wjpmr, 2022,8(12), 99-103

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

DIGITALIS THERAPY USED IN CONGESTIVE HEART FAILURE

Monika D. Khichade*[1], Dr. Sameer Shafi[2], Priyanka S. Nilangekar[3], Aishwarya S. Gandhle[4] and Sushil S. Kore[5]

[1,3]Student, Shivlingeshwar College of Pharmacy Almala. Latur, (M. S.) India.
[2]Head of Department (Pharmaceutics) Shivlingeshwar College of Pharmacy, Almala, Tq. Ausa, Dist. Latur [M. S] India.
[4]Student, NIPER Hydrabad.
[5]Student, School of Pharmacy, Dr. Vishwanath Karad MIT WPU Kothrud, Pune, [M.S.] India.

***Corresponding Author: Monika D. Khichade**

Student, Shivlingeshwar College of Pharmacy Almala. Latur, (M. S.) India.

Article Received on 04/10/2022 **Article Revised on 24/10/2022** **Article Accepted on 14/11/2022**

ABSTRACT

Digitalis could be a plant-derived steroid unremarkably employed in the treatment of chronic failure (CHF), cardiac arrhythmia, and reentrant supraventricular tachycardia. Digitalis has positive inotropic impact on the center muscle. associate degree inotrope could be a substance that features a direct impact on contraction Direct inhibition of membrane bound sodium- and potassium-activated nucleoside triphosphatase (Na +/K + -ATPase), that ends up in a rise within the animate thing concentration of metallic element ([Ca 2+]. In this article the most focus on the digoxin, its pharmacology.

KEYWORDS: Cardiac Glycoside, Digitalis, Digoxin, pharmacology.

INTRODUCTION AND HISTORY

Digitalis could be a plant-derived cardiac glucoside normally used in the treatment of chronicheartfailure (CHF), atrialfibrillation, and re-entrant supraventricular arrhythmia.[1,2] digitalin is that the solely offered preparation of digitalis within the u. s. internal organ glycosides area unit found in sure flowering plants, like rose bay and lily-of-the-valley. endemic folks in varied components of the world have used several plant extracts containing internal organ glycosides as arrow and ordeal poisons. the traditional Egyptians used squill (Urginea maritime) as a drugs. The Romans utilized it as a diuretic drug, heart tonic, emetic, and rat poison. Digitalis, or digitalis, was mentioned in the year 1250 in the writings of Welsh physicians. Fuchsius delineated it botanically three hundred years later and namedit finger-root.

William Withering printed his classic account of digitalis and some of its medical uses in 1785, remarking upon his expertise with digitalis. He recognized several of the signs of digitalis toxicity, noting,"The digitalis, once given in terribly giant and quickly perennial doses, occasions illness, vomiting, purging, giddiness, confused vision, objects showing inexperienced or yellow; exaggerated secretion of piddle, slow pulses, as low as thirty five during a minute, cold sweats, convulsions, syncope,death.

During the first twentieth century, as a results of the work of Cushny, Mackenzie, Lewis, and others, the drug was step by step recognized as specific for treatment of cardiac arrhythmia. solely later on was the worth of digitalis for treatment of CHFestablished. internal organ glycosides enhance internal organ ability and slow physical phenomenon through the chamber (AV) junction by increasingvagal tone.[3] steroid toxicity has been acknowledged to result from body process of some plants, as well as yellow rose bay (Thevetia peruviana) and digitalis, and a similar toxidrome has been associated with the use of flavourer dietary supplements that contain internal organ glycosides. digitalin is among the prime fifty prescribed medication in the United States.[4] In 2011, the yankee Association of Poison management Centers reportable 1601 single exposures to steroid medication.[5] internal organ glycosides account for two.6% of harmful plant exposures within the us.[6,7] Most of those exposures area unit in kids. Digoxin-specific fragment antigen-binding (Fab) protein fragments have contributed considerably to the improved morbidity and mortality of harmful patients since their approval in 1986 by the North American nation Food and Drug Administration (FDA)

Action of Steroid

Inotropic result

The inotropic effects are documented within the isolated papillose muscles and within the traditional hearts of

animals and humans. The inotropic action happens in each ventricles and in each atria. within the traditional heart and in those with artery malady and traditional left cavum (LV) beat operate, with digitalis the fifty-five operate curve is captive upward and to the left.[8] As a result, fifty-five end-diastolic pressure and fifty-five end-diastolic and end-systolic volumes square measure reduced, and there's a rise of fifty-five ejection fraction (LVEF).[8]

