated Malaria.

Sultan Qaboos Univ Med J. 2013 Aug;13(3):E476-8. Epub 2013 Jun 25.

Busari OA, Fadare J, Agboola S, Gabriel O, Elegbede O, Oladosu Y.

Acute dystonic reactions (ADR) are extrapyramidal effects that usually occur after the initiation of a wide variety of drugs or triggering factors besides neuroleptics. We report the case of a 54-year-old man who was admitted with an approximately 10-hour history of muscle twitching around the eyes, face and neck after he took the first dose of oral chloroquine phosphate (1 g [600 mg base]) prescribed for uncomplicated malaria. He was given intravenous diazepam (10 mg statum) followed by 10 mg of oral diazepam 3 times a day. The symptoms improved within 30 minutes of treatment, and he was discharged 14 hours later after a complete recovery.

Chloroquine-induced acute dystonic reactions in the presence of metronidazole.

Drug Intell Clin Pharm. 1988 Apr;22(4):308-10.

Achumba JI, Ette EI, Thomas WO, Essien EE.

A 30-year-old woman underwent laparotomy and was placed on a seven-day course of metronidazole and ampicillin postoperatively. Chloroquine therapy for malaria was instituted on the sixth day and the patient developed acute dystonic reactions after a single dose. Diphenhydramine therapy before chloroquine administration did not prevent the development of the dystonic reactions. The extrapyramidal symptoms subsided upon diazepam administration and chloroquine withdrawal even though metronidazole therapy was continued. It is suggested that the combination of pyrimethamine and sulfadoxine be used in place of chloroquine for malaria chemotherapy in patients on metronidazole therapy.

Exacerbations of bipolar disorder triggered by chloroquine in systemic lupus erythematosus--a case report.

Lupus. 2014 Feb;23(2):188-93. doi: 10.1177/0961203313513818. Epub 2013 Dec 2.

Bogaczewicz J, Sobów T, Bogaczewicz A, Robak E, Bienkowski P, Sysa-Jedrzejowska A, Wozniacka A.

We report the case of a male patient with SLE who presented with an exacerbation of bipolar disorder triggered by chloroquine. Firstly, when the patient was diagnosed with SLE, he underwent six months of therapy with chloroquine without any psychiatric symptoms. Later, the SLE returned and the patient was prescribed chloroquine again, without any mental illness. When the third exacerbation of SLE occurred, it coincided with a severe depressive episode with psychotic features that became aggravated for the first time after the administration ofchloroquine. The chloroquine was subsequently replaced

with hydroxychloroquine for the next six months without any behavioral problems, following which, the SLE and mood disorder were in remission. Later, a bipolar disorder relapse occurred, manifested by a manic episode, and in the following three months, despite psychiatric treatment, a manic episode with psychotic features developed four days after chloroquine was prescribed for arthritis. It was the second time that the mood disorder was exacerbated by chloroquine. Since that time, chloroquine has been withdrawn. Currently the patient is undergoing treatment with hydroxychloroquine and psychiatric drugs with good response. Our case points out that although chloroquine-induced psychosis is rare, patients presenting with behavioral changes need physicians' attention in order to diagnose early and efficiently treat encountered mood disorders.

Chloroquine-induced myopathy and neuropathy: progressive tetraparesis with areflexia that simulates a polyradiculoneuropathy. Two case reports.

Rev Neurol. 2003 Mar 16-31;36(6):523-6.

Becerra-Cuñat JL1, Coll-Cantí J, Gelpí-Mantius E, Ferrer-Avellí X, Lozano-Sánchez M, Millán-Torné M, Ojanguren I, Ariza A, Olivé A.

Case 1: a 75 year old female with rheumatoid arthritis treated with daily doses of 250 mg of chloroquine for four years. The patient visited because of several months history of predominantly proximal progressive tetraparesis with areflexia. Analytical tests and lumbar puncture were normal. Electromyogram (EMG): proximal myopathic and distal neuropathic patterns. Muscular biopsy: vacuolar myopathy with accumulations of phagolysosomes, lipids, lipofuscin, myelinic curvilinear bodies. Case 2: a 74 year old female with arthropathy treated with daily doses of 250 mg of chloroquine for nine months. The patient presented a progressive proximal paraparesis with generalised areflexia. Analytical tests and lumbar puncture were normal. EMG: mixed sensory motor polyneuropathy, myogenic pattern with high frequency discharges in the iliac psoas and a neurogenic pattern in the distal muscles. Muscular biopsy: vacuolar myopathy suggesting a myopathy due to chloroquine. After stopping treatment with this drug the patients progressed favourably.

CONCLUSION:

Chloroquine can induce a clinical pattern that suggests a polyradiculoneuropathy. It is important to establish a history of having taken this drug. If this is indeed the case, then an electromyographic study of the most proximal muscles should be performed in order to detect a myogenic pattern and the same exploration should be applied to the distal muscles to reveal a neurogenic pattern. The final diagnosis will be established by muscular biopsy.

