Review on Toxicity of Antihypertensive Drugs

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Abstract

Adverse drug reactions are common and pose a serious health problem, limiting treatment options, causing compliance issues, and even leading to therapy discontinuation. Hypertension is a chronic disease that is regarded as a major risk factor for cardiovascular disease. To achieve a target blood pressure in an individual patient, a wide range of anti-hypertensive agents are available as single or combination therapy, whereas combination therapy increases the risk of developing Adverse Drug Reaction. Hypertensive patients frequently have coexisting disease conditions such as hyperlipidemia, impaired glucose metabolism, and renal impairment, which increase the risk of Cardio Vascular morbidity and mortality. When treating hypertensive patients, comprehensive management of both hypertension and concomitant Cardio Vascular Disease risk factors is essential. Some of the rare and serious Adverse Drug Reactions that occurred in patients treated with these drugs included beta-blockers causing psoriasis, calcium channel blockers causing gingival hyperplasia, peripheral oedema, Angiotensin Converting Enzyme inhibitors causing ankle oedema, and thiazide diuretics causing hyponatremia and hyperglycemia. Asymptomatic hypertension is more common and necessitates lifelong treatment with antihypertensive agents, predisposing to Adverse Drug Events. In order to improve treatment outcomes and reduce morbidity and mortality associated with adverse drug reactions, healthcare professionals must monitor adverse drug reactions in patients taking antihypertensive drugs.

Keywords: Adverse drug reactions, Hypertension, hyperlipidemia, glucose metabolism

Introduction

Hypertension is a chronic disease that is regarded as a major public health issue and a significant cardiovascular risk factor when the systolic blood pressure is greater than 140 mmHg and the diastolic blood pressure is greater than 90 mmHg1-2. According to the Global Burden of Disease Study, hypertension is the third most preventable cause of death in the world and the second most common condition in Westernized countries3. In the year 2000, it was also discovered that the world had 1 billion people with hypertension, with the number expected to rise to 1.56 billion by 2025. Hypertension becomes more common with age and is a treatable risk factor for stroke, Ischemic Heart Disease, renal insufficiency, and dementia4,5. Although public awareness of hypertension diagnosis has grown, improvements in cardiovascular disease rates have not kept pace6. Despite numerous guidelines emphasising the importance of achieving optimal blood pressure control in high-risk patients such as diabetics, only about 29% of hypertensive patients have blood pressure under control to a target of 140/90 mmHg6-10. A wide range of antihypertensive medications are currently available for the treatment of hypertension11. Thiazide diuretics, Beta Blockers, Long Acting Calcium Channel Antagonists, Angiotensin Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers have all been shown to improve outcomes12-14. Adverse drug reactions are regarded as one of the leading causes of death. ADRs are estimated to account for 6% of hospital admissions, with 6-15% of hospitalised patients experiencing serious ADRs15. Antihypertensive medications are frequently associated with Adverse Drug Reactions, which can limit treatment options and decrease patient compliance, thereby impairing Blood Pressure control. Different discontinuation rates for different classes of antihypertensive medications were thought to be related to their different rates of adverse symptoms16-19. Typically, two or more antihypertensive medications are required to achieve blood pressure control; however, increasing the number of antihypertensive medications in a regimen may result in even more adverse effects20. In light of the potential side effects of antihypertensive drugs, we have highlighted some of the potential adverse drug reactions caused by antihypertensive medications in this article.

Beta blockers triggered negative effects

Beta blockers are a type of antihypertensive agent that is widely used to treat both cardiovascular and non-cardiovascular diseases such as hypertension, Ischemic Heart Disease, arrhythmias, heart failure, hyperthyroidism, glaucoma, and anxiety disorders21. They should be used in conjunction with calcium channel blockers if used to treat vasospastic angina pectoris. Beta blockers are classified into three types: older beta nonspecific agents (e.g., propanolol); 1 specific agents (e.g., atenolol, metoprolol, and bisoprolol); and beta blockers with additional properties (e.g., Carvedilol and Nebivolol). Beta blockers work by blocking either 1 receptor (cardio selective) or 2 receptors (non-cardio selective). The newer Beta blockers produce better central aortic blood pressure control than older Beta blockers, particularly Carvedilol, which has better tolerability and outcome than...
older agents. When used alone or in combination with diuretics, beta blockers have a negative impact on glucose and lipid metabolism. As a result, beta blockers are not recommended as first-line therapy in the elderly or when hypertension is complicated by other diseases such as diabetes mellitus or abnormal glucose tolerance. The most common adverse effects of these drugs fall into two categories: a) those caused by known pharmacological consequences, such as bronchospasm, heart failure, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud’s phenomenon; and b) those caused by unknown pharmacological consequences. Other reactions that do not seem to be caused by adrenergic receptor blockade, such as unusual occulo-muco cutaneous reactions and the possibility of oncogenesis. According to one study, long-term hypertension and beta blocker use may be risk factors developing psoriasis.

