

7. BÖLÜM

HİPERTANSİYON TEDAVİSİNDE DİÜRETİKLER

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GİRİŞ

İdrar itrah hızını ve dolayısıyla idrar hacmini artıran ilaçlara diüretik denir. Bu ilaçlar böbreklerde nefronları ve toplayıcı tübüleri etkilemek yoluyla su reabsorbsiyonunu azaltarak idrar oluşumunu artırır; böylece diürez sağlarlar. Diüretiklerin çoğu birincil olarak sodyum iyonunun bazıları da hem sodyum (Na) hem de klorür (Cl) iyonunun böbrek tübüllerinden reabsorbsiyonunu azaltırlar. Diüretiklerin bu etkisine natriürez denir. Ultrafiltratın ozmotik basıncının yaklaşık %90'undan sorumlu olan Na ve Cl geri emilemeyince su ikincil olarak bu iyonlara katılır ve diürez gerçekleşir.

Diüretikler sadece idrar hacmini değil, asıl olarak sodyum iyonunun atılımını artırmak için de kullanılırlar. Bu sayede ekstraselüler sıvı hacmi ve eğer varsa ödem azaltılır (1).

DİÜRETİKLER İLE İLGİLİ TEMEL FİZYOLOJİK KAVRAMLAR

Böbreklerde idrar oluşumunu gerçekleştiren asıl fonksiyonel birim nefron'dur. Bir nefron birbirini izleyen 4 bölümden oluşur: i)Glomerül, ii) Proksimal tübül, iii)Henle kıvrımı iv)Distal tübül. Ek olarak nefronlardan gelen filtratı böbrek pelvisine taşıyan toplayıcı tübüller ve toplatıcı kanallar da bunlardan sonra gelir. İdrar oluşumunda üç temel fizyolojik olay vardır. Bunlar: Glomerüler filtrasyon, Tübüler reabsorbsiyon ve 'Tübüler Sekresyon' dur. Dakikada süzülen sıvı hacmi (Glomerüler Filtrasyon Hızı) yaklaşık olarak 130 ml kadardır. Süzülen sıvının reabsorbe olma oranı %99'dur. Glomerüler filtrasyon hızı sabit kalıp, tübüllerden suyun reabsorbsiyon oranı %99'dan %98'e düşse, oluşan idrarın hacmi iki kat olur. Bu nedenle tübüllerde suyun geri emilimini engelleyen ilaçlar güçlü diüretiklerdir.

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neden olur. Spironolakton ve triamterenden, hamile kadınlarda fetüsün feminizasyon riski nedeniyle kaçınılmalıdır. (Gebelik Kategorisi C). Hamile kadınlarda eplerenon ile yeterli ve iyi kontrollü çalışmalar yoktur. (Gebelik Kategorisi B) Amilorid bir folik asit antagonistidir ve hamilelik sırasında kullanımından kaçınılmalıdır. (68)

