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Adverse drug reactions induced by antihypertensive agents

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Abstract
Hypertension is a clinical condition where the blood pressure is elevated than normal [1, 2]. Hypertension is the leading cause of morbidity and mortality worldwide which requires long therapy associated with severe ADR's. Antihypertensive drugs includes thiazide diuretics, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists and beta-blockers.

Keywords: Adverse drug reactions, antihypertensive agents, angiotensin converting enzyme

Introduction

Adverse reactions in antihypertensive occur in about 25% of patients. World Health Organization (WHO) defines "An adverse drug reaction (ADR) is any response to a drug which is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or the modification of physiological function". ADR makes patient experience more worse conditions than former [2]. ADR are more frequent in people with old age, the most vulnerable population is 60-90 [4], followed by 50-59 [1, 4] and even slightly less in age group of 40-49 [1, 4]. The major reason of chance is higher in age greater than 50, polypharmacy, age-related pharmacokinetic changes, pharmacodynamic variations, substantial co-morbidity levels compromised organ functions, decreased BMR (basal metabolic rate) [3, 4, 5]. The incidence of ADR is more common in female, it may be because of emotion quotient in females are greater than male [4, 5, 20, 21]. The appraisal that a drug is causing an adverse reaction is commonly based on clinical decree. The WHO and Naranjo's scale are used which categorizes the causality relationship into definite, probable, possible or unlikely which is commonly used for the assessment of the exact nature of ADR. The Naranjo score indicated a probable relationship between antihypertensive drugs [1, 2, 4]. On causality assessment, majority of the reactions exposed as ADR is a result of antihypertensive agent categorized as probable in nature, followed by possible [20]. Avoidance of adverse drug reactions can be achieved by appropriate drug selection and dosage, and also by the determination of spectrum of pharmacological actions of the different compounds in reducing blood pressure [2], through ADR monitoring (pharmacovigilance) and continuous monitoring of patients [5].

Antihypertensive therapy and associated ADR

To control elevated blood pressure, often requires two or more antihypertensive medications. The major combination of antihypertensive medicines are diuretics and calcium channel blockers [2]. Though with increasing number of antihypertensive medications in a regimen leads to major adverse drug reactions [4, 6, 43]. Amlodipine and atenolol combination therapy leads to greater risk of ADRs than the monotherapy [43]. The most common and preventable ADR's are associated to the Central Nervous System (dizziness, headache, depression), Musculo-Skeletal complaints (back pain, fatigue ankle and pedal edema) Gastrointestinal events (diarrhea, abdominal pain, anorexia, nausea, vomiting) Cardiovascular events [1, 2, 5, 7, 43].

Other system which get affected are renal and urinary disorders, respiratory, thoracic, reproductive system and breast disorder, mediastinal disorder, connective tissue disorder, skin and sub cutaneous disorder, eye disorder, psychiatric disorder [2, 20].

Out of all the major ADR hypotension, hyponatremia, cough, hyperkalemia, hypokalemia and swollen foots are the most common [4]. As the consequence of these ADR's many patients ab to discontinue their therapy in the mid-way [2].

CCB induced adverse drug reactions

Calcium channel blocker, the most common antihypertensive drug. (1, 2, 7, 46) They have been observed to be used in patients with hypertension as well as in cardiovascular diseases.

Calcium channel blockers produce their desired therapeutic effects by preventing calcium ions influx through the cell membranes. This is done by binding to L-type calcium channels, located on vascular smooth muscles, cardiac myocytes and cardiac nodal tissues. By this blockade, calcium channel blockers cause relaxation of vascular smooth muscles, vasodilation, which will ultimately cause reduction in heart rate and decrease in conduction velocity within the heart. The common ADR with the usage were ankle edema, pedal edema, gastro-esophageal reflux, gingival enlargement, headache, abdominal pain, back pain, palpitation, frequent micturition, flushing, dizziness, insomnia, flushing [1, 2, 5, 45].

Some studies illustrate that calcium channel blockers also acting as a possible cause of depression and suicide [8]. out of all these ADRs the major problem is found to be angle edema. Among other drugs the patients receiving Amlodipine are observed with more ADR [1, 5].

Ankle Edema

Ankle edema is caused because of vasodilation in the distal arterioles which leads to increase in intravascular capillary pressures and increased venous pressures, in the lower extremities and ultimately leakage of fluid into the extracellular space [1, 5].

Gerd
It is found to be an uncommon side effect, because calcium channel blockers are known to decrease the lower esophageal sphincter (LOS) pressure in a dose-dependent manner, and impair esophageal clearance [1].

Gingival Enlargement
The major reason for this seems to be uncertain and more commonly occurring in male [6]. Genetic predisposition and pharmacokinetic variables are among the factors implicated in its pathogenesis [6, 8].

Increase in Micturition
These finding should de further investigated and no sound result have been found [2].

Oral adverse drug reactions
Apart from all these ADR the calcium channel blockers have also been associated with angioedema of the tongue or lips, peri-orbital and lip angioedema shortly after Nifedipine therapy been initiated (50 mg a day), recalcitrant oral ulcers have been observed. This may be because of Non-polymorphic variation (CYP3A4) in metabolism phenotype or interaction by substrate competition/inhibition (CYP3A4) [8].

Diuretics induced ADR
The major ADR observed with diuretics are complaints of diarrhea, impotence, joint pain, paranesthesia, hypotension, heavy sweating, hyponatremia, excessive micturition, agranulocytosis, leucopenia and thrombocytopenia, dizziness, hyperglycemia and thirst, hypokalemia are the most frequent ADR related to diuretics [1, 3, 7, 8, 9, 16, 21, 22]. Ototoxicity is also as a rare ADR of loop diuretic [3, 11, 12, 15]. The ADR is observed commonly with Thiazides, Hydrochlorothiazide and Furosemide. All these side effects could be related to the fluid or electrolytes imbalance caused by these medicines, due to sodium ions depletion.

Dryness of mouth
This occur due to dehydration and leads to increase in level of salivary lactobacillus contribute reduced salivary gland function paying way for salivary gland hypofunction [3, 14].

Hyperglycemia
The patients treated with diuretics have been observed with hyperglycemic level [8, 9]. This is because on diuretic therapy results in hypokalemia, even though serum potassium may be normal but intracellular potassium deficiency observed, contribute to hyperglycemia by attenuation of endogenous insulin release [13].

Ototoxicity
Furosemide treatment in higher dose is commonly contributes to ototoxicity. (3,1211,15). This take place because cystic dilations had observed in the stria vascularis, located in lateral cochlear wall which is responsible for sending auditory signals from the cochlea to the central nervous system and dark cells of the vestibular system results in sudden hearing loss and ataxia in those patients after furosemide administration(11) or it can also be the result of long-term inhibition of the endocochlear potential has been resulting in decreased auditory nerve activity, and causes impairment in hearing [12].

ACE induced adverse drug reaction
Generally ACE inhibitors or angiotensin receptor antagonists are the drugs which is used in the treatment of hospitalized patients [4]. ACE inhibitors are of p-ACEI (phosphonate group containing ACEI) and d-ACEI (di-carboxyl group containing ACEI). The major drug which exhibit ADR are captopril enalapril, lisinopril, ramipril [8, 20, 21].
The major ADR experienced by ACE inhibitors are dry cough, dizziness, diarrhea, abdominal pain, deterioration in renal function, taste disturbances, hypotension (more in p-ACEIs), nausea (more in d-ACEIs) [22] and angioedema tongue ulcerations preceded by loss of taste, slight leukopenia, thrombocytopenia, dry mouth hyperkalemia and urticarial [1, 2, 8, 19, 20, 22]. Cough as ADR is typically irritating, dry and non-productive in nature and is not dose related. ACEIs have to be replaced by Angiotensin Receptor Blockers (ARBs) when ADR occur for prolonged duration [44].

Dry cough, urticaria and angioedema
Dry cough and urticaria is mediated by the accumulation of bradykinin, substance P, (vasoactive molecule) and/or prostaglandins in the lungs and skin because of the involvement of immunological processes of human body [1, 8, 18, 23, 43, 44, 45]. The phosphate group present in p-ACEIs is also a major factor for the development of dry cough. (22) An increase in the level of Dipeptidyl-Peptidase IV, which is one of the important metabolizers of bradykinin and substance P, contribute to angioedema [25, 26].

Ulceration of tongue
The patient receiving captopril are at a risk of development of tongue ulceration and the reason for that is captopril is metabolized by a polymorphic CYP enzyme, imply abnormal drug metabolism [8].

Dry mouth
The administration of ACEIs may cause dry mouth because of the reduction in salivary flow rate lisinopril is an example [8]. ACE Inhibitor selectively stimulates medullary imidazoline receptors which will inhibit centrally sympathetic outflow and potently suppress levels of circulating plasma noradrenaline.

Beta blockers induced adverse drug reactions
Patients receiving beta blockers mainly atenolol complaints of tremor, bradycardia, dry lips, dizziness, abnormal sensation in head, cramps in legs, angioedema, dry mouth, oral ulcerations, lupus erythematosus, SJS, oculo-mucocutaneous syndrome, and manifestations of hematological disorders, mouth paresthesia, headache, depression, psoriasis, insomnia [1, 2, 4, 5, 8]. Other studies shows that the major ADR occurs in beta blockers are diarrhea, dizziness, claudication, hypoglycemia (especially in insulin receiving patients) [38, 39] and bradycardia. Depression, insomnia, along with worsening heart failure, palpitations, chest pain and tachycardia are significantly less frequent in the beta blocker [34].

Tremor
Tremor could be caused because of unblocked beta-2 receptor on skeletal muscle since atenolol is beta-1 selective blocker [1].

Psoriasis

Psoriasis is occured by T-cell mediated hyper proliferation of keratinocytes and inflammatory processes based on complex genetic background [27, 28]. Some studies shows that Beta Blockers causes patients psoriasis vulgaris in patient hospitalized for long term [29, 30, 31, 32].

Bradycardia

This is majorly caused because of the administration of metoprolol or carvedilol. The major reason for the development of bradycardia is by antagonizing the actions of catecholamines produced by the sympathetic nerves at the cell receptor [42].

Occulomusculo-Cutaneous Syndrome and SLE

These are majorly caused by Practolol and is majorly caused by high concentration of ANA which is antinuclear antibody, an unusual antibody directed against structures within the nucleus of the cell. They are cutaneous adverse reactions.

Hypoglycemia

Studies shows that there is an increase in chance of developing hypoglycemia with the administration of beta blockers which will lead to the development of cardiovascular complication. However, the mechanism of this is yet to be clarified but may be by the inhibition of the release of glucose from the liver and they can also block the release of insulin by interacting with nerve signals to the pancreas and can thus lower insulin levels even when blood glucose is high [38, 39, 40, 41].

Claudication

Claudication can be condition in which cramping pain in the leg is induced by exercise, typically caused by obstruction of the arteries. The beta blocker is contraindicated in critical limb ischemia. But the studies show that since the β-blocker especially nebivolol possesses vasodilating, endothelium-dependent, NO-releasing properties that might be beneficial in peripheral arterial disease [35, 36, 37].

Adverse drug reaction indused by ARB

Patient on taking ARBs have been observed with angioedema have been reported in rare cases and also observed in some individuals who have a previous history of ACEI-induced angioedema. This is majorly caused because of abnormal metabolism by a polymorphic enzyme (CYP2D6) [8]. Dizziness have also been observed by patient taking ARBs [1].

Conclusion

Hypertension is one of the most alarming clinical condition resulting in severe health problems. And thus requires long term therapy which increases the complication. Hence proper medical care and lifestyle modifications are required. The treatment provided must be monitored for ADR and elucidations for them should be primed to avoid such life threatening issues. And to ensure this the healthcare provider must have appropriate knowledge of antihypertensive drugs and ADR caused by them.

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