Available online at ajdhs.com

Asian Journal of Dental and Health Sciences

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Review on Toxicity of Antihypertensive Drugs

Devraj Rajak, Deepali Sahu, Anushree Jain, Rubeena Khan, Basant Khare, Prateek Kumar Jain, Bhupendra Singh Thakur*

Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001

Article Info:

Article History:

Received 13 Sep 2022
Reviewed 08 Nov 2022
Accepted 25 Nov 2022
Published 15 Dec 2022

Cite this article as:

Rajak D, Sahu D, Jain A, Khan R, Khare B, Jain PK, Thakur BS, Review on Toxicity of Antihypertensive Drugs, Asian Journal of Dental and Health Sciences. 2022; 2(4):64-68

DOI: http://dx.doi.org/10.22270/ajdhs.v2i4.28

*Address for Correspondence:

Bhupendra Singh Thakur, Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001

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 mmHg[1-2]. 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 countries[3]. 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 dementia[4,5]. Although public awareness of hypertension diagnosis has grown, improvements in cardiovascular disease rates have not kept pace[6]. 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 mmHg[6-10]. A wide range of antihypertensive medications are currently available for the treatment of hypertension[11]. Thiazide diuretics, Beta Blockers, Long Acting Calcium Channel Antagonists, Angiotensin Converting Enzyme Inhibitors, and Angiotensin II Receptor Blockers have all been shown to improve outcomes[12-14]. 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 ADRs[15]. 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 symptoms[16-19]. 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 effects[20]. 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 disorders[21]. 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[22]. 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[23]. 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. b) 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[24]. According to one study, long-term hypertension and beta blocker use may be risk factors developing psoriasis[25].

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[26-28]. It is distinguished by T-cell-mediated keratinocyte hyperproliferation and inflammatory processes that are based on a complex genetic background[26,27]. 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[29-33] 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[34-37].

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[37-40].

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 anti-hypertension 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[41-44].

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[45-48].

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[49-53].

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 substitution 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, Isradipine). If changing the regimen is not an option, the lesions should be managed surgically or non-surgically [54-59].

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 Lacidipine and Lecanidipine 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, anon-DHPagent,seems to be associated with lowest incidence of ankle edema[60-63].

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[61].

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 dihydropyridine 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[61].

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. Angioedema 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[64-68].

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[66,67].

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[66-67], Epinephrine 1:1000 (0.3-0.5ml).

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 (spirinolactone, eplerenone), achieving effective hypertension control and correcting hypokalemia without the need for extensive diagnostic assessment of adrenalictomy[69-71].

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[72].

Management

(1)Stop using thiazide diuretics. (2) Regulardiet(usuallysupplementedwithpotassium) (3) Restrictingwaterintake (4) If the hyponatremia is severe or symptomatic, Furosemide and isotonic saline should be administered[73].

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[74].

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[75].

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[76].

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.

References

1. Raghu Kumar V, Raghu Ram V, Guru Prasad B, Mohanta G.P and Manna P.K: A study of adverse drug reactions due to anti-hypertensive drugs in a tertiary care teaching hospital. International Journal of Pharmacy and Life Sciences 2011; 2:767-772.

2. Aellig HW: Adverse reactions to World Health Organisation preventing chronic diseases: a vital investment. Geneva, Switzerland: WHO; 2005.

3. Murray CJ, Lopez AD: Mortality by cause for eight regions of the world: Global burden of disease study. Lancet 1997; 349: 1269-1276. https://doi.org/10.1016/S0140-6736(96)07493-4

4. Michel Joffres et al., Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. British Medical Journal 2013; 3:e003423. https://doi.org/10.1136/bmjopen-2013-003423

5. Peter Lloyd- Sherlock, John Beard, Nadia Minicuci, Shah Ebrahim and SomnathChatterji.:Hypertension among older adults in low- and middle-income countries: Prevalence, awareness and control.

International Journal of Epidemiology 2014; 1-13. https://doi.org/10.1093/ije/dyt215

6. The sixth report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. Archives of Internal Medicine 1997; 157:2413- 2446. https://doi.org/10.1001/archinte.1997.00440420033005

7. 1999 World Health Organisation- International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines subcommittee.Journal of Hypertension 1999; 17:151-183. https://doi.org/10.1097/00004872-199917020-00001

8. Kaplan NM: Guidelines for the management of hypertension. Canadian Journal of Cardiology 2000; 16:1147-1152.

9. Ramsay L et al., Guidelines for the management of hypertension: Report of the third working party of the British hypertension society. Journal of Human Hypertension 1999; 13:569-592. https://doi.org/10.1038/sj.jhh.1000917

10. Scottish Intercollegiate Guidelines network. Hypertension in older people.A national clinical guideline. 2001. SIGN publication no. 49.

11. DabhadeSuhas, Bhosle Deepak, AtreKavita: Review on pharmacovigilance study of telmisartan in hypertension patients. Asian Journal of Pharmaceutical and Clinical Research 2013; 6:17-20.

12. Collins R, MacMahon S: Blood pressure, anti-hypertensive drug treatment and the risk of stroke and of coronary heart disease. British Medical Bulletin 1994; 50:272- 298. https://doi.org/10.1093/oxfordjournals.bmb.a072892

13. Neal B, Mac Mahon S and Chapman N: Effects of ACE inhibitors, Calcium antagonists and other blood pressurelowering drugs: results of prospectively designed overuse of randomised trials. Blood pressure lowering treatment trialists' Collaboration. Lancet 2000; 355:1955-1964. https://doi.org/10.1016/S0140-6736(00)03307-9

14. Zia Al Sabbah, AijazMansoor, UpendraKaul: Angiotensin receptor blockers-advantages of the new sartans. Journal of the Association of Physicians of India 2013; 61:464- 470.

15. Hussain A, Aqil M, Alam M.S, Khan M.R, Kapur P and Pillai K.K: A pharmacovigilance study of antihypertensive medicines at South Delhi hospital. Indian Journal of Pharmaceutical Sciences 2009; 71:338-341. https://doi.org/10.4103/0250-474X.56018

16. DegliEsposti E, Sturani A and Di Martino N: Long term persistence with anti-hypertensive drugs in new patients. Journal of Human Hypertension 2002; 16:439-444. https://doi.org/10.1038/sj.jhh.1001418

17. DegliEsposti L, DegliEsposti E and Valpiani G: A retrospective, population- based analysis of persistence with anti-hypertensive drug therapy in primary care practice in Italy. Clinical Therapeutics 2002; 24:1347- 1357. https://doi.org/10.1016/S0149-2918(02)80039-X

18. Monana M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R and Avorn J: The effects of initial drug choice and comorbidity on anti-hypertensive therapy compliance: results from a population-based study in the elderly. American Journal of Hypertension 1997; 10:697-704. https://doi.org/10.1016/S0895-7061(97)00056-3

19. Ross SD, Akhras KS, Zhang S, Rozinsky M and Nalysnyk L: Discontinuation of anti-hypertensive drugs due to adverse events: A systematic review and meta-analysis. Pharmacotherapy 2001; 21:940-953. https://doi.org/10.1592/phco.21.11.940.34520

20. Allhat Officers and co-ordinators for the ALLHAT collaborative research group. Major outcomes in high-risk hypertensive patients randomized to angiotensinconverting enzyme inhibitor or Calcium channel blocker vs diuretic: The anti-hypertensive and lipid lowering treatment to prevent heart attack trial. The Journal of the American Medical Association.2002; 288:2981-2997. https://doi.org/10.1001/jama.288.23.2981

21. Lionel F, Baker: Triggering psoriasis: the role of infections and medications. Clinics in Dermatology 2007; 25:606- 615. https://doi.org/10.1016/j.clindermatol.2007.08.015

22. Jeffery. Martin: Hypertension Guidelines: Revisiting the JNC 7 recommendations. The Journal of Lancaster General Hospital 2008; 3:91-97.

23. Treatment with antihypertensive drugs. JSH Guidelines.Hypertension Research.2009; 32:33-39. https://doi.org/10.1038/hr.2008.5

24. William H. Frishman: Beta-adrenergic blockers, adverse effects and drug interactions. Journal of American Heart Association 1988; 11:II 21- II 29. https://doi.org/10.1161/01.HYP.11.3_Pt_2.II21

25. Joanna Lyford: Hypertension and beta-blockers may raise risk of psoriasis. The Pharmaceutical Journal 2014; 293.

26. Jain M, Jain A, Khare B, Jain DK, Khan R, Jain D. An Update on the Recent Emergence of Candida auris. Asian Journal of Dental and Health Sciences. 2022; 2(1):14-9. https://doi.org/10.22270/ajdhs.v2i1.11

27. Kormeili T, Lowe NJ, Yamauchi PS: Psoriasis: Immunopathogenesis and evolving immune-modulators and systemic therapies; U.S. Experiences. British Journal of Dermatology 2004; 151:3-15. https://doi.org/10.1111/j.1365-2133.2004.06009.x

28. Thao Nguyen, Jashin J Wu: Relationship between tumour necrosis factor- α inhibitors and cardiovascular disease in psoriasis: A review. The Permanente Journal 2014; 18:49- 54. https://doi.org/10.7812/TPP/13-092

29. Brauchli Y.B, Jick S.S, Curtin F and Meier C.R: Association between Beta blockers, other antihypertensive drugs and psoriasis: Population-based casecontrol study. British Journal of Dermatology 2008; 158:1299-1307. https://doi.org/10.1111/j.1365-2133.2008.08563.x

30. Jat D, Thakur N, Jain DK, Prasad S, Yadav R. Iris ensata Thunb: Review on Its Chemistry, Morphology, Ethno Medical Uses, Phytochemistry and Pharmacological Activities. Asian Journal of Dental and Health Sciences. 2022; 2(1):1-6. https://doi.org/10.22270/ajdhs.v2i1.9

31. Tsankov N, Kasandjieva J and Drenovska K: Drugs in exacerbation and provocation of psoriasis. Clinics in Dermatology 1998; 16:333-51. https://doi.org/10.1016/S0738-081X(98)00005-4

32. Naldi L, Parazzini F, Peli L, Chatenoud L and Cainelli T: Dietary factors and the risk of psoriasis. Results of an Italian case-control study.British Journal of Dermatology 1996; 134:101-106. https://doi.org/10.1046/j.1365-2133.1996.d01-734.x

33. Naldi L et al., Cigarette smoking, body mass index and stressful life events as risk factors for psoriasis: Results from an Italian case-control study. Journal of Investigative Dermatology 2005; 125:61-67. https://doi.org/10.1111/j.0022-202X.2005.23681.x

34. Steinkraus V, Steinfath M and Mensing H: Beta adrenergic blocking drugs and psoriasis. Journal of the American Academy of Dermatology 1992; 27:266-267. https://doi.org/10.1016/S0190-9622(08)80738-4

35. Halevy S, Livni E: Psoriasis and psoriasiform eruptions associated with propranolol - the role of an immunological mechanism. Archives of Dermatological Research 1991; 283:472-473. https://doi.org/10.1007/BF00371785

36. Cohen AD, Bonneh DY, Reuveni H, Vardy DA, Naggan L and Halevy S: Drug exposure and Psoriasis vulgaris: casecontrol and case-crossover studies. ActaDermatoVenereologica 2005; 85:299-303. https://doi.org/10.1080/00015550510032823

37. Khatri S, Dhanoriya C, Jain DK. Zika virus (ZIKV) disease: past, present and future. Journal of Drug Delivery and Therapeutics. 2018; 8(6-s):320-7. https://doi.org/10.22270/jddt.v8i6-s.2076

38. Yadav R, Jha M, Prasad S, Jat D, Jain DK. Mayaro virus (MAYV) Disease: Past, present and future. J Pharm Biol Sci. 2022; 10(1):7-16.

39. Obrien M, Koo J: The mechanism of Lithium and Beta blocking agents in inducing and exacerbating psoriasis. Journal of Drugs in Dermatology 2006; 5:426-432.

40. Ockenfels HM et al., Tyrosine phosphorylation in psoriasis T-cells is modified by drugs that induce or improve psoriasis. Dermatology 1995; 191:217-225. https://doi.org/10.1159/000246549

41. Drs M Keefe, Hamlet N W and Rebecca E I Kerr: Psoriasis is a side effect of beta blockers. British Medical Journal 1987; 295: 1352. https://doi.org/10.1136/bmj.295.6609.1352-a

42. O'Brian M, Koo J: The mechanism of Lithium and Beta blocker agents in inducing an exacerbating psoriasis. Journal of Drugs in Dermatology 2006; 5:426-433.

43. Hypertension: Clinical Management of primary hypertension in adults. NICE Guidelines. 2011.

44. Tsankov N, Irena A and Kasandjieva J: Drug-induced psoriasis: Recognition and management. American Journal of Clinical Dermatology 2000; 1: 159-165. https://doi.org/10.2165/00128071-200001030-00003

45. Peter Trenkwalder: Anti-hypertensive treatment with calcium channel blockers: pharmacological pornography or useful intervention? Nephrology Dialysis Transplantation 2004; 19:17-20. https://doi.org/10.1093/ndt/gfg431

46. HarikrishnaMakani MD, Sripal Bangalore MD, MHA, Jorge Romero MD, Omar Wever-Pinzon MD, Franz H. Messerli MD: Effect of Renin-Angiotensin System Blockade on Calcium Channel Blocker-Associated Peripheral Edema. The American Journal of Medicine 2011; 124:128-135. https://doi.org/10.1016/j.amjmed.2010.08.007

47. Khatri S, Jain DK. Autism spectrum disorder (ASD): past, present and future. CIBTech Journal of Pharmaceutical Sciences. 2018; 7(4):1-25.

48. Livada R and Shiloah J: Calcium channel blocker-induced gingival enlargement. Journal of Human Hypertension 2014; 28:0-14. https://doi.org/10.1038/jhh.2013.47

49. Shetty AK, Shah HJ, Patil MA and Jhota KN: Idiopathic gingival enlargement and its management. Journal of Indian Society of Periodontology 2010; 14:263-265. https://doi.org/10.4103/0972-124X.76935

50. Vishakha Grover, AnoopKapoor and Marya CM: Amlodipine-induced gingival hyperplasia. Journal of Oral Health and Community Dentistry 2007; 1:19-22. https://doi.org/10.5005/johcd-1-1-19

51. Murat Sucu, Murat Yucc and VedatDavutoglu: Amlodipine-induced massive gingival hypertrophy. Canadian Family Physician 2011; 57:436-437.

52. Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ and Thomason JM: Prevalence of gingival overgrowth induced by calcium channel blockers: A community-based study. Journal of Periodontology 1999; 70:63-67 https://doi.org/10.1902/jop.1999.70.1.63

53. Pristant LM and Herman W: Calcium channel blocker induced gingival overgrowth. The Journal of Clinical Hypertension 2002; 4:310-311 https://doi.org/10.1111/j.1524-6175.2002.01095.x

54. Lucas RM, Howell LP, Wall BA: Nifedipine- induced gingival hyperplasia. A histochemical and ultrastructural study.Journal of Periodontology 1985; 56:211-215. https://doi.org/10.1902/jop.1985.56.4.211

55. Barclay S, Thomason JM, Idle JR, Seymour RA: The incidence and severity of Nifedipine induced gingival over growth. Journal of Clinical Periodontology 1992; 19:311- 314. https://doi.org/10.1111/j.1600-051X.1992.tb00650.x

56. Duncan MR, Berman B: Stimulation of collagen and glycosaminoglycan production in cultured human adult dermal fibroblast by recombinant human interleukin-6. Journal of Investigative Dermatology 1991; 97:686-689. https://doi.org/10.1111/1523-1747.ep12483971

57. Gautam SP, Rai JP, Billshaiya U, Jain N, Vikram P, Jain DK. Formulation and evaluation of mouth dissolving tablet of loperamide. International Journal of Pharmaceutical Sciences and Research. 2013; 4(5):1782.

58. Patel AN, Rai JP, Jain DK, Banweer JI. Formulation, development and evaluation of cefaclor extended release matrix tablet. Int J Pharm Pharm Sci. 2012; 4(4):355-7.

59. Torpet LA, Kragelund C, Reibel J and Nauntofte B: Oral adverse drug reaction to cardiovascular drugs. Critical Reviews in Oral Biology and Medicine 2004; 15:28-46. https://doi.org/10.1177/154411130401500104

60. Katheryn P, Traues MD and James S. Edema: Diagnosis and Management. American Academy of Family Physicians 2013; 88:102-110.

61. Domenic A. Sica: Calcium channel-related peripheral oedema; can it be resolved? The Journal of Clinical Hypertension 2003; 5:291-295. https://doi.org/10.1111/j.1524-6175.2003.02402.x

62. Messerli FH and Groossman E: Pedal oedema-not all dihydropyridine calcium antagonist are created equal. American Journal of Hypertension 2002; 15:1019-1020. https://doi.org/10.1016/S0895-7061(02)03087-X

63. Sirker A, Missouris CG and Macgregor G: Dihydropyridine calcium channel blockers and peripheral side effects. Jounal of Human Hypertension 2001; 15:745- 746. https://doi.org/10.1038/sj.jhh.1001248

64. Rajeev Kumar, Ramji Sharma, KhemrajBairwa, Ram Kumar Roy, Arun Kumar and AtulBaruwa: Modern Development in ACE inhibitors. Der Pharmacia Lettre 2010; 2:388-419.

65. Pandey SP, Khan MA, Dhote V, Dhote K, Jain DK. Formulation development of sustained release matrix tablet containing metformin hydrochloride and study of various factors affecting dissolution rate. Sch Acad J Pharm. 2019; 8(3):57-73.

66. Jain P, Nair S, Jain N, Jain DK, Jain S. Formulation and evaluation of solid dispersion of lomefloxacin hydrochloride. Int J Res Pharm Sci 2012; 3(4):604-608.

67. Upendra Kaul, Aijaz Mansoor and Zia Al Sabbah: Angiotensin Receptor Blockers-Advantages of the New Sartans. Journal of the Association of Physicians of India 2013; 61:464- 470.

68. Philip BabatundeAdebayol and Olutayo Christopher Alebiosu: ACE-I induced Angioedema: A case report and Review of literature 2009; 2: 7181. https://doi.org/10.4076/1757-1626-2-7181

69. Sharabi Y, Illan R, Kamari Y, Cohen H, Nadler M, Grossman E and Messerli FH: Diuretic induced hyponatraemia in elderly hypertensive women. Journal of Human Hypertension 2002; 16:631-635. https://doi.org/10.1038/sj.jhh.1001458

70. Domenic A. Sica: Diuretics related side effects: development and treatment. The Journal of Clinical Hypertension 2004; 6:532-540. https://doi.org/10.1111/j.1524-6175.2004.03789.x

71. Lawrence R. Krakoff: Diuretics for hypertension. American Heart Association 2005; 112:127-129. https://doi.org/10.1161/CIRCULATIONAHA.105.570192

72. Patel NS, Jain DK, Nagar H, Patel A, Chandel HS. Evaluation of analgesic and antipyretic activity of Tridax procumbens leaves extract. RGUHS J Pharm Sci. 2011; 1(3):226-31. https://doi.org/10.5530/rjps.2011.3.9

73. Kyu Sig Hwang and Gheun-Ho Kim: Thiazide-induced hyponatremia. Electrolyte Blood Press 2010; 8:51-57. https://doi.org/10.5049/EBP.2010.8.1.51

74. Anil K. Mandal, Linda M. Hiebert: Is Diuretic-Induced Hyperglycemia Reversible and Inconsequential? Journal of Diabetes Research and Clinical Metabolism 2012; 1:1-4. https://doi.org/10.7243/2050-0866-1-4

75. Padwal R, Laupacis: A Antihypertensive therapy and incidence ot Type 2 diabetes. Diabetes Care 2004, 27:247- 255. https://doi.org/10.2337/diacare.27.1.247

76. Halderman JH, Elahi D, Anderson DK, Raizes GS, Tobin JD, Shocken D, Andres R: Prevention of glucose intolerance of thiazide diuretics by maintenance of body potassium. Diabetes 1983, 32:106-111. https://doi.org/10.2337/diabetes.32.2.106