

# BÖLÜM 14



## KALP YETERSİZLİĞİNDE DİGİTALLER

Tayyar CANKURT<sup>1</sup>

### GİRİŞ

Digitaler(kardiyak glikozitler)digitalis lanata ve digitalis purperiadan üretilen kardiyak ilaçlardır.<sup>1</sup> Digitalis lanata(yüksük otu) zehirli bir bitkidir ve toksik etkileri uzun yıllardan beri bilinmektedir.<sup>2</sup> Aktif glikozit digitoksin; Digitalis purperiadan, digoksin ise Digitalis lanatadan elde edilir.<sup>1</sup> Digoksin günümüzde kullanılan en yaygın preparattır.<sup>3</sup> İki yüzyıldan fazla bir süredir kardiyak glikozitler kalp yetmezliğinde pozitif inotropik ve atriyal fibrilasyonlu hastalarda negatif kronotropik etkileri için kullanılmaktadır.<sup>4</sup>

1970'lerde digoksin toksite insidansı fazlaydı ve artan mortalite ile ilişkiydi. Düşük doz kullanımı, idame dozu, serum digoksin konsantrasyonlarının izlenmesi ve ilaç etkileşimi hakkında daha iyi bilgilerin elde edilmesine bağlı olarak 1980'lerde digoksin toksitesinde azalma oldu.<sup>5,6</sup> İlk defa 1991 yılında Hamlyn ve ark. memelilerde Ouobain adında endojen bir kardiyak glikozid göstermişlerdir. Ouobain böbrek üstü bezlerinden salgılanır. Salgılanması anjiotensinII, vasopressin, ACTH ve katekolominler tarafından kontrol edilir.<sup>7</sup>

### FARMAKOLOJİSİ

Dünyada en çok kullanılan digital preparatı digoksindir. Digoksin intaravenöz ve oral yoldan kullanılır. Digoksinin oral yoldan verilmesinden sonra yaklaşık %70'i emilir.<sup>8</sup> Digoksinin %25'i serum albumine bağlanır. Digoksinin büyük ölçüde kas dokuya bağlanmasından dolayı dağılım hacmi geniştir. Yağ dokuya ise neredeyse

<sup>1</sup> Uzm. Dr., Amasya Üniversitesi S.Ş.E.A.H, Kardiyoloji Bölümü, tayyarcankurt@yahoo.com

ğinde digoksin ventrikül hızı >110 ise batablokörler'e yeterli yanıt alınamazsa 0,25-0,5 mg i.v verilebilir. Digitoksin bu durumlarda digoksine güçlü bir alternatiftir. Ancak yeterli çalışmalar yoktur. Kalp yetmezliğinde serum digoksin düzeyi 0,5-0,8 ng/ml aralığında tutulmalıdır.<sup>38</sup> Kronik kullanımda 0,125-0,25 mg dozunda kullanılan digoksinin özellikle böbrek yetmezliği ve ileri yaş hastalarda kullanımına dikkat edilmelidir.

## KAYNAKLAR

1. Kayaalp, O. (2002), Rasyonel Tedavi Yönünden Tıbbi Farmakoloji (10.bs.). Ankara: Hacettepe-Taş Kitapçılık.
2. Salman Kanji, Robert D Maclean Cardiac glycoside toxicity: more than 200 years and counting Crit Care Clin. 2012 Oct;28(4):527-35. ,10.1016/j.ccc.2012.07.005.
3. Jiri Patočka, Eugenie Nepovimova, Wenda Wu, Digoxin: Pharmacology and toxicology-A review, Environ Toxicol Pharmacol. 2020 Oct;79:103400.,10.1016/j.etap.2020.103400.
4. Withering W. An Account of the Foxglove and some of its Medical Uses With Practical Remarks on Dropsy and Other Diseases: London: G. G. J. and J. Robinson, 1785.
5. Beller GA, Smith TW, Abelman WH, Haber E, Hood WB. Digitalis intoxication: A prospective clinical study with serum level correlations. N Engl J Med 1971;284:990-999.
6. Mahdyoon H, Battilana G, Rosman H, Goldstein S, Gheorghide M. The evolving pattern of digoxin intoxication: Observations at a large urban hospital from 1980 to 1988. Am Heart J 1990;120:1189-1194.
7. Hamlyn, J.M., Blaustein, M.P., Bova, S., DuCharme, D.W., Harris, D.W., Mandel, F., Mathews, W.R., Ludens, J.H. (1991), Identification and characterization of a ouabain-like compound from human plasma. Proceedings of the National Academy of Sciences of the United States of America, 88 (21), 6259-63.
8. Hausner H, Derving Karsbøl J, Holst AG, Jacobsen JB, Wagner FD, Golor G, Anderson TW. Effect of Semaglutide on the Pharmacokinetics of Metformin, Warfarin, Atorvastatin and Digoxin in Healthy Subjects. Clin Pharmacokinet. 2017; 56(11): 1391-1401.
9. Norman R Saunders, Katarzyna M Dziegielewska, Kjeld Møllgård Recent Developments in Understanding Barrier Mechanisms in the Developing Brain: Drugs and Drug Transporters in Pregnancy, Susceptibility or Protection in the Fetal Brain? Annu Rev Pharmacol Toxicol ,2019 Jan 6;59:487-505, 10.1146.
10. Albert CL, Kamdar F, Hanna M. Contemporary Controversies in Digoxin Use in Systolic Heart Failure. Curr Heart Fail Rep. 2016; 13(5): 197-206.
11. Palmer KG, Lebin JA, Cronin MT, Crataegus mexicana (Tejocote) Exposure Associated with Cardiotoxicity and a Falsely Elevated Digoxin Level, J Med Toxicol 2019 Oct;15(4):295-298,10.1007/s13181-019-00727-w.
12. Ochs, H.R., Grube, E., Greenblatt, D.J., Arendt, R., Bodem, G. (1981), Pharmacokinetics and pharmacodynamics of intravenous digoxin and digitoxin, Klinische Wochenschrift, 59 (16) 889-97.
13. Francke, D.E. (2006), Bioavailability of digoxin, The Annals of Pharmacotherapy, 40(6), 1185.
14. 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): 258-267.
15. Oliver J Ziff, Dipak Kotecha ,Digoxin: The good and the bad, Trends Cardiovasc Med. 2016 Oct;26(7):585-95.doi: 10.1016/j.tcm.2016.03.011.
16. Smith TW. Digitalis. Mechanisms of action and clinical use. N Engl J Med 1988;318:358-65.
17. McMahon WS, Holzgrefe HH, Walker JD et al. Cellular basis for improved left ventricular

