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ADVERSE DRUG REACTIONS ASSOCIATED WITH ANTI-HYPERTENSIVE DRUGS AND ITS MANAGEMENT

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ABSTRACT: Adverse Drug Reactions associated with drugs are common and impose a serious health related problem, which can limit the treatment options, compliance and even leads to discontinuation of therapy. Hypertension is a chronic disease condition which is considered to be one of the major cardiovascular risk factor. For the treatment of hypertension a wide range of anti-hypertensive agents are available as single or combination therapy to achieve a target blood pressure in individual patient, whereas the combination therapy increases the risk of developing Adverse Drug Reaction. Hypertensive patients often have concomitant disease condition such as hyperlipidemia, impaired glucose metabolism and renal impairment, leading to an increased rate of Cardio Vascular morbidity and mortality. Therefore, a comprehensive management of both hypertension as well as concomitant Cardio Vascular Disease risk factors is critical when treating hypertensive patients. Beta-blockers provoked psoriasis, calcium channel blockers induced gingival hyperplasia, peripheral oedema, Angiotensin Converting Enzyme inhibitors produced ankle oedema and thiazide diuretics produced hyponatremia, hyperglycemia are some of the rare and serious Adverse Drug Reaction occurred in patients treated with these drugs. More often hypertension is asymptomatic and requires a lifelong treatment with antihypertensive agents, predisposing to Adverse Drug Events. Monitoring of adverse drug reactions by healthcare professionals is necessary in the patients taking antihypertensive drugs, in order to improve the treatment outcomes and to reduce the morbidity and mortality related to adverse drug reactions.

INTRODUCTION: Hypertension is a chronic disease which is considered to be one of the major public health problem and a significant cardiovascular risk factor, where the systolic blood pressure is more than 140 mmHg and diastolic blood pressure is more than 90 mmHg [1, 2].

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The Global Burden of Disease Study found that hypertension was the third most preventable cause of death worldwide and the second most common condition in Westernized countries [3]. In the year 2000, it was also found that the world was estimated to have 1 billion people with hypertension and predicted to increase to 1.56 billion by 2025 [4]. The prevalence of hypertension increases with age, and is readily treatable risk factor for stroke, Ischemic Heart Disease, renal insufficiency and dementia [5]. Although public awareness about diagnosis of hypertension has increased, improvement in cardiovascular disease

rates have not been followed parallel [6]. Despite many guidelines, which emphasize the importance of achieving optimal blood pressure control in high risk patients such as those with diabetes, only about 29% of hypertensive patients have blood pressure under control to a target of 140/90 mmHg [6-10]. For the treatment of hypertension, a broad range of antihypertensive medications are currently available [11].

Outcome benefits have been demonstrated for Thiazide diuretics, Beta Blockers, Long acting Calcium Channel Antagonists, Angiotensin Converting Enzyme inhibitors and Angiotensin II Receptor Blockers [12-14]. Adverse Drug Reactions are considered among one of the leading causes of mortality. It was estimated that 6% of hospital admissions are estimated to be due to ADRs and about 6-15% of hospitalized patients experience serious ADR [15]. Antihypertensive medications are frequently associated with Adverse Drug Reactions which may limit treatment options and reduce patient compliance, which may hinder Blood Pressure control. It was believed that different discontinuation rates for various classes of antihypertensive medications are probably related to their different rates of adverse symptoms [16-19]. Achieving Blood Pressure control usually requires two or more antihypertensive medications, however; increase in the number of antihypertensive medications in a regimen may lead to even more adverse effects [20].

In view of adverse effects related to antihypertensive drugs, in this article we are highlighting some of the potential adverse drug reactions caused by anti hypertensive medications.

Beta Blockers Provoked Adverse Effects:

Beta blockers are very commonly used class of antihypertensive drugs, used to treat both cardiovascular and non-cardiovascular diseases, including hypertension, Ischemic Heart Disease, arrhythmias, heart failure, hyperthyroidism, glaucoma and anxiety disorders [21]. If they are used for the management of vasospastic angina pectoris, they should be used concomitantly with Calcium Channel Blockers. There are 3 main types of Beta blockers: the older beta nonspecific agents (e.g. Propanolol); the β1 specific agents (e.g. Atenolol, Metoprolol and Bisoprolol) and beta blockers with additional properties (e.g. Carvedilol and Nebivolol). Beta blockers produce their action by blocking either β1 receptors (cardio selective) or β2 receptors (non -cardio selective). The newer Beta blockers tend to produce better central aortic blood pressure control than other Beta blockers, particularly Carvedilol with improved tolerability and outcome than the other agents [22].

