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REVIEW ARTICLE

Pharmacodynamic interactions of thiazide diuretics

Naina Mohamed Pakkir Maideen[1]

ABSTRACT

Thiazide diuretics are used as one of the first-line agents to treat hypertension. However, the treated patients may have to receive multiple medications to treat comorbidities ensuing in drug-induced side effects. The present review was conducted using keywords such as drug interactions, pharmacodynamic drug interactions, thiazide diuretics, hydrochlorothiazide, chlorthalidone, and indapamide. The abovementioned words were searched in databases such as Medline, PubMed, PubMed Central (PMC), Google Scholar, ScienceDirect, Cochrane Library, and reference lists. Thiazides are diuretics, known to interact with drugs such as digoxin, flecainide, and dofetilide pharmacodynamically through thiazide-induced hypokalemia, hyponatremia, and hypovolemia respectively. The pharmacological interaction of thiazide diuretics with drugs such as lithium, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, antidiabetic, and Vitamin D has been reported. Herbs such as licorice and ginkgo were also studied for their interactivity with thiazides. Doctors and pharmacists are required to be well aware of drug-induced side effects of thiazide. This step is crucial for preventing adverse side effects.

Keywords: Drug interactions, thiazide diuretics, hydrochlorothiazide, chlorthalidone, indapamide.

Introduction

Diuretics, also known as water pills, are of two types: (1) thiazide diuretics, including chlorothiazide and hydrochlorothiazide and (2) thiazide-like drugs such as indapamide and chlorthalidone [1]. Thiazide diuretics are primarily prescribed in the management of hypertension and edema associated with chronic heart failure, renal dysfunction, and hepatic cirrhosis. Besides, these drugs are also used to treat high blood pressure included by corticosteroids and estrogen.

The guidelines from the Eighth Joint National Committee and American College of Cardiology/American Heart Association task force [2,3] recommend thiazide diuretics as the preliminary drug to treat hypertension. Thiazide diuretics inhibit Na^+–Cl^- symporter at distal convoluted tubule. This results in the inhibition of reabsorption of Na^+ and Cl^- ions with increased excretion of Na^+ and water [4].

Hypertension is the most important risk factor of cardiovascular diseases (CVD). It has been estimated that, in 2012, 17.5 million people succumbed to CVD. It includes coronary heart diseases attributing to 7.4 million deaths and stroke-associated deaths accounting for 6.7 million [5,6]. The incidence of hypertension is high worldwide, with more than 1.39 billion people diagnosed in the year 2010 [7].

Drug interaction is defined as the interference of effects of a drug by concomitantly administered drug(s), supplements, food, tobacco smoke, or alcohol [8,9]. The majority of drug-to-drug interactions result in enhanced adverse effects. Hence, they are considered preventable medication errors. Emergency hospital admissions of approximately 6.5% are due to adverse drug effects [10]. Furthermore, among them, drug interactions accounted for 49% of admissions [11].

An inappropriate use of multiple medications is known as polypharmacy. This practice increases the probability of drug interactions due to the high number of concomitant medications [12]. The prevalence of polypharmacy-induced drug interactions is higher among patients with hypertension, especially older patients, since they receive many medications to treat various comorbid conditions [13]. Hence, care should be taken by prescribers and pharmacists while suggesting thiazide diuretics, to prevent their serious side effects.

Digoxin

Digoxin is a digitalis glycoside and is indicated in the management of patients with conditions such as congestive

Correspondence to: Naina Mohamed Pakkir Maideen
Pharmacologist, Dubai Health Authority,
Dubai, UAE.
Email: nmmaideen@dha.gov.ae
Full list of author information is available at the end of the article.
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heart failure, atrial flutter (AFL), or atrial fibrillation (AF) [14,15]. The combined therapy of thiazide diuretics and digoxin results in more than three-fold increase in the risk of hospitalization for digoxin intoxication. Digoxin, in combination with hydrochlorothiazide, is a potential risk for emergency hospitalization [16]. Thiazide diuretic-induced hypokalemia increases myocardial sensitivity for digoxin. Subsequently, an increased myocardial uptake of digoxin results in digoxin intoxication [17].

It is recommended to monitor the signs and symptoms of digoxin toxicity in patients receiving thiazide diuretics and digoxin concomitantly [18].

