



## Adverse Drug Reactions Associated with Anti-Hypertensive Drugs and its Management

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### ABSTRACT

Some type of drugs can cause serious health related problems as adverse drug reactions are associated with them. This may limit the treatment options, patient compliance and may also result in the discontinuation of the treatment. Hypertension is a chronic disease which is categorized under one of the major cardiovascular risk factors. A wide variety of antihypertensive agents are available in the market for the treatment of hypertension, which can be used as single or combination therapy and it increases the risk of development of adverse drug reactions. Hypertensive patients affected by concomitant disease condition such as hyperlipidaemia, impaired glucose metabolism and renal impairment may be prone to an increased level of cardiovascular morbidity and mortality. So a comprehensive management of hypertension as well as concomitant cardiovascular disease risk factor is critical in treating hypertensive patients. Beta blockers induce psoriasis and calcium channel blockers causes gingival hyperplasia as well as peripheral oedema. Angiotensin converting enzyme inhibitor produces ankle oedema and thiazide diuretics causes hypernatremia and also hyperglycaemia. These are some of the rare and serious adverse drug reactions associated with patients who are being treated with these drugs. Moreover hypertension is a symptomatic condition and requires lifelong treatment with antihypertensive agents, predisposing to adverse drug events. So monitoring the adverse drug reactions by healthcare professionals is important for the patients consuming antihypertensive drugs in order to improve the treatment outcomes and to reduce the morbidity and mortality related to adverse drug reactions.

**Keywords:** Hypertension, Adverse drug reaction, Beta blockers, Angiotensin converting enzyme inhibitors, Calcium channel blockers.

### INTRODUCTION

Adverse reactions and drug-drug interactions are common occurrences with many drug classes and in particular with antihypertensive medications. These occurrences take many forms including electrolyte changes, alteration in level of renal functions, nonspecific or idiosyncratic side effects as well as the side effects specifically related to systemic drug levels. There is a possible chance of interaction between the antihypertensive agents and the CYP450 enzyme system and a keen study of this system is needed to avoid what can cause life threatening drug-drug interactions with antihypertensive medications.

Hypertension considered as a chronic disease is one of the major public health problem and a significant cardiovascular risk factor, where the systolic blood pressure is more than 140mmHg and the diastolic blood pressure is more than 90mmHg<sup>1-2</sup>. The prevalence of hypertension increases with age and if untreated there will be a huge risk factor for stroke, ischemic heart disease, renal insufficiency and dementia<sup>3</sup>. Despite many guidelines being available which point out the importance of achieving optimal blood pressure control in high risk patients suffering from diabetes, only about 29% of hypertensive patients have blood pressure under control to a target of 140/90mmHg<sup>4-8</sup>. For the treatment of hypertension a broad range of antihypertensive drugs are available<sup>9</sup>.

The benefits have been demonstrated for thiazide diuretics, beta blockers, long acting calcium channel antagonists, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers<sup>10-12</sup>. Adverse drug reactions are considered to be one of the major reasons for the mortality. 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 more adverse effects<sup>13</sup>.

#### Beta blockers influence in producing Adverse Effects

Beta blockers can be used as antihypertensive drugs to treat both cardiovascular and non-cardiovascular diseases, including hypertension, ischemic heart disease, arrhythmias and heart failure, hyperthyroidism, glaucoma and anxiety disorders<sup>14</sup>. 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.

- (1) The older beta nonspecific agents: e. g. Propranolol
- (2) The beta 1 specific agents: e. g. Atenolol
- (3) Beta blockers with additional properties: e. g. Carvedilol

Beta blockers produce their action by blocking either  $\beta_1$ -receptor or  $\beta_2$ -receptors.



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 etc. Adverse effects produced by these two drugs can be categorised into two.

(1) These that result from known pharmacological consequences.

e. g. Heart failure, bradycardia, heart block, etc.

(2) Other reactions that do not appear to result from  $\beta$ -adrenergic receptor blockage.

e.g. Unusual ocular-mucocutaneous reactions and the possibility of oncogenesis<sup>15</sup>.

The studies proved that long standing hypertension and long term use of beta blockers may be a risk factor in developing psoriasis<sup>16</sup>.