Beta blockers exert adverse effects on glucose and lipid metabolism when used alone or in combination with diuretics. Therefore, Beta blockers are not considered as the first line treatment in elderly patients or when hypertension is complicated by other diseases such as diabetes mellitus, abnormal glucose tolerance [23]. Mainly adverse effects of these drugs can be divided into two broad categories: a) those that result from known pharmacological consequences e.g. bronchospasm, heart failure, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication and Raynaud's phenomenon. b) Other reactions that do not appear to result from β adrenergic receptor blockade e.g. unusual occulo-muco cutaneous reactions and the possibility of oncogenesis [24]. A study suggested that longstanding hypertension and long term use of beta blockers may be a risk factor developing psoriasis [25].

Beta Blockers Provoked Psoriasis:

Psoriasis is a common autoimmune inflammatory skin disease that affects about 2-3% of the US population and over 125 million patient's world-wide [26-28]. It is characterized by T-cell mediated hyper proliferation of keratinocytes and inflammatory processes based on complex genetic background [26, 27]. Various potential risk factors includes smoking, alcohol consumption, trauma, infections, endocrine factors, stressful life events, as well as exposure to drugs such as Beta blockers, Angiotensin Converting Enzyme Inhibitors(ACEI), antimalarials, Non Steroidal Anti-Inflammatory Drugs (NSAID), lithium, Interferons, as well of the acute withdrawal of systemic or potent topical corticosteroids [29-33]. Various case control and cross over studies shows that Beta Blockers as a major aggravating factor in patients who were hospitalized with psoriasis vulgaris [34, 35, 36-37].

Mechanism:

The mechanism for the exacerbation of psoriasis with β blocker use is thought to be related to a blockade in the activation of the messenger system of cyclic adenosine 3' 5'-cyclic monophosphate, results in decreased intracellular concentrations of calcium which in turn causes an accelerated proliferation of keratinocytes or polymorph nuclear leukocytes, both of which may play a role in inducing psoriasis [37-40].

Management:

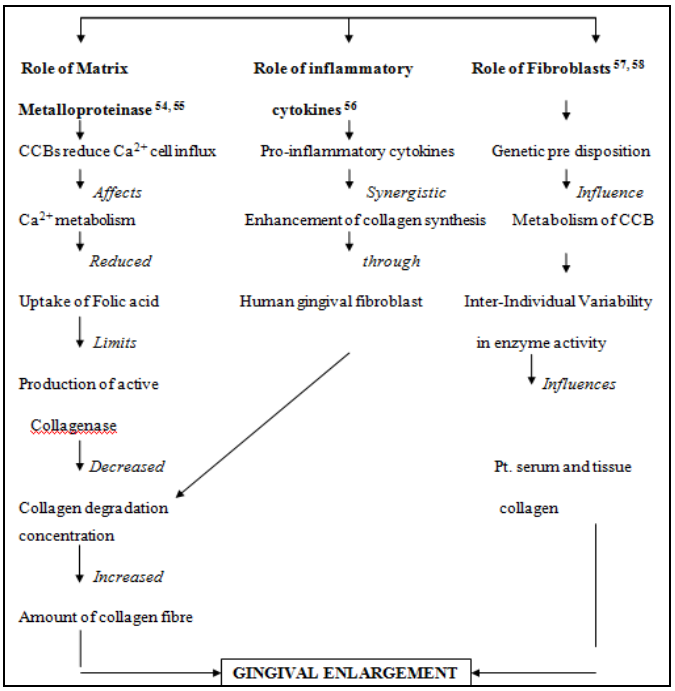
Beta blockers are widely used and have a good safety record [41]. In case of β blockers provoked psoriasis switching from one Beta blocker to the other results in reintroduction psoriasis form skin lesions. So, alternative class of anti hypertensive has to be chosen [42]. According to new anti-hypertension guidelines, thiazide diuretics or calcium channel blocker can be used as first line treatment for hypertension [43]. For the management of drug provoked psoriasis, the use of conventional therapeutic agents like topical and systemic drugs can be recommended. If psoriasis is present only in localized areas, emollients can be helpful [44].