- pump function after digoxin therapy in experimental left ventricular failure. *J Am Coll Cardiol* 1996;28:495-505.
18. Dobre D, Borer JS, Fox K et al. Heart rate: a prognostic factor and therapeutic target in chronic heart failure. The distinct roles of drugs with heart rate-lowering properties. *Eur J Heart Fail* 2014;16:76-85.
  19. Schoner W, Scheiner-Bobis G. Endogenous and exogenous cardiac glycosides and their mechanisms of action. *Am J Cardiovasc Drugs* 2007;7:173-89.
  20. Slatton M, Irani WN, Hall SA, et al. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? *J Am Coll Cardiol*, 1997;29:1206-1213.
  21. Archer J., Dargan P. *Cardiovascular poisoning Medicine*. 2020;48(3):199-202.
  22. Wang ZQ, Zhang R, Chen MT, Wang QS, Zhang Y, Huang XH, Wang J, Yan JH, Li YG. Digoxin Is Associated With Increased All-cause Mortality in Patients With Atrial Fibrillation Regardless of Concomitant Heart Failure: A Meta-analysis. *J Cardiovasc Pharmacol*. 2015; 66(3): 270-275.
  23. Marck PV, Pierre SV. Na/K-ATPase Signaling and Cardiac Pre/Postconditioning with Cardiotonic Steroids. *Int J Mol Sci*. 2018; 19(8). pii: E2336.; 10.3390/ijms19082336.
  24. Shi L, Sun LD, Odel JG. Colored floaters as a manifestation of digoxin toxicity. *Am J Ophthalmol Case Rep*. 2018; 10: 233-235.
  25. Vyas, A., Bachani, N., Thakur, H., Lokhandwala, Y. (2016), Digitalis toxicity: ECG vignette, *Indian HeartJournal*, 68 (Suppl 2), 223-5.
  26. Satar, S. (2009), *Acilde Klinik Toksikoloji*. Akademisyen Kitabevi. Ankara, Türkiye.
  27. Wright, J.M., Page, R.L., Field, M.E. (2015), *Antiarrhythmic drugs in pregnancy*, *Expert Review of Cardiovascular Therapy*, 13 (12), 1433-44.
  28. Ziff, O.J., Lane, D.A., Samra, M., Griffith, M., Kirchhof, P., Lip, G.Y., Steeds, R.P., Townend, J., Kotecha, D. (2015), *Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data*. *British Medical Journal*, 351, h4451.
  29. Pincus M (2016) *Management of digoxin toxicity*. *Australian Prescribers* 39(1): 18-20.
  30. Teerlink JR SK, Opie LH. *Heart failure In: Opie LH, Gersh BJ. Drugs for the Heart*. 8th ed. Philadelphia. Elsevier Saunders 2013:169-223.
  31. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency. Minimising renal and extrarenal toxicity. *Drug Saf* 1997;16:205-31.
  32. CDC (2016) *Heart Failure Fact Sheet*. Retrieved from.
  33. Lee DC, Johnson RA, Bingham JB, Leahy M, Dinsmore RE, et al. (1982) *Heart Failure in Outpatients A Randomized Trial of Digoxin versus Placebo*. *N Engl J Med* 306(12): 699-705.
  34. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, et al. (1989) *A Comparison of Oral Milrinone, Digoxin, and Their Combination in the Treatment of Patients with Chronic Heart Failure*. *N Engl J Med* 320(11): 677-683.
  35. Ziff OJ, Lane DA, Samra M et al. *Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data*. *Bmj* 2015;351:h4451.
  36. Gheorghide M, Young JB, Uretsky B, on behalf of the PROVED and RADIANCE Investigators. *Predicting clinical deterioration after digoxin withdrawal in heart failure (abstr)*. *Circulation* 1993;88:1-604.
  37. Kotecha D, Piccini JP. *Atrial fibrillation in heart failure: what should we do?* *Eur Heart J* 2015;36:3250-7.
  38. *European Heart Journal* (2021) 42, 35993726 *ESC GUIDELINES 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*, 10.1093.