**Beta blocker induced psoriasis**

Psoriasis is a common autoimmune inflammatory skin disease that affects approximately 2-3% of the US population and over 125 million patients globally. It is distinguished by T-cell-mediated keratinocyte hyperproliferation and inflammatory processes that are based on a complex genetic background. Smoking, alcohol consumption, trauma, infections, endocrine factors, stressful life events, and exposure to drugs such as Beta blockers, Angiotensin Converting Enzyme Inhibitors (ACEI), antimalarials, Non Steroidal Anti-Inflammatory Drugs (NSAID), lithium, Interferons, and acute withdrawal of systemic or potent topical corticosteroids are all potential risk factors. Several case control and cross-over studies show that Beta Blockers are a major aggravating factor in patients with psoriasis vulgaris who are hospitalized.

**Mechanism**

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

**Management**

Beta blockers are widely used and have a good track record of safety. In the case of blockers that have caused psoriasis, switching from one to the other results in the reintroduction of psoriasis-like skin lesions. As a result, an alternative class of antihypertensive medication must be chosen. Thiazide diuretics or calcium channel blockers can be used as first-line treatment for hypertension, according to new antihypertension guidelines. Traditional therapeutic agents such as topical and systemic drugs can be recommended for the treatment of drug-induced psoriasis. Emollients can be beneficial if psoriasis is only present in a few areas.

**Calcium channel blockers induced adverse effects**

Calcium channel blockers (CCBs) are a diverse class of drugs that are the most commonly used antihypertensive medications. CCBs exert their therapeutic effects by binding to L-type calcium channels found on vascular smooth muscles, cardiac myocytes, and cardiac nodal tissues, which prevent calcium ions from passing through cell membranes. CCBs cause relaxation of vascular smooth muscles and vasodilation through this blockage, resulting in a reduction in heart rate and a decrease in conduction velocity within the heart. Despite well-known side effects, such as flushing, headache, or palpitation with DHPs, constipation with Verapamil, and gingival enlargement and ankle oedema with Nifedipine. CCBs are well tolerated.

**Gingival Enlargement**

Gingival enlargement is a proliferative fibrous gingival lesion that causes aesthetic and functional issues. More than 20 prescription medications are currently linked to gingival enlargement, and they can be broadly classified into three groups: anticonvulsants, calcium channel blockers (CCB), and immunosuppressants. Both patients and clinicians may be concerned about drug-induced gingival hyperplasia. The prevalence of CCB-induced gingival overgrowth is unknown. Although several studies have been conducted to investigate this question, the results from previous studies range from 20% to 83%, with Diltiazem and Amlodipine providing estimates of 74% and 3.3%, respectively. Males are 3.3 times more likely than females to experience overgrowth.

**Management**

Because drug-induced gingival overgrowth has not been reported with any of these drugs, the most effective treatment for these lesions is discontinuation of the offending medication and substituted with another class of antihypertensive such as beta blockers, diuretics, or ACEI. Another option is to replace the CCB medication with one that has a lower risk of causing gingival enlargement (e.g. Verapamil, Lisradipine). If changing the regimen is not an option, the lesions should be managed surgically or nonsurgically.

**Peripheral oedema**

Oedema is the accumulation of fluid in intracellular tissue caused by an abnormal increase in interstitial fluid volume, which results in decreased plasma oncotic pressure, increased capillary permeability, or lymphatic obstruction. Because of its dose-dependent nature, the frequency of peripheral oedema with CCB therapy varies widely in the literature, ranging from 5% to as high as 70%. Ankle oedema is more common in the Dihydropyridine (DHP) group of CCBs, though Lecandipine and Lecandipine may cause it less frequently than Nifedipine and Amlodipine. This is more common in women and is associated with upright posture, age, and the selection and dosage of CCB. Diltiazem, onan-DHPagent seems to be associated with lowest incidence of ankle oedema.

**Mechanism of CCB induced oedema**

The increased capillary hydrostatic pressure caused by greater dilation of pre-capillary vessels than post-capillary vessels causes CCB-induced oedema. This effect is mediated by resistance vessels being more sensitive to CCB-induced reductions in myogenic vascular reactivity than capacitance vessels.

**Management**

The standard treatment for CCB-induced oedema is to discontinue therapy and replace it with an alternative class of antihypertensive, such as thiazide diuretics, ACEIs, or ARBs. Some studies have also shown that switching from dihydropryridine CCB to non-dihydropyridine CCBs like Verapamil or Diltiazem reduces oedema. CCB-related peripheral oedema may not be physiologically corrected, and it is recommended that diuretics be prescribed to patients solely for the purpose of correcting the oedema state.