Calcium Channel Blockers Induced Adverse Effects:

Calcium channel blockers (CCBs) are heterogeneous class of drugs which are the most commonly used antihypertensive drug [45, 46]. CCBs produce their therapeutic effects by preventing calcium ions influx through the cell membranes by binding to L-type calcium channels, which are located on vascular smooth muscles, cardiac myocytes and cardiac nodal tissues. Through this blockage, CCBs cause relaxation of vascular smooth muscles and vasodilatation, this leads to reduction in heart rate and a decrease in conduction velocity with in the heart. CCBs are well tolerated, despite well known side effects mostly at the initiation of treatment, such as flush, headache or palpitation with DHPs and constipation with Verapamil, and gingival enlargement and ankle oedema with Nifedipine [47, 48].

Gingival Enlargement:

Gingival enlargement is a proliferative fibrous lesion of the gingival tissue that causes esthetic and functional problems [49]. Currently, more than 20 prescription medications are associated with gingival enlargement which can be broadly classified into three categories: anticonvulsants, Calcium Channel Blockers (CCB) and Immunosuppressant's [50]. Drug induced gingival hyperplasia can be a serious concern for both patients and clinicians [51]. The prevalence of gingival overgrowth induced by CCBs is uncertain. Although several studies examining this question, results are conflicting from previous studies ranges from 20% to 83%, of which particularly Diltiazem and Amlodipine gives an estimate of 74% and 3.3% respectively [52]. Overgrowth occurs 3.3 times more commonly in males than females [53].



Management:

The most effective treatment of these lesions is cessation of the offending medication and substitution with another class of antihypertensive like beta blocker, diuretics or ACEI, since drug induced gingival overgrowth has not been reported with any of these drugs. Another option is substitution with other CCB medications that has a lower risk of inducing gingival enlargement (e.g. Verapamil, Isradipine). If regimen change is not an option, the lesions should be managed with or without surgical intervention [59].

Peripheral Oedema:

Oedema is the accumulation of fluid in the intra-cellular tissue that results from abnormal expansion

in interstitial fluid volume, leads to decreased plasma oncotic pressure and increased capillary permeability or lymphatic obstruction [60]. The frequency of peripheral oedema with CCB therapy are quiet varied in the literature, because of the dose dependent nature and can ranged from 5% to as high as 70%. Ankle oedema occurs more frequently in Dihydropyridine (DHP) group of CCBs, although some agents like Lacidipine and Lecanidipine may cause it less frequently compared to Nifedipine and Amlodipine. This is more commonly seen in women and relates to upright posture, age, and the choice and dose of CCB [61, 62]. Diltiazem, a non-DHP agent, seems to be associated with lowest incidence of ankle oedema [63].

Mechanism of CCB Induced Oedema:

CCB-induced oedema is caused primarily by the increased capillary hydrostatic pressure that results from greater dilation of pre-capillary than post capillary vessels. This effect is mediated by the greater sensitivity of resistance vessels than the capacitance vessels to CCB-induced reductions in myogenic vascular reactivity [61].

Management:

The usual approach to patients with CCB-induced oedema involves cessation of therapy and substitution with an alternative class of anti-hypertensive like thiazide diuretics or ACEI or ARB's. Some studies also shown that oedema will diminish upon conversion from dihydropyridine CCB to non-dihydropyridine CCB such as Verapamil or Diltiazem. CCB related peripheral oedema may not be physiologically corrected and it is advised to routinely prescribe diuretic to patients for the sole purpose of correcting the oedema state [61].

Angiotensin-Converting Enzyme Inhibitors Induced Angio-Oedema

ACE inhibitors have consistently shown beneficial effects on mortality, morbidity and quality of life in all stages of symptomatic heart failure resulting from impaired left ventricular systolic function [64]. ACE inhibitors act by inhibiting the production of angiotensin-II, a potent vasoconstrictor and growth promoter, and increased concentrations of vasodilator bradykinin by inhibiting its degradation. Usually ACE inhibitors are started at a low dose and gradually titrated to highest tolerated maintenance dose. The adverse effects of ACE inhibitors include dry cough, dizziness and deterioration in renal function, hypotension, and angio-oedema [65]. The use of ACE inhibitors increased significantly over recent years and more adverse reactions have been reported including severe angio-oedema of the upper airways and even death due to asphyxiation [66].