Flecainide

Flecainide is a class one antiarrhythmic drug extensively used to manage patients with AF [19]. Thiazide diuretic-induced hyponatremia can increase flecainide-mediated cardio toxicity. The administration of flecainide along with thiazide diuretic results in recurrent syncope, weakness, and fatigue due to electrolyte imbalance in patients. The concomitant use of flecainide in a patient receiving thiazide diuretic should be avoided to prevent cardiotoxicity [20].

The cardiac conduction could be improved in the case of flecainide toxicity by increasing extracellular sodium levels through the administration of sodium bicarbonate [21].

Dofetilide

Dofetilide is a class III antiarrhythmic agent that is approved for use in the management of patients with atrial arrhythmias including AF and AFL [22]. The coadministration of chlorthalidone in a patient taking dofetilide for atrial arrhythmias resulted in hypotension, warranting the discontinuation of the former drug. Moreover, the blood pressure was later maintained to normal by the administration of low-dose amlodipine along with lisinopril [23].

Lithium

Lithium is a mood stabilizer and is used widely as a first-line agent to prevent and treat bipolar disorder [24]. A combined therapy of thiazide diuretics and lithium resulted in lithium toxicity by increasing the reabsorption of sodium and lithium at proximal convoluted tubule [25].

The concomitant use of lithium with thiazide diuretics resulted in elevated plasma concentrations of lithium [25]. Since lithium has a narrow therapeutic index, therefore, combination treatments including lithium and thiazide diuretics should be avoided [26].

ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the first-line drugs to treat hypertensive patients with comorbidities such as diabetes, ischemic heart disease, heart failure, and chronic kidney diseases [2]. The excessive reduction of blood pressure and symptomatic hypotension can occur in patients receiving thiazide diuretics and ACE inhibitors concurrently. The effect is due to the depletion of sodium and water volume by thiazide-based diuretics [27].

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammation, pain, and fever. They include drugs such as ibuprofen, diclofenac, naproxen, and many others [28]. They can increase blood pressure through the inhibition of renal prostaglandins, leading to sodium and fluid retention and vasoconstriction [29]. Hence, the antihypertensive effect of thiazide diuretics could be decreased by the coadministration of NSAIDs. Thiazide diuretics may exacerbate NSAID-associated nephrotoxicity [30].

The monitoring of vital parameters in patients receiving thiazide diuretics and NSAIDs concomitantly is crucial [31]. These include tracking of blood pressure, renal function, and serum potassium in high-risk elderly, Blacks, and participants with low renin hypertension. The patients receiving NSAIDs may be recommended to take calcium channel blockers as the synthesis of renal/extra renal prostaglandins does not affect them [32].

Antidiabetics

Thiazide diuretics may induce glucose intolerance and hyperglycemia through impaired sensitivity, increased resistance, and increased basal concentrations of insulin [33]. Hence, they decrease the efficacy of antidiabetic drugs such as sulfonylureas by interfering with blood glucose levels.

The patients on combined therapy of thiazide diuretics along with oral hypoglycemic drugs or insulin should be monitored closely for blood glucose levels [34].

Vitamin D

Vitamin D is a fat-soluble vitamin and helps to prevent fractures by increasing the intestinal absorption of calcium [35]. The risk of hypercalcemia might be exacerbated by Vitamin D supplementation in patients receiving thiazide diuretics, subsequently decreasing the urinary excretion of calcium [36].

Licorice (*Glycyrrhiza glabra*)

Licorice is an herb used widely in Chinese medicine to treat various ailments [37]. Licorice is associated with hypertension, hypokalemia, and edema and may attenuate the antihypertensive efficacy of thiazide diuretics [38]. The coadministration of hydrochlorothiazide and licorice in healthy volunteers resulted in hypokalemia due to additive effects. A close monitoring of blood potassium levels is recommended in patients receiving thiazide diuretics and licorice [39].

Ginkgo (*Ginkgo biloba*)

Ginkgo biloba is an herb used to manage various neurological, psychological, and behavioral problems [40]. The coadministration of *G. biloba* and thiazide diuretics might cause an elevated blood pressure in patients [41].

Conclusion

Thiazide diuretics interact pharmacodynamically with drugs, such as digoxin, flecainide, and dofetilide through thiazide-induced hypokalemia, hyponatremia, and hypovolemia respectively. The pharmacological interaction of thiazide diuretics with lithium, ACE inhibitors, NSAIDs, antidiabetics, Vitamin D, and herbs such as licorice and ginkgo has been reported. It is the responsibility of medical practitioners and pharmacists to be well informed of the drug interaction profile of thiazide diuretics. This knowledge is required for the minimization of associated side effects due to possible drug interactions.