### Beta Blockers Accelerates Psoriasis

Psoriasis is a common autoimmune inflammatory skin disease that affects 125 million patient's worldwide<sup>17-19</sup>. Various risk factors includes smoking, alcohol consumption, trauma, infections, endocrine factors, stressful life events as well as exposure to drugs such as beta blockers, ACEI, antimalarial, NSAID, lithium, interferon as well as the acute withdrawal of systemic or potent topical corticosteroids<sup>20-24</sup>. Various studies show that beta blockers may be a factor in patients who were hospitalized with psoriasis vulgaris<sup>25-28</sup>.

### Management

Beta blockers are widely used antihypertensive drugs. During the treatment of hypertension the use of one beta blocker may result in psoriasis and if we substitute any other beta blocker it may further result in the appearance of skin lesions. In that case an alternative class of antihypertensive has to be chosen<sup>29</sup>. Based on the new anti hypertension guidelines, thiazide diuretics or calcium channel blocker can be used as first line treatment for hypertension<sup>30</sup>. For the management of drug induced psoriasis conventional therapeutic agents like topical and systemic drugs can be recommended. If psoriasis is present only in localized area, emollients can be helpful<sup>31</sup>.

### How Calcium Channel Blockers Produce Adverse Effects

Calcium channel blockers are the class of drugs which are the most commonly used antihypertensive drug<sup>32-33</sup>. Calcium channel blockers 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 blockade, calcium channel blockers causes relaxation of vascular smooth muscles and vasodilation, which in turn

causes reduction in heart rate and a decrease in conduction velocity within the heart.

### Gingival Enlargement

Gingival enlargement is a proliferative fibrous lesion of the gingival tissue that causes esthetic and functional problems<sup>34</sup>. There are various medications associated with gingival enlargement which can be broadly classified into three categories.

(1) Anticonvulsants

(2) Calcium channel blockers and

(3) Immunosuppressants<sup>35</sup>.

Drug induced gingival hyperplasia is a major concern for both patients and clinicians<sup>36</sup>. The prevalence of gingival overgrowth induced by calcium channel blockers is uncertain. Overgrowth occurs 3.3 times more commonly in males than females<sup>37</sup>.

### Management

The most effective treatment of these lesions is cessation of the offending medication and substitution with another class of antihypertensive like beta blockers, diuretics or angiotensin converting enzyme inhibitors, since drug induced gingival overgrowth has not been reported with any of these drugs. Another option is substitution with calcium channel blockers medications that has a lower risk of inducing gingival enlargement (e.g. Verapamil). If regimen change is not an option, then lesions should be managed with or without surgical intervention<sup>38</sup>.

### Peripheral Oedema

Oedema is the condition of accumulation of fluids in the intracellular tissue that causes the abnormal expansion of interstitial fluid volume which leads to decreased plasma oncotic pressure and increased capillary permeability or lymphatic obstruction<sup>39</sup>. The frequency of peripheral oedema with calcium channel blocker therapy is quite varied in the literature because of the dose dependent nature and can range from 5% to as high as 70%. Ankle oedema occurs more frequently in dihydropyridine group of calcium channel blockers.

### Mechanism of calcium channel blocker induced oedema

Calcium channel blocker induced oedema is caused because of 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 that of the capacitance vessels to calcium channel blocker induced reductions in myogenic vascular reactivity<sup>40</sup>.

### Management

The usual way to treat patients with calcium channel blocker induced oedema involves cessation of therapy and substitution with an alternative class of antihypertensive like thiazide diuretics or angiotensin



converting enzymes or angiotensin receptor blockers. Studies show that oedema will diminish upon conversion from dihydropyridine calcium channel blocker to non dihydropyridine calcium channel blocker such as veerapamil or diltiazem. Calcium channel blocker related peripheral oedema may not be physiologically corrected and it is advised to routinely prescribe diuretic or patients for the sole purpose of correcting the oedema state<sup>40</sup>.