Angio-oedema is a sudden localized and asymmetric swelling of skin or mucous membrane caused by transient increase in endothelial permeability causing plasma extravasation. Angio-oedema due to ACE inhibitors is usually characterized by oedematous area of skin, slightly red and not accompanied by urticaria. In most cases angio-oedema is located in oro-facial and/or peri-oral area and/or upper airways [67]. ACE inhibitors induced angio-oedema can affect between 0.1% to 0.5% patients taking the drug [68].

Mechanism of Acei Induced Angio-Oedem:

The mechanism remains unclear. One hypothesis is that bradykinin, which is normally degraded by Kinase-II/ACE. Patients treated with ACEI, the degradation of bradykinin is inhibited and thus accumulation of bradykinin in tissues occurs. In this regard, plasma bradykinin has been shown to increase up to 12-fold during angio-oedema attack [66, 67].

Management:

- Immediately discontinue ACE inhibitor/ARB.
- Supportive measures include airway management, fluid replacement therapy and measurement of vital signs should be initiated promptly.
- In severe cases when upper airways or GI tract are involved, bradykinin receptor antagonist I catibint has been used as an effective treatment option.
- Epinephrine 1:1000 (0.3-0.5ml), Corticosteroids [66, 67].

Thiazide Diuretics Induced Hyponatremia:
Diuretics are currently recommended by the seventh report of the joint national commission (JNC) on prevention, detection, evaluation and treatment of high blood pressure report as first line therapy for the treatment of hypertension among all age groups [69, 70]. Diuretics can be divided into three distinct sub-classes, and each of this has an important role to play in the management of most hypertensive patients [71]. Type II diabetes, impaired serum cholesterol level and Hyperuricemia (Gout) may also occur during the course of thiazide diuretic treatment. In few patients hypokalemia may develop on low dose thiazide diuretics, a diagnosis of primary aldosteronism may be considered which can be managed by the addition of potassium sparing drugs (spirinolactone, eplerenone), may achieve effective control of hypertension and can correct hypokalemia without the need for extensive diagnostic assessment of adrenalictomy [71].

Mechanism:
Thiazide diuretics block sodium chloride co-transport in distal convoluted tubule. As a result sodium excretion is increased, while excretion of free water is reduced, results in hyponatraemia [72].

Management:

- Discontinue thiazide diuretics.
- Regular diet (usually supplemented with potassium)
- Restricting water intake
- Administration of Furosemide and either isotonic saline or if the hyponatremia is severe or symptomatic [73].

Thiazide Diuretic Induced Hyperglycemia:
Diabetes is a major cardiovascular risk factor, Hyperglycemia is more common and severe adverse effect seen with thiazide diuretics than other classes of antihypertensive agents [74].

Mechanism of Thiazide Induced Hyperglycemia
Low serum potassium has been considered an important mechanism in the pathogenesis of diuretic induced hyperglycemia. It is important to understand that the levels of serum potassium does not necessarily co-relate with intracellular potassium stores. Therefore serum Potassium may be normal but intracellular potassium deficit still persist and hence attenuates endogenous insulin release and cause hypoglycemia [75- 77].

Management:
Patients with Diuretic-Induced Hyperglycemia are often labeled as Type-II Diabetes and prescribed with oral anti-diabetic agents. Since Hypertension is more prevalent than diabetes, and because of the use of thiazide diuretics to treat hypertension, thiazides induced hyperglycemia is very common. Therefore, according to some authors consider the usage of thiazide diuretics to treat hypertension is safe and effective. The complication of elevated glucose level is reversible and thus, inconsequential [78].

CONCLUSION: There is a need for safe, effective and simple therapies to treat hypertension in order to achieve recommended BP targets rapidly and rigorously, but with good tolerability and sustained patient adherence. The use of combination therapy as first- line treatment will help more patients promptly to achieve BP goals and fixed dose combinations provide a means for simple, but flexible dosing. As the present review is related to ADR profile of anti-hypertensive agents, it may be helpful in selection of appropriate medicines for hypertensive patients, enhancing patient adherence with the therapy by selecting medicines of lesser ADR profile, reducing unnecessary economic burden to the patients due to unwanted effects of the therapy. It is important to remember that most ADR's would subside once the offending agent is discontinued or dosage reduced. Therefore monitoring of adverse effects due to antihypertensive medications, particularly of serious nature is mandatory. Hence, physicians, clinical pharmacists and other health care professionals should report life threatening complications, hospitalizations (initial or prolonged) associated with anti-hypertensive drugs.

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