WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review on Digoxin, Digoxin Toxicity and Management of Digoxin

Chandan Kumar[1], Dr. Kaushal Kishore Chandrul[2]

[1]Student of B.PHARMA 4th Year,.[2]Principle
Department Of Pharmacy
Mewar University,Chittorgarh, India

ABSTRACT

The principle focal point of this survey article was to talk about digoxin, reasons for digoxin poisonousness, the board of digoxin harmfulness in patients, and how it very well may be dealt with. Digoxin has a place with a class of medications known as heart glycosides. Digoxin originates from foxglove leaves. In spite of the fact that found in 1785, digoxin had been being used for over 2000 years back. Patients experiencing cardiovascular breakdown and taking digoxin need to take diuretics to dry out abundance water from their bodies. Diuretics upgrade potassium misfortune, and resultant potassium levels increment the danger of digitalis harmfulness. Patients should be persistently checked by clinicians for any signs or side effects of digoxin poisonousness as they utilize the accessible preventive measures. A portion of these measures are: surveying electrolytes, estimating digoxin serum fixations, assessing pharmacotherapy medicines for any conceivable medication communications, and deciding digoxin treatment putting together it with respect to pharmacokinetic boundaries. In case of digoxin poisonousness event, the clinical state of the patient ought to be evaluated so as to execute treatment. On the off chance that suitable consideration is taken, digoxin treatment can be sheltered, successful, and savvy. At long last, digoxin harmfulness can be dealt with utilizing actuated charcoal, which brings down poisonousness levels in patients from 30% to 40% inside 12-18 hours. Explicit digoxin counter acting agent parts (digoxin invulnerable Fab) can be utilized in the treatment of hazardous digoxin poisonousness. The sections accessible in the market are DigiFab and Digi Bind, which begin from ovine, assembled and cleaned from sheep, vaccinated with human egg whites and joined with digoxin. These digoxin particles consolidate with immunizer sections to keep them from joining with their receptors.

Keywords:Pharmacology and pharmacokinetics of digoxin, Mechanism of action, Drug interaction, Risk factors of digoxin, Management of digoxin toxicity and summary.

Introduction

Digoxin originates from foxgloves leaves , presented in 1785.Digoxin goes under the classification of cardiovascular glycosides ,implies it is cardinolide that is 5 memberd lactone ring with one twofold bond present at C17 position .We can use digoxin in CHF(Congestive heart failure),Arterial fibrillation, Blood vessel vacillate, Supra ventricular tachycardia and cardiovascular arrhythemia[1].Digoxin is one of the oldest cardiac medications still in use. Both the current Canadian guidelines for heart failure and atrial fibrillation and the American College of Cardiology Foundation–American Heart Association guideline for the management of heart failure include digoxin as a treatment option[2-4].

Pharmacology and pharmacokinetics of digoxin

Digoxin is composed of a sugar (glycone) and a cardenolide (aglycone) moieties; its molecular formula is $C_{41}H_{64}O_{14}$, and its molecular weight is 780.95 Da (Figure 1). Digoxin is sold under the brand name Lanoxin and is considered one of the top poisons in the world due to: i) Wide availability, and, ii) Narrow therapeutic window [5].

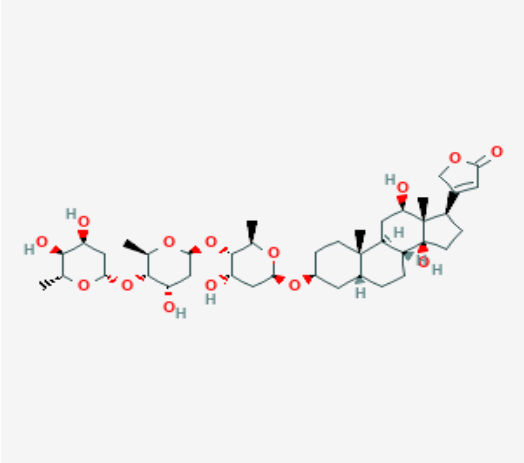

Fig 1: chemical structure of digoxin[5].