List of Abbreviations

CVD	Cardiovascular diseases
AFL	Atrial flutter
AF	Atrial fibrillation
ACE	Angiotensin-converting enzyme
NSAIDs	Non-steroidal anti-inflammatory drugs

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Author details

Naina Mohamed Pakkir Maideen[1]

1. Pharmacologist, Dubai Health Authority, Dubai, United Arab Emirates

References

1. Liang W, Ma H, Cao L, Yan W, Yang J. Comparison of thiazide-like diuretics versus thiazide-type diuretics: a meta-analysis. J Cell Mol Med. 2017;21(11):2634–42. https://doi.org/10.1111/jcmm.13205
2. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20. https://doi.org/10.1001/jama.2013.284427
3. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127–248. https://doi.org/10.22141/2307-1257.7.1.2018.122220
4. Alon US. The effects of diuretics on mineral and bone metabolism. Pediatr Endocr Rev . 2018;15(4):291–7.
5. Cappuccio FP, Miller MA. Cardiovascular disease and hypertension in sub-Saharan Africa: burden, risk and interventions. Intern Emerg Med. 2016;11(3):299–305. https://doi.org/10.1007/s11739-016-1423-9
6. Cifkova R, Fodor G, Wohlfahrt P. Changes in hypertension prevalence, awareness, treatment, and control in high-, middle-, and low-income countries: an update. Curr Hypertens Rep. 2016;18(8):62. https://doi.org/10.1007/s11906-016-0669-y
7. Bloch MJ. Worldwide prevalence of hypertension exceeds 1.3 billion. J Am Soc Hypertens. 2016;10(10):753. https://doi.org/10.1016/j.jash.2016.08.006
8. Mohamed N, Maideen P. Thiazolidinediones and their drug interactions involving CYP enzymes. Am J Physiol Biochem Pharmacol. 2018;8(2):47–54. https://doi.org/10.5455/ajpbp.20181022083057
9. Maideen NM. Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine. World J. Pharm.. 2019;8(2):14–25. https://doi.org/10.5497/wjp.v8.i2.14
10. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med. 2015;13(1):74. https://doi.org/10.1186/s12916-015-0322-7
11. Pedrós C, Formiga F, Corbella X, Arnau JM. Adverse drug reactions leading to urgent hospital admission in an elderly population: prevalence and main features. Eur J Clin Pharmacol. 2016;72(2):219–26. https://doi.org/10.1007/s00228-015-1974-0
12. Salwe KJ, Kalyansundaram D, Bahurupi Y. A study on polypharmacy and potential drug-drug interactions among elderly patients admitted in department of medicine of a tertiary care hospital in Puducherry. J Clin Diagn Res. 2016;10(2):FC06. https://doi.org/10.7860/jcdr/2016/16284.7273
13. Mukete BN, Ferdinand KC. Polypharmacy in older adults with hypertension: a comprehensive review. J Clin Hypertens. 2016;18(1):10–8. https://doi.org/10.1111/jch.12624
14. Maideen NMP. Pharmacologically relevant drug interactions of α-glucosidase inhibitors. J Diabetes MetabDisord Control. 2019; 6(2):28–30.
15. Maideen NMP. Pharmacologically relevant drug interactions of glucagon-like peptide-1 receptor agonists. J Anal Pharm Res. 2019; 8(2):51–3.

16. Wang MT, Su CY, Chan AL, Lian PW, Leu HB, Hsu YJ. Risk of digoxin intoxication in heart failure patients exposed to digoxin–diuretic interactions: a population-based study. Br J Clin Pharmacol. 2010;70(2):258–67. https://doi.org/10.1111/j.1365-2125.2010.03687.x

17. Steiness E. Diuretics, digitalis and arrhythmias. Acta Medica Scandinavica Supplementum. 1981;647:75–8. https://doi.org/10.1111/j.0954-6820.1981.tb02641.x

18. Magro L, Conforti A, Del Zotti F, Leone R, Iorio ML, Meneghelli I, et al. Identification of severe potential drug-drug interactions using an Italian general-practitioner database. Eur J Clin Pharmacol. 2008;64(3):303–9. https://doi.org/10.1007/s00228-007-0394-1

19. Aliot E, Capucci A, Crijns HJ, Goette A, Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. Europace. 2010;13(2):161–73. https://doi.org/10.1093/europace/euq382

20. Khavandi A, Walker PR. Flecainide cardiotoxicity precipitated by electrolyte imbalance. Caution with thiazide diuretics. Emerg Med J. 2007;24(5):e26. https://doi.org/10.1136/emj.2006.044362