KAYNAKLAR

1. Kayaalp, O. *Tıbbi Farmakoloji*. 2000. Diüretik İlaçlar; 635-660. Hacettepe Taş Kitabevi.
2. Brater DC. Diuretic therapy. *N Engl J Med* 1998;339:387-95
3. Kaski JK, Haywood C, Mahida S, et al. *Oxford handbook of drugs in cardiology*. 1st edition. Oxford University Press, Oxford, UK; 2010. p.1-729
4. Freis ED, Reda DJ, Materson BJ. Volume (weight) loss and blood pressure response following thiazide diuretics. *Hypertension* 1988;12:244-50
5. Beermann, B. Groschinsky-Grind, M. Rose'n A. Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol Ther* 1976;19(5 Pt 1):531-7
6. Materson BJ, Oster JR, Michael UF, et al. Dose response to chlorthalidone in patients with mild hypertension. Efficacy of a lower dose. *Clin Pharmacol Ther* 1978;24:192-8
7. Cushman WC, Khatri I, Materson BJ, et al. Treatment of hypertension in the elderly. III. Response of isolated systolic hypertension to various doses of hydrochlorothiazide: results of a Department of Veterans Affairs cooperative study. *Arch Intern Med* 1991;151:1954-60
8. Jounela AJ, Lilja M, Lumme J, et al. Relation between low dose of hydrochlorothiazide, anti-hypertensive effect and adverse effects. *Blood Press* 1994;3:231-5
9. Reilly RF, Ellison DH. Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. *Physiol Rev* 2000;80:277-313
10. Rodan AR, Cheng CJ, Huang CL. Recent advances in distal tubular potassium handling. *Am J Physiol Renal Physiol* 2011;300:F821-7
11. Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. *Hypertension* 2010;56:463-70
11. Zhou MS, Schulman IH, Jaimes EA, Raj L. Thiazide diuretics, endothelial function, and vascular oxidative stress. *J Hypertens* 2008;26:494-500
12. Mironneau J, Savineau JP, Mironneau C. Compared effects of indapamide, hydrochlorothiazide and chlorthalidone on electrical and mechanical activities in vascular smooth muscle. *Eur J Pharmacol* 1981;75:109-13
13. Freis ED, Wanko A, Wilson IM, et al. Chlorothiazide in hypertensive and normotensive patients. *Ann NY Acad Sci* 1958;71:450-5
14. Wilson IM, Freis ED. Relationship between plasma and extracellular fluid volume depletion and the antihypertensive effect of chlorothiazide. *Circulation* 1959;20:1028-36
15. van Brummelen P, Man in 't Veld AJ, Schalekamp MA. Hemodynamic changes during long-term thiazide treatment of essential hypertension in responders and nonresponders. *Clin Pharmacol Ther* 1980;27:328-36
16. Shah S, Khatri I, Freis ED. Mechanism of antihypertensive effect of thiazide diuretics. *Am Heart J* 1978;95:611-18
17. Conway J, Lauwers P, Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration.

- Lancet 2003;362:1527-35
18. Wilson IM, Freis ED. Relationship between plasma and extracellular fluid volume depletion and the antihypertensive effect of chlorothiazide. *Circulation* 1959;20:1028-36
 19. Lake CR, Ziegler MG, Coleman MD, Kopin IJ. Hydrochlorothiazide-induced sympathetic hyperactivity in hypertensive patients. *Clin Pharmacol Ther* 1979;26:428-32
 20. Roos JC, Boer P, Koomans HA, et al. Haemodynamic and hormonal changes during acute and chronic diuretic treatment in essential hypertension. *Eur J Clin Pharmacol* 1981;19:107-12
 21. Vaughan ED Jr, Carey RM, Peach MJ, et al. The renin response to diuretic therapy. A limitation of antihypertensive potential. *Circ Res* 1978;42:376-81
 22. Hughes AD. How do thiazide and thiazide-like diuretics lower blood pressure? *J Renin Angiotensin Aldosterone Syst* 2004;5:155-60
 23. Calder JA, Schachter M, Sever PS. Potassium channel opening properties of thiazide diuretics in isolated guinea pig resistance arteries. *J Cardiovasc Pharmacol* 1994;24:158-64
 24. Pickkers P, Garcha RS, Schachter M, et al. Inhibition of carbonic anhydrase accounts for the direct vascular effects of hydrochlorothiazide. *Hypertension* 1999;33:1043-8
 25. Zhu Z, Zhu S, Liu D, et al. Thiazide-like diuretics attenuate agonist induced vasoconstriction by calcium desensitization linked to Rho kinase. *Hypertension* 2005;45:233-9
 26. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159-219
 27. Welling PG. Pharmacokinetics of the thiazide diuretics. *Biopharm Drug Dispos* 1986;7:501-35
 28. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-92
 29. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med* 2009;361:2153-64
 30. Veterans Administration Cooperative Study Group on antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. *JAMA* 1967;202:1028-34
 31. Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003;362:1527-35
 32. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as firstline agents. A systematic review and meta-analysis. *JAMA* 1997;277:739-45
 33. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665
 34. 2018 ESC/ESH Guidelines for the management of arterial hypertension *European Heart Journal* (2018) 39, 3021–3104
 35. Weber MA, Jamerson K, Bakris GL, et al. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. *Lancet* 2013;381:537-45
 36. Messerli FH, Makani H, Benjo A, et al. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2011;57:590-600
 37. Wing LM, Reid CM, Ryan P, et al.; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for