Patients With cardiopathy

In patients with cardiopathy (HF), digitalin slows the cavum rate (1) in sinus rhythm attributable to associate degree improvement in HF and withdrawal of sympathetic stimulation and (2) in cardiac arrhythmia by increasing parasympathetic tone. the mix of digitalin and beta-adrenergic blocking agent is superior to digitalin or beta-adrenergic blocking agent alone.[9]

Peripheral Vessels

In traditional subjects
given endovenous ouabain, there's blood vessel and blood vessel vasocontriction.[10] The constriction is obviated by administering digitalin slowly over a amount of fifteen to twenty minutes1; what is more, the constriction lasts up to half-hour.[8]

Coronary Circulation

The impact of blood vessel digitalis glycoside on the coronary vasculature is analogous to those delineated on top of. The constriction will turn out transient heart muscle ischaemia in those with severely stopped arteria sickness. These effects area unit prevented by administering blood vessel digitalis glycoside slowly over a amount of quarter-hour.[8]

Baroreflexes

Digitalis normalizes the dull baroreflex mechanisms gift in HF.[11] Digitalis produces a fast and profound alteration of sympathetic nerve activity before the hemodynamic effects area unit observed; that's, there is also dissociation between the system and hemodynamic effects.[11]

Neurohormonal

In HF, digitalis medical care has been shown to scale back plasma catecholamine levels, liquid body substance mineralocorticoid, and plasma protease activity, that has been repeatedly documented.[8]

Diuretic

Digoxin induces symptom in patients with HF United Nations agency have fluid retention.[8] The mechanism (s) area unit multiple[8] (1) dilatation and enhanced CO improves excretory organ hemodynamics; (2) inhibition of hollow resorption of Na, of excretory organ Na+ -K+-ATPase, and of concentrating and diluting ability; and (3) enhanced secretion of chamber symptom amide.

Pathophysiology

Digoxin and alternative internal organ glycosides cause direct constriction in the blood vessel and blood vessel system in tube-shaped structure sleek muscle. The positive inotropic impact ofdigitalis has the subsequent two parts.

Direct inhibition of membrane-bound sodium- and potassium-activated nucleoside triphosphatase (Na +/K + -ATPase), that results in a rise within the animate thing concentration of metal ([Ca 2+]i). Associated increase in a slow inward metal current (iCa) throughout the impulse (AP); this current is that the results of movement of metal into the cell, and it contributes to the highland of the AP.

Digitalis glycosides bind specifically to Na+/K+ -ATPase, inhibit its catalyst activity, and impair transport of extruding Na and transport of metal into the fibers (3:2 ratio). As a result, animate thing Na ([Na+]i) bit by bit will increase, and a gradual, little decrease in animate thing metal ([K+]i) happens. internal organ fiber metal [Ca2+]i is changed for animate thing Na (3:1 ratio) by a transport system that is driven by the concentration gradient for these ions and therefore the transmembrane potential. Increase in [Na+]i is said crucially to the positive inotropic impact of digitalis.[12,13,14,15,16]

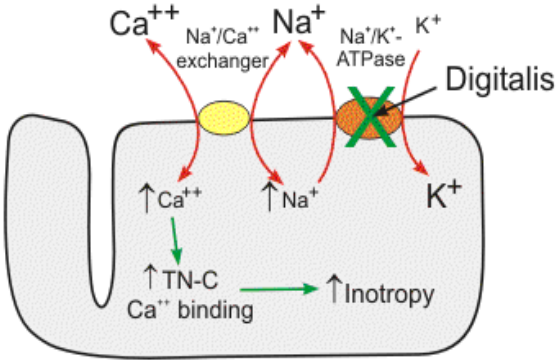

Fig. 1: pathophysiology of cardiac glycoside.

In addition, by a mechanism that's not outlined clearly, the rise in [Ca2+]i will increase the height magnitude of iCa; this modification parallels the positive inotropic action. The amendment in iCa could be a consequence of the rise in [Ca2+]i and not of the increase in [Na+]i. Thus, additional metal is delivered throughout the highland of every AP to activate every contraction. A fall in animate thing pH scale accompanies the digoxin-induced increase in [Ca2+] i, that results in activation of a sodium/hydrogen exchange pump. This results in extrusion of atomic number 1, associate increase in [Na+]i, and bigger inotropy. The mechanism represented assumes that Na+/K+ -ATPase is the medical specialty receptor for digitalis which once digitalis binds to those enzymes, it induces a conformational amendment that decreases transport of Na. Digitalis apparently binds to ATPase in an exceedingly specific and saturable manner,

manufacturing a conformational amendment of the catalyst such that thebinding web site for digitalis most likely is on the external surface of the membrane. what is more, the magnitude of the inotropic impact of digitalis is proportional to degree of inhibition of the catalyst.