### **Angiotensin Converting Enzyme Inhibitors Induced Angioedema**

Angiotensin converting enzyme inhibitors shows the useful effects on mortality, morbidity and quality of life in all stages of symptomatic heart failure resulting from impaired left ventricular systolic function<sup>41</sup>. Angiotensin converting enzyme 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 Angiotensin converting enzyme inhibitors are started at a low dose and gradually increased to get a highest tolerated maintenance dose. The adverse effects of angiotensin converting enzyme inhibitors include dry cough, dizziness and deterioration in renal function, hypotension and angioedema<sup>42</sup>. The use of angiotensin converting enzyme inhibitors increased significantly over recent years and more adverse reactions have been reported including severe angioedema of the upper airways and even death due to asphyxiation<sup>43</sup>.

Angioedema is a sudden localized and asymmetric swelling of skin or mucous membrane caused by transient increase in endothelial permeability resulting in plasma extravasations. Angioedema due to Angiotensin converting enzyme inhibitors is usually characterized by oedematous area of skin, slightly red and not accompanied by urticaria. In most cases angioedema is located in oro facial or perioral area or upper airways<sup>44</sup>. Angiotensin converting enzyme inhibitors induced angioedema can affect between 0.1% to 0.5% patients taking the drug<sup>45</sup>.

### **Mechanism of angiotensin converting enzyme inhibitors induced angioedema**

The bradykinin is normally degraded by kinase-II/ ACE. In patients who are treated with angiotensin converting enzyme, the degradation of bradykinin is inhibited and thus accumulation of bradykinin in tissues occur. Plasma bradykinin has been shown to increase up to 12-folds during angioedema attack<sup>43, 44</sup>.

### **Management**

First measure is to immediately discontinue ACE-inhibitor/ARB. The supportive measures include airway management and fluid replacement therapy. In severe cases when upper airway gastro intestinal tract are involved, then bradykinin receptor antagonist can be used as an effective treatment option.

### **Thiazide diuretic induced Hyponatremia**

Diuretics are recommended for the prevention, detection, evaluation and treatment of high blood pressure as first line therapy for the treatment of hypertension among all age groups<sup>46,47</sup>. Diuretics can be broadly classified into three distinct sub classes and each class have an important role in the management of most hypertensive patients<sup>48</sup>. 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, and then a diagnosis of primary aldosteronism may be considered. It can be managed by the addition of potassium sparing drugs (e. g. Spironolactone) that may achieve effective control of hypertension and thus can correct hypokalaemia without the need for extensive diagnostic assessment of adrenalactomy<sup>48</sup>.

### **Mechanism**

Thiazide diuretics block sodium chloride co transport in distal convoluted tubule. As a result sodium excretion of free water is reduced, resulting in hypernatremia<sup>49</sup>.

### **Management**

Discontinue thiazide diuretics, administer regular diet, (usually supplemented with potassium), restricting the intake of water.

### **Thiazide Diuretic Induced Hyperglycaemia**

Diabetes is a major cardiovascular risk factor, hyperglycaemia is more common and severe adverse effect is seen with thiazide diuretics than other classes of antihypertensive agents<sup>50</sup>.

### *Mechanism of Thiazide Induced Hyperglycemia*

Low serum potassium has been considered an important mechanism in the pathogenesis of diuretic induced hyperglycaemia. 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 hypoglycaemia<sup>51-53</sup>.

### *Management*

Patients with diuretic induced hyperglycaemias are often considered as having type II diabetes and are prescribed with oral anti diabetic agents. Hypertension is more prevalent than diabetes. Due to the use of thiazide diuretic to treat hypertension, thiazides induced hyperglycaemia is very common. Therefore, according to the literature, the usage of thiazide diuretics to treat hypertension is safe and effective. The complication of elevated glucose level is reversible and thus inconsequential<sup>54</sup>.



## CONCLUSION

There is a need for safe, effective and simple therapies to treat hypertension in order to achieve recommended blood pressure targets rapidly and rigorously, but with good tolerability and sustained patient adherence. The use of combination therapy as first line treatment will promptly help more patients to achieve blood pressure goals and fixed dose combinations will provide means for simple but flexible dosing. This review is associated with adverse drug reaction profile of antihypertensive drugs. The article is helpful in the selection of appropriate medicines for hypertensive patients. It enhances patient adherence with the therapy by selecting the medicines of lesser adverse drug reaction profile, reducing unnecessary economic burden to the patient due to unwanted effects of the therapy. It is important to remember that most adverse drug reactions 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 and hospitalizations associated with anti hypertensive drugs.

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