The bioavailability of digoxin varies depending on the dose.In tablets form, the bioavailability ranges from 60% to 80%;a value of 70% is often used as the standard. Whilst soft-gelatin digoxin capsules appear to get completely absorbed (bioavailability=100%) and digoxin elixir exhibits a bioavailability of approximately 80%.When digoxin is given intravenously, it is known to have a bioavailability of 100%.Based on the ideal body weight,the average volume of digoxin distribution is about 7.3 l/kg[6].Therefore, digoxin is distributed widely throughout the body. Though digoxin is water-insoluble, Na^+/K^+-ATPase pumps are located in all tissues and digoxin binds to these pumps, accounting for its wide distribution throughout the body's tissues[7].Equations are also available for more patient-specific calculations of digoxin's volume of distribution that consider patient weight and creatinine clearance.In addition, other factors may alter its volume of distribution: quinidine and hypothyroidism decrease volume, and hyperthyroidism increases volume.Digoxin distributes relatively slowly, following a two-compartment model. Complete distribution generally takes at least three to four hours. Since the heart responds as part of the second compartment, therapeutic effects are delayed until distribution is complete[8].The clearance of digoxin involves both metabolic and renal clearance from the body. In about 10% to 30% of the population, metabolic elimination partially occurs as a result of digoxin conversion by Eubacteriumlentum in the gut to digoxin-reduction products[9].Another component of digoxin metabolism is postulated to occur because of hepatic conversion to 3-keto-digoxigenin and 3-epidigoxigenin metabolites, followed by conjugation[10].Additionally, digoxin is metabolized in the stomach by gastric acid, which removes digitoxose sugars to form deglycosylated congeners. These sugars are hydrolyzed, and the resulting products are oxidized and undergo epimerization through hepatic uridine diphosphoglucose-glucuronosyltransferase, followed by conjugation[11,12].

Renal clearance of digoxin is generally equivalent to creatinine clearance. In patients with heart failure, both the metabolic and renal components of digoxin clearance decrease, but the metabolic component decreases more dramatically. Clearance of digoxin is also decreased in patients with hypothyroidism and in drug interactions with amiodarone, quinidine, and verapamil. Alternatively, clinical hyperthyroidism may increase digoxin clearance[13].In patients with normal renal function, the half-life of digoxin ranges from 36 to 48 hours. In those with renal insufficiency, the half-life can increase to six days[8,10].

- **Digoxin Mechanisms of action**

Digoxin's primary mechanism of action is through inhibition of sodium-potassium adenosine triphosphatase (ATPase). Its role in heart failure patients is based on its inotropic properties, due to inhibition of sodium-potassium ATPase which leads to increased intracellular calcium concentrations through the sodium-calcium exchanger [14,15]. This causes the cardiac action potential to lengthen which causes lower heart rates as well as increases myocardial contractility due to the increased calcium for sarcomeric excitation-contraction coupling[15]. Digoxin also has neurohormonal effects and causes improved baroreceptor sensitivity, decreases norepinephrine concentration, and decreases activation of the renin-angiotensin system[14,16,17].The increase in the force of cardiac contraction is attributed to digoxin's binding to the Na^+/K^+-ATPase pump.By binding to the K^+-binding site of the pump, digoxin leads to inhibition of the pump.The consequent rise in Na^+ concentration causes

slowing of Ca^{+2} efflux via the Na^{+}/Ca^{+2} exchanger and a relative increase in intracellular Ca^{+2}.The extra Ca^{+2} increases the action potential of cardiac cells with more activation of the contractile machinery[18].