Seizures following chloroquine treatment of type II lepra reaction: a case report.

Lepr Rev. 1998 Jun;69(2):178-81.

Ebenso BE.

A case of tonic-clonic seizures following chloroquine treatment for leprosy reactions in a Nigerian male is reported. Seizures were controlled with phenytoin sodium capsules. A casual relationship between the seizures and chloroquine is suggested. There have been no previous reports of this adverse reaction in leprosy patients receiving chloroquine for treatment of reactions. The author recommends that chloroquine be used with caution especially in patients with seizures.

REGULATORY UPDATE AND MEDICAL NEWS

Compiled by Dr Swati Patil

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

FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes.

The U.S. Food and Drug Administration (FDA) is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke. NSAIDs are widely used to treat pain and fever from many different long- and short-term medical conditions such as arthritis, menstrual cramps, headaches, colds, and the flu. NSAIDs are available by prescription and OTC. Examples of NSAIDs include ibuprofen, naproxen, diclofenac, and celecoxib

The risk of heart attack and stroke with NSAIDs, either of which can lead to death, was first described in 2005 in the Boxed Warning and Warnings and Precautions sections of the prescription drug labels. Since then, we have reviewed a variety of new safety information on prescription and OTC NSAIDs, including observational studies,1 a large combined analysis of clinical trials,2 and other scientific publications.1 These studies were also discussed at a joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee held on February 10-11, 2014.

Based on our review and the advisory committees' recommendations, the prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes.[Internet]. [Cited 2016March 29]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm

FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes

The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. We are requiring changes to the labels of all opioid drugs to warn about these risks.

Opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity. Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol. Cortisol helps the body respond to stress.

Recommendations and information for patients and health care professionals

Serotonin syndrome:Patients taking an opioid along with a serotonergic medicine should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms generally start within several hours to a few days of taking an opioid with another medicine that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase.

Health care professionals should discontinue opioid treatment and/or use of the other medicine if serotonin syndrome is suspected.

Adrenal insufficiency:

Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. Health care professionals should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.We are requiring a new statement about adrenal insufficiency to be added to the Warnings and Precautions section of all opioid labels.

Decreased sex hormone levels:Patients should inform their health care professionals if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility. Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.

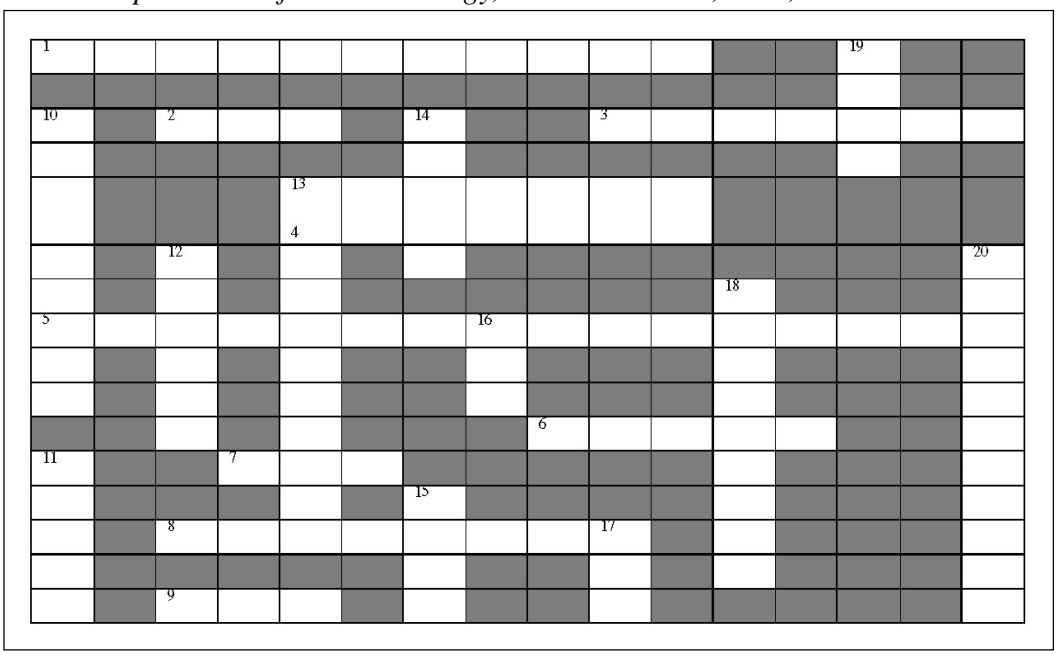
FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes.[Internet]. [Cited 2016March29]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm

CROSSWORD PUZZLE

Dr. Sharmada Nerlekar *, Dr Abhilasha Rashmi**

**Associate Professor, **Assistant Professor,*

Department of Pharmacology, LTMMC & GH, Sion, Mumbai-22



ACROSS

Q1. ---------is a specific drug that has been combined with nicotinic acid to minimize the adverse effect of flushing.(11)