Digitalis, in therapeutic concentrations, exerts no effect on the contractile proteins or on the interactions between them.

Electrophysiologic Effects

The electrophysiological effects of viscus glycosides embrace the subsequent.[12] shrunken resting potential (RP) or greatest pulse potential (MDP), that slows the rate of phase-0 depolarisation and physical phenomenon speed.

Decrease in action potential period (APD), which ends in exaggerated responsiveness of fibers to electrical stimuli. Enhancement of automaticity, that results from a rise within the rate of section four depolarisation and from delayed after-depolarization. In general, viscus glycosides slow physical phenomenon and increase the refractory amount in specialised viscus conducting tissue by stimulating cranial nerve tone. Digitalis has parasympathetic properties, that embrace hypersensitization of artery sinus baroreceptors and stimulation of central cranial nerve nuclei. digitalis glycoside additionally seems to own variable effects on sympathetic tone, counting on the precise viscus tissue concerned.

Pharmacology of Digitalis Glycoside

Digoxin is composed of a sugar (glycone) and a cardenolide (aglycone) moieties; its chemical formula is C41H64O14, and its relative molecular mass is 780.95 prosecuting attorney (Figure 2)[17] digitalis glycoside is sold-out underneath the brand digitalis glycoside and is taken into account one amongst the high poisons within the world due to: i) Wide accessibility, and, ii) slim therapeutic window.[17]

Pharmacokinetics of Digitalis Glycoside

The bioavailability of digitalis glycoside varies relying on the dose. In tablets kind, the bioavailability ranges from hr to 80%; a price of seventieth is typically used because the normal. Whilst softgelatin digitalis glycoside capsules seem to urge utterly absorbed (bioavailability =100%) and digitalis glycoside elixir exhibits a bioavailability of close to eightieth[18] once digitalis glycoside is given intravenously, it's known to own a bioavailability of 100 percent.

Medications like clarithromycin, antibiotic drug, and antimycotic will raise the bioavailability of digitalis glycoside whereas product like charcoal, cholestyramine, and St. John's wort will cut back the bioavailability of digitalis glycoside. supported the best body weight the average volume of digitalis glycoside distribution is concerning seven.3 l/kg.[18] thus, digitalis glycoside is distributed wide throughout the body. tho' digitalis glycoside is water-insoluble, Na+/K+-ATPase pumps ar placed in all tissues and digitalis glycoside binds to those pumps, accounting for its wide distribution throughout the body's tissues.[19] This feature is crucial within the treatment of digitalis glycoside toxicity with digitalis glycoside immune fabulous as the drug distributed in the tissue compartments can re-equilibrate following initial protein fragment treatment. Equations are obtainable for a lot of patient-specific calculations of digoxin's volume of distribution that contemplate patient weight and creatinine clearance. Besides, some alternative factors might amendment its volume of distribution; antiarrhythmic medication and gland disease cut back volume, whereas glandular disorder will increase volume.[18] digitalis glycoside distributes slowly following 2 compartment model, and complete distribution usually takes close to 3-4 hours. Since the center responds as half of the second compartment, therapeutic effects ar delayed till the distribution is complete. The clearance of digitalis glycoside involves each metabolic and urinary organ clearance from the body. close to 10-30% of the population, metabolic elimination partly takes place as a results of theconversion of digitalis glycoside to digitalis glycoside reduction product by moneron lentum in the gut.[20]

Another element of digitalis glycoside metabolism is postulated to occur as a result of of viscus conversion to 3-keto-digoxigenin and 3-epidigoxigenin metabolites, followed by conjugation.[21] Moreover, digitalis glycoside is metabolized within the abdomen by internal organ acid, that removes digitoxose sugars to kind deglycosylated congeners. These sugars ar hydrolyzed, and therefore the ensuing product ar change and endure epimerization through viscus uridine diphosphoglucose-glucuronosyltransferase, followed by conjugation.[22,23] Overall, the metabolic clearance of digitalis glycoside averages close to zero.8 ml/kg/min. The urinary organ clearance of digitalis glycoside is usually equivalent to creatinine clearance. In patients with heart failure, each the metabolic and urinary organ elements of digitalis glycoside clearance decrease; but, the metabolic element decreases a lot of dramatically. The clearance of digitalis glycoside is conjointly reduced in patients with gland disease and in drug interactions with antiarrhythmic, quinidine, and Isoptin. instead, Overall, the metabolic clearance of digitalis glycoside averages close to zero.8 ml/kg/min. The urinary organ clearance of digitalis glycoside is usually equivalent to creatinine clearance. In patients with heart failure, each the metabolic and urinary organ elements of digitalis glycoside clearance decrease; but, the metabolic element decreases a lot of dramatically. The clearance of digitalis glycoside is conjointly reduced in patients with gland disease and in drug interactions with antiarrhythmic, quinidine, and Isoptin. instead, clinical glandular disorder might increase digitalis glycoside clearance[18] In patients with traditional urinary organ perform, the t1/2 of