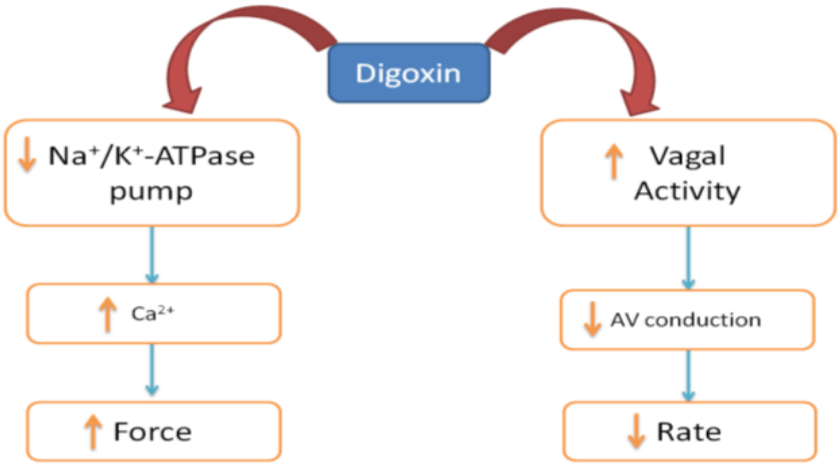

Fig 2: Mechanisms of action of digoxin.

Digoxin Drug Interactions

Digoxin is known to interact with a wide variety of medications (table 1). One mechanism of drug interaction with digoxin is change in absorption due to increased contact time in the small intestine.This can occur with concomitant use of anticholinergic agents, e.g., atropine, diphenhydramine, phenothiazines, scopolamine, and benztropine, which slow gastrointestinal motility[19].Two other mechanisms believed to account for many drug interactions with digoxin are the inhibition of P-glycoprotein, located in the brush borders of the proximal tubule, and inhibition of digoxin metabolism, secondary to a lack of *Eubacteriumlentum* in the gastrointestinal tract[9].The antibiotics clarithromycin, erythromycin, and tetracycline alter the flora of the gut, leading to decreased digoxin metabolism and consequent increases in digoxin levels. The antiarrhythmics quinidine, amiodarone, and verapamil inhibit P-glycoprotein in the kidney, resulting in decreased renal clearance of digoxin[9,19].

Table 1

Potential Interactions with Digoxin

Increase Serum Levels	
Amiodarone	Propafenone
Benzodiazepines	Propantheline
Bepridil	Quinidine
Cyclosporine	Quinine
Diphenoxylate	Spironolactone
Indomethacin	Tetracyclines
Itraconazole	Verapamil
Macrolides	
Decrease Serum Levels	
Oral aminoglycosides	Metoclopramide
Al^{+++}/Mg^{++}-containing antacids	Neomycin
Antineoplastics	Penicillamine
Activated charcoal	Rifampin
Cholestyramine	St. John's wort
Colestipol	Sulfasalazine
Kaolin/pectin	
Enhance Pharmacodynamic Effects	
Beta-blockers	Succinylcholine
Calcium	Sympathomimetics
Verapamil	Diuretics
Diltiazem	
Antagonize Pharmacodynamic Effects	
Thyroid hormones	

Adapted from reference 42.

Digoxin can lead to life-threatening hyperkalemia. This potential adverse effect of digoxin could cause interactions with medications that also affect potassium homeostasis, such as ACE inhibitors, angiotensin receptor–blocking drugs, spironolactone, eplerenone, and potassium supplements.Both pharmacokinetic and pharmacodynamic mechanisms should be noted regarding digoxin drug interactions[19].

Risk factors of digoxin toxicity

Patients at highest risk of digoxin toxicity include those with kidney failure, heart failure, and dehydration[19].Hypoxia secondary to chronic pulmonary disease, hypokalemia, hypomagnesemia, and hypercalcemia are also indicated to increase the risk of developing arrhythmias induced by digoxin[5,20]. The mechanism for the increase in digoxin toxicity risk secondary to hypokalemia derives from the fact that when K+ is low, more K+ -binding sites are open for digoxin binding, increasing the effective concentration of digoxin within the heart[21].

Management of digoxin toxicity

Activated charcoal (AC) can be utilized in the treatment of digoxin harmfulness and can prompt a 30-40% drop in digoxin levels inside 12-18 hours.Unlike the utilization of digoxin antibodies, the drop-in digoxin levels delivered by initiated charcoal doesn't totally turn around the remedial impacts of digoxin in patients with cardiovascular sickness [22].This may be a beneficial strategy in patients whose digoxin concentrations do not significantly exceed those in the therapeutic range and who could benefit from conservative medical care[22].Digoxin-specific antibody fragments, or digoxin immune