Q2. Side effects of Ginkgo biloba are mild upper -----symptoms and increased risk of bleeding.(3)

Q3. Risk of ----tumour may be increased with clomiphene citrate.(7)

Q4. The advantage of Nalmefene over Naltrexone is that it lacks-----toxicity.(7)

Q5. Abciximab should not be used second time since risk of -------increases.(16)

Q6. Carbamazepine produces dose related -----toxicity.(5)

Q7. Combined-----given to perimenopausal women is found to increase the risk of breast cancer, gall stones and migraine.(3)

Q8. The most common side effect of cilostazol indicated for intermittent claudication in patients with heart failure is---------.(8)

Q9. Prucalopride which improves symptoms in constipation predominant-----is believed to be free of cardiovascular risk.(3)

BELOW

Q10. Gemfibrozil + Statin increases the risk of --------.(8)

Q11. Few cases of sudden loss of vision due to------ among users of PDE-5 inhibitors have been reported.(5)

Q12. Olanzapine may increase the incidence of-----in the elderly.(6)

Q13. Bleeding due to overdose is the most serious complication of heparin therapy and----- is generally the first sign.(10)

Q14. The most important adverse effect due to Gossypol is-------kalaemia.(4)

Q15. -----may be a severe reaction due to LamotrigIne particularly in children.(4)

Q16. The effect of pharmacological doses of glucocorticoids on the-----is mild euphoria sometimes progressing to cause insomnia,hypomania or depression.(3)

Q17. Though the clinical use of chloramphenicol for systemic infections is now highly restricted due to fear of fatal toxicity,it is highly effective in conjunctivitis and external -------infections.(3)

Q18. -----a newer aldosterone antagonist is much less likely to cause hormonal disturbances in comparison to spironolactone.(10)

Q19. Adverse effects like weight gain, increased facial-----and occasional vaginal spotting may be noted with Tibolone.(4)

Q20. On repeated administration, antibodies against the lepirudin-thrombin complex may develop resulting in the possibility of --------.(11)

CROSSWORD ANSWERS

1. LAROPIPRANT 2. GIT 3. OVARIAN 4. HEPATIC 5. THROMBOCYTOPENIA 6. NEURO 7. HRT 8. HEADACHE 9. IBS 10. MYOPATHY 11. NAION (NonArteritic Ischaemic Optic Neuropathy) 12. STROKE 13. HAEMATURIA 14. HYPO 15. RASH 16. CNS 17. EAR 18. EPLERENONE 19. HAIR 20. ANAPHYLAXIS.

ALPHABET 'J-K' PUZZLE

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

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

1 J									
2	K								
3		J							
4			K						
5				J					
6					K				
7						K			
8							K		
9								K	
10									K

1. Atropine, Hyoscine, Hyoscyamine and Tropane alkaloids are the poisonous ingredients present in Datura stramonium commonly known as _____.
2. In children, antipsychotic drug induced acute dystonic reactions and _____ clear within an hour when antiparkinsonian drugs like Benztropine or Diphenhydramine are administered.
3. Allergic reactions are seen with Vitamin B12 _____ due to sensitivity to its preservative Benzyl alcohol.
4. Rapid development of tolerance, possibly by down regulation of Motilin receptors, and undesirable antibiotic effects have limited the use of Erythromycin as a _____ agent.
5. Intake of Cannabis during pregnancy is associated with problems in learning and memory of the fetus due to _____ effect on the developing endocannabinoid system of the brain.
6. The _____ receptor antagonist, Aprepitant, used as an antiemetic drug, is contraindicated in patients on Cisapride or Pimozide, in whom life threatening QT prolongation has been reported.
7. Patients taking Cys LT1 receptor antagonists like _____ may develop eosiniphilia and vasculitis with features similar to Churg Strauss Syndrome.
8. The major complication associated with Recombinant human IL-11, _____, is fluid retention, especially in elderly patients and it often requires diuretic therapy.
9. Praziquantal, initially approved for treatment of _____ infestations, but afterwards used widely to treat other trematodes and cestodes also, is contraindicated in ocular cysticercosis to avoid irreversible damage of eye.
10. One of the major disadvantages of this modality of local anaesthesia is premature release of tourniquet producing toxic blood levels of local anaesthetic.

ALPHABET 'J-K' PUZZLE:

1. Jimson Weed 2. Akathesias 3. Injections 4. Prokinetic 5. Marijuana's 6. Neurokinin 7. Pranlukast 8. Oprelvekin 9. Liver Fluke 10. Bier's Block

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

Please feel free to contact us for the same.

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

Address for correspondence :

Dr. Sudhir Pawar

Department of Pharmacology,

College Building, LTMMC & LTMGH,

Sion, Mumbai-400022.

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

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DDF, Department of Pharmacology
Lokmanya Tilak Municipal General Hospital
and Lokmanya Tilak Municipal Medical College, Sion Mumbai