- hypertension in the elderly. *N Engl J Med* 2003;348:583-92101.
38. Jamerson K, Weber MA, Bakris GL, et al.; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417-28
 39. The Multiple Risk Factor Intervention Trial Research Group. Coronary heart disease death, nonfatal acute myocardial infarction and other clinical outcomes in the multiple risk factor intervention trial. *Am J Cardiol* 1986;58:1-13
 40. Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887-98
 41. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* 2004;43:4-9
 42. Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008;168:207-17
 43. Marre M, Puig JG, Kokot F, et al. Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: the NESTOR Study. *J Hypertens* 2004;22:1613-22
 44. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-41
 45. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis* 2008;52:144-53
 46. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 1998;158:741-51
 47. Mantel-Teeuwisse AK, Kloosterman JM, et al. Drug-Induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Saf* 2001;24:443-56
 48. Hueskes BA, Roovers EA, Mantel-Teeuwisse AK, et al. Use of diuretics and the risk of gouty arthritis: a systematic review. *Semin Arthritis Rheum* 2012;41:879-89
 49. Briet M, Schiffrin EL. Aldosterone: effects on the kidney and cardiovascular system. *Nat Rev Nephrol* 2010;6:261-73
 50. McManus F, McInnes GT, Connell JM. Drug Insight: eplerenone, a mineralocorticoid-receptor antagonist. *Nat Clin Pract Endocrinol Metab* 2008;4:44-52
 51. Teiwes J, Toto RD. Epithelial sodium channel inhibition in cardiovascular disease: a potential role for amiloride. *Am J Hypertens* 2007;20:109-17
 52. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, et al. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Arch Intern Med* 2008;168:1159-64
 53. Colussi G, Catena C, Sechi LA. Spironolactone, eplerenone and the new aldosterone blockers in endocrine and primary hypertension. *J Hypertens* 2013;31:3-15
 54. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003;16:925-30
 55. Burgess ED, Lacourcie' re Y, Ruilope-Urioste LM, et al. Long-term safety and efficacy of the selective aldosterone blocker eplerenone in patients with essential hypertension. *Clin Ther* 2003;25:2388-404
 56. Karagiannis A, Tziomalos K, Papageorgiou A, et al. Spironolactone vs. eplerenone for the

- treatment of idiopathic hyperaldosteronism. *Expert Opin Pharmacother* 2008;9:509-15
57. Parthasarathy HK, Me´nard J, White WB, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens* 2011;29:980-90
 58. Ouzan J, Pe´rault C, Lincoff AM, et al. The role of spironolactone in the treatment of patients with refractory hypertension. *Am J Hypertens* 2002;15:333-9
 59. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003;16:925-30
 60. Lane DA, Shah S, Beevers DG. Low-dose spironolactone in the management of resistant hypertension: a surveillance study. *J Hypertens* 2007;25:891-4
 61. Chapman N, Dobson J, Wilson S, et al.; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007;49:839-45
 62. Burgess ED, Lacourcie`re Y, Ruilope-Urioste LM, et al. Long-term safety and efficacy of the selective aldosterone blocker eplerenone in patients with essential hypertension. *Clin Ther* 2003;25:2388-404
 63. Flack JM, Oparil S, Pratt JH, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. *J Am Coll Cardiol* 2003;41:1148-55
 64. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;1:940-51
 65. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. *Heart Fail Rev* 2005;10:23-9
 66. McManus F, McInnes GT, Connell JM. Drug Insight: eplerenone, a mineralocorticoid-receptor antagonist. *Nat Clin Pract Endocrinol Metab* 2008;4:44-52
 67. Teiwe J, Toto RD. Epithelial sodium channel inhibition in cardiovascular disease: a potential role for amiloride. *Am J Hypertens* 2007;20:109-17