21. Goldman MJ, Mowry JB, Kirk MA. Sodium bicarbonate to correct widened QRS in a case of flecainide overdose. J Emerg Med. 1997;15(2):183–6. https://doi.org/10.1016/s0736-4679(96)00345-9

22. Wells R, Khairy P, Harris L, Anderson CC, Balaji S. Dofetilide for atrial arrhythmias in congenital heart disease: a multicenter study. Pacing Clin Electrophysiol. 2009;32(10):1313–8. https://doi.org/10.1111/j.1540-8159.2009.02479.x

23. Crist L, Dixon D. Considerations for dofetilide use in the elderly. Consult Pharm. 2014;29(4):270–4. https://doi.org/10.4140/tcp.n.2014.270

24. Finley PR. Drug interactions with lithium: an update. Clin Pharmacokinet. 2016;55(8):925–41. https://doi.org/10.1007/s40262-016-0370-y

25. Nunes RP. Lithium interactions with non-steroidal anti-inflammatory drugs and diuretics–a review. Arch Clin Psychiatry (São Paulo). 2018;45(2):38–40. https://doi.org/10.1590/0101-60830000000153

26. Couffignal C, Chevillard L, El Balkhi S, Cisternino S, Declèves X. The pharmacokinetics of lithium: In: The science and practice of lithium therapy. Cham, Switzerland: Springer; 2017. pp. 25–53. https://doi.org/10.1007/978-3-319-45923-3_2

27. Mignat C, Unger T. ACE inhibitors. Drug Saf. 1995;12(5):334–47. https://doi.org/10.2165/00002018-199512050-00005

28. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015;11:1061. https://doi.org/10.2147/tcrm.s79135

29. Snowden S, Nelson R. The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardiol Rev. 2011;19(4):184–91. https://doi.org/10.1097/crd.0b013e31821ddcf4

30. Webster J. Interactions of NSAIDs with diuretics and β-blockers. Drugs. 1985;30(1):32–41. https://doi.org/10.2165/00003495-198530010-00004

31. Houston MC. Nonsteroidal anti-inflammatory drugs and antihypertensives. Am J Med. 1991;90(5):S42–7. https://doi.org/10.1016/0002-9343(91)90485-g

32. Polónia J. Interaction of antihypertensive drugs with anti-inflammatory drugs. Cardiology. 1997;88(Suppl. 3):47–51. https://doi.org/10.1159/000177507

33. May M, Schindler C. Clinically and pharmacologically relevant interactions of antidiabetic drugs. Ther Adv Endocrinol Metab. 2016;7(2):69–83. https://doi.org/10.1177/2042018816638050

34. Hammad MA, Tangiisuran B, Kharshid AM, Abdul-Aziz N, Hassan Y, Aziz NA et al. Drug-drug interaction-related uncontrolled glycemia. J Pharm Bioallied Sci. 2017;9(4):221.

35. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293(18):2257–64. https://doi.org/10.1001/jama.293.18.2257

36. Robien K, Oppeneer SJ, Kelly JA, Hamilton-Reeves JM. "Drug-vitamin D interactions: a systematic review of the literature." Nutr Clin Pract. 2013;28(2):194–208. https://doi.org/10.1177/0884533612467824

37. Yang R, Wang LQ, Yuan BC, Liu Y. The pharmacological activities of licorice. Planta Med. 2015;81(18):1654–69. https://doi.org/10.1055/s-0035-1557893

38. Mansoor G.A. Herbs and alternative therapies in the hypertension clinic**.** Am J Hypertens. 2001;14:971–75. https://doi.org/10.1016/s0895-7061(01)02172-0

39. Hukkanen J, Ukkola O, Savolainen MJ. Effects of low-dose liquorice alone or in combination with hydrochlorothiazide on the plasma potassium in healthy volunteers. Blood Press. 2009;18(4):192–5. https://doi.org/10.1080/08037050903072515

40. Maideen NM, Balasubramaniam R. Pharmacologically relevant drug interactions of sulfonylurea antidiabetics with common herbs. J Herbmed Pharmac. 2018;7(3):200–10.

41. Chen XW, S Serag E, B Sneed K, Liang J, Chew H, Pan SY et al. Clinical herbal interactions with conventional drugs: from molecules to maladies. Curr Med Chem. 2011;18(31):4836–50. https://doi.org/10.2174/092986711797535317