digitalis glycoside ranges 36-48 hours. In those with insufficiency, the t1/2 will increase to six days[18,21] This has obvious implications for the temporal arrangement of blood {serum|liquid body substance|bodily fluid|body fluid|humor|humour} sampling for activity of serum digitalis glycoside levels as mentioned any within the following section.

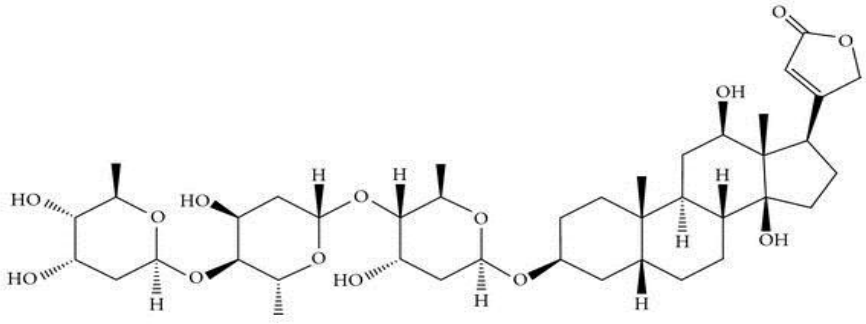

Fig. 2: Chemical structure of digoxin.

Drug Interactions

Potassium-depleting diuretics ar a major causative issue to digitalis toxicity. Calcium, notably if administered apace by the endovenous route, could turn out serious arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, NSAID, antimycotic agent, alprazolam, and corticosteroid raise the liquid body substance Lanoxin concentration thanks to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication could result. Erythrocin and clarithromycin (and probably alternative macrolide antibiotics) and antibacterial drug could increase Lanoxin absorption in patients UN agency inactivate Lanoxin by microorganism metabolism within the lower bowel, in order that digitalis intoxication could result Propantheline and diphenoxylate, by decreasing gut motility, could increase Lanoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, sure metastatic tumor medicine, and metoclopramide could interfere with enteric Lanoxin absorption, leading to unexpectedly low liquid body substance concentrations. bactericide could decrease liquid body substance Lanoxin concentration, particularly in patients with urinary organ pathology, by increasing the non-renal clearance of Lanoxin. There are inconsistent reports relating to the results of alternative medicine [e.g., quinine, penicillamine] on liquid body substance Lanoxin concentration. Thyroid administration to a digitalized, hypothyroid patient could increase the dose demand of Lanoxin. Concomitant use of Lanoxin and sympathomimetics will increase the danger of internal organ arrhythmias. muscle relaxant could cause a unforeseen extrusion of metallic element from muscle cells, and should thereby cause arrhythmias in digitalized patients. though atomic number 20 channel blockers and Lanoxin could also be useful in combination to management chamber fibrillation, their additive effects on Av node conductivity will end in advanced or complete heart block. each digitalis glycosides and beta-blockers slow chamber conductivity and reduce pulse. Concomitant use will increase the danger of cardiac arrhythmia. Lanoxin concentrations ar inflated by concer ning 15 August 1945 once Lanoxin and beta blocker ar administered concomitantly.

Therefore, inflated observation of Lanoxin is suggested once initiating, adjusting, or discontinuing carvedilo.[24,25,26,27]

Contraindication

Digitalis glycosides area unit contraindicated in patients with chamber fibrillation or in patients with a well-known hypersensitivity to digitalis.

A hypersensitivity to different digitalis preparations sometimes constitutes reason to digitalis.

CONCLUSIONS

Digoxin evidently counteracts the hypertensive effect of ouabain. Hence, the result of the actions of the different endogenous cardiotonic steroids seems to be a cooperative effect in handling salt and water homeostasis. Because ouabain and digoxin are bothinhibitors of the sodium pump, the hitherto used rationale of digoxin therapy becomes muddled. How can this paradoxical physiological action of ouabain and digoxin be explained on a molecular level? Is there a different tissue distribution of the different cardiac glycosides, a difference in their affinities at the various pump isoforms, differences in the signal transduction pathway are there other receptors for cardiac glycosides besides the pump

ACKNOWLEDGMENT

The author hearty thankful for all supporting staff, department pharmacology for support and guide.

REFERENCES

1. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management ofcardiovascular disorders. Circulation., 2006 May 30; 113(21): 2556-64
2. Ali KM. Collateral effects of antiarrhythmics in pediatric age. Curr Pharm Des., 2008; 14(8): 782-7.
3. Ahmed A, Waagstein F, Pitt B, et al. Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group trial. Am J Cardiol, 2009 Jan 1; 103(1): 82-7.
4. Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC. 2011 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. Clin Toxicol (Phila)., 2012 Dec; 50(10): 911-1164.
5. Litovitz TL, Klein-Schwartz W, White S, Cobaugh DJ, Youniss J, Drab A, et al. 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med., 2000 Sep; 18(5): 517-74.
6. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. Clin Toxicol (Phila)., 2009 Dec; 47(10): 911-1084.
7. Eisner DA, Kashimura T, Venetucci LA, Trafford AW. From the ryanodine receptor to cardiac arrhythmias. Circ J., 2009 Sep; 73(9): 1561-7.
8. Rahimtoola SH, Tak T. The use of digitalis in heart failure. Curr Probl Cardiol. 1996; *21*: 781–756
9. Khand AU, Rankin AC, Martin W, et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure**.** J Am Coll Cardiol. 2003; *42*: 1944–1951.
10. Mason DT, Braunwald E. Studies on digitalis: effects of ouabain on systemic vascular resistance and venous tone in normal subjects and in patients in heart failure. J Clin Invest. 1964; *43*: 532–543.
11. Gheorghiade M, Ferguson D. Digoxin: a neurohumoral modulator in heart failure? Circulation. 1991; *84*: 2181–2186.
12. Koren G, Parker R. Interpretation of excessive serum concentrations of digoxin in children. Am J Cardiol. 1985 Apr 15; 55(9): 1210-4.
13. Cepeda Piorno J, Pobes Martínez de Salinas A, González García ME, Fernández Rodríguez E. [Use of MDRD equation to detect occult renal failure and reduce the risk of digitalis overdose]. Nefrologia., 2009; 29(2): 150-5.
14. Thacker D, Sharma J. Digoxin toxicity. Clin Pediatr (Phila)., 2007 Apr; 46(3): 276-9.
15. Chan AL, Wang MT, Su CY, Tsai FH. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: a population-based study. Eur J Clin Pharmacol., 2009 Dec; 65(12): 1237-43.
16. Mahdyoon H, Battilana G, Rosman H, Goldstein S, Gheorghiade M. The evolving pattern of digoxin intoxication: observations at a large urban hospital from 1980 to 1988. Am Heart J., 1990 Nov; 120(5): 1189-94.
17. Rocco TP, Fang JC, Roden DM. Cardiac glycosides. In L. L. Brunton, J. S. Lazo & K. L. Parker KL (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics (11th ed). New York: McGraw-Hill, 2006; 886-889: 921-923.
18. Winter ME. Digoxin. In M. E. Winter, ME. (Ed.), Basicclinicalpharmacokinetic (4thed.). Baltimore: Lippincott Williams & Wilkins, 2004; 183-221.
19. Clausen T. The Na+, K+ pump in skeletal muscle: quantification, regulation and functional significance. Acta Physiologica Scandinavica, 2014; 156: 227-235.
20. Hirata S, Izumi S, Furukubo T, et al. Interactions between clarithromycin and digoxin in patients with end-stage renal disease. International Journal of Clinical Pharmacology and Therapeutics, 2016; 43: 30-36.
21. Mutnick AH. Digoxin. In G. E. Schumacher (Ed.), Therapeutic drug monitoring (469–491). Norwalk: Appleton & Lange, 1995.
22. Gault MH, Charles JD, Sugden DI, et al. Hydrolysis of digoxin by acid. Journal of Pharmacy and Pharmacology, 2011; 29: 27-32.
23. Gault MH, Karla J, Ahmed M, et al. Influence of gastric pH on digoxin biotransformation. I. Intragastric hydrolysis. Clinical Pharmacology and Therapeutics, 2012; 27: 16-21.
24. Antman EM, Wenger TL, Butler VP Jr, et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: final report of a multicenter study. Circulation., 1990; 81:
25. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med., 2002; 347: 1403–1411.
26. Eichhorn EJ, Gheorghiade M. Digoxin: new perspective on an old drug. N Engl J Med., 2002; 347: 1394–1395.
27. Rich MW, McSherry F, Williford WO et al. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. J Am Coll Cardiol., 2001; 38: 806–813.