**Angiotensin-converting enzyme inhibitors induced angio-oedema**

In all stages of symptomatic heart failure caused by impaired left ventricular systolic function, ACE inhibitors have...
consistently shown beneficial effects on mortality, morbidity, and quality of life ACE inhibitors work by preventing the production of angiotensin-II, a potent vasoconstrictor and growth promoter, as well as increasing the concentrations of the vasodilator bradykinin by preventing its degradation. ACE inhibitors are typically started at a low dose and gradually increased to the highest tolerated maintenance dose. Dry cough, dizziness, deterioration in renal function, hypotension, and angio-oedema are all side effects of ACE inhibitors. The use of ACE inhibitors has increased significantly in recent years, and more adverse reactions, including severe angio-oedema of the upper airways and even death due to asphyxiation, have been reported. Angio-oedema is a sudden, asymmetric swelling of the skin or mucous membrane caused by a transient increase in endothelial permeability, resulting in plasma extravasation. Angio-oedema caused by ACE inhibitors is typically characterised by oedematous skin that is slightly red and is not accompanied by urticaria. Angio-oedema is most commonly found in the oro-facial and/or peri-oral areas, as well as the upper airways. Angio-oedema caused by ACE inhibitors can affect 0.1% to 0.5% of patients taking the drug.

Mechanism of ACE induced angio-oedem

The mechanism is still unknown. One theory is that bradykinin, which is normally degraded by Kinase-II/ACE, is involved. In patients receiving ACEI, bradykinin degradation is inhibited, resulting in bradykinin accumulation in tissues. Plasma bradykinin levels have been shown to rise up to 12-fold during angioedema attacks.

Management

1. Discontinue ACE inhibitor/ARB immediately. (2) Airway management, fluid replacement therapy, and vital sign monitoring should all be initiated as soon as possible. (3) Bradykinin receptor antagonist I catibint has been used as an effective treatment option in severe cases involving the upper airways or GI tract. (4) Corticosteroids, Epinephrine 1:1000 (0.3-0.5 ml).

Thiazide diuretics induced hyponatremia

Diuretics are currently recommended as first-line therapy for the treatment of hypertension in all age groups by the seventh report of the Joint National Commission (JNC) on prevention, detection, evaluation, and treatment of high blood pressure. Diuretics are classified into three types, each of which plays an important role in the treatment of most hypertensive patients. During the course of thiazide diuretic treatment, Type II diabetes, low serum cholesterol levels, and hyperuricemia (Gout) may occur. In a few patients, hypokalemia may develop on low-dose thiazide diuretics, prompting a diagnosis of primary aldosteronism, which can be managed with the addition of potassium sparing drugs (spironolactone, eplerenone), achieving effective hypertension control and correcting hypokalemia without the need for extensive diagnostic assessment of adenolcitomy.

Mechanism

Thiazide diuretics interfere with sodium chloride cotransport in the distal convoluted tubule. As a result, sodium excretion increases while free water excretion decreases, resulting in hyponatraemia.

Management

1. Stop using thiazide diuretics. (2) Regular diet (usually supplemented with potassium). (3) Restricting water intake (4) If the hyponatraemia is severe or symptomatic, Furosemide and isotonic saline should be administered.

Thiazide Diuretic Induced Hyperglycemia

Diabetes is a major risk factor for cardiovascular disease. Hyperglycemia is a more common and severe adverse effect of thiazide diuretics than other classes of antihypertensive agents.

Mechanism of thiazide induced hyperglycemia

Low serum potassium has been implicated in the pathogenesis of diuretic-induced hyperglycemia. It is critical to understand that serum potassium levels do not always correlate with intracellular potassium stores. As a result, while serum potassium levels may be normal, intracellular potassium deficiency persists, reducing endogenous insulin release and causing hypoglycemia.

Management

Patients with Diuretic-Induced Hyperglycemia are frequently diagnosed with Type II Diabetes and prescribed oral anti-diabetic medications. Because hypertension is more common than diabetes, and because thiazide diuretics are used to treat hypertension, thiazide-induced hyperglycemia is very common. As a result, some authors believe that using thiazide diuretics to treat hypertension is both safe and effective. The complication of high glucose levels is reversible and thus insignificant.

Conclusion

To achieve recommended BP targets quickly and rigorously, but with good tolerability and sustained patient adherence, there is a need for safe, effective, and simple therapies to treat hypertension. The use of combination therapy as first-line treatment will help more patients achieve BP goals more quickly, and fixed dose combinations allow for simple but flexible dosing. Because the current review is concerned with the ADR profile of antihypertensive agents, it may be useful in selecting appropriate medicines for hypertensive patients, improving patient adherence with therapy by selecting medicines with lower ADR profiles, and reducing unnecessary economic burden to patients due to unwanted effects of the therapy. It is important to remember that most ADRs will go away once the offending agent is stopped or the dosage is reduced. As a result, monitoring of adverse effects from antihypertensive medications, particularly those of a serious nature, is required. As a result, physicians, clinical pharmacists, and other health care professionals should report any life-threatening complications or hospitalizations (initial or extended) associated with antihypertensive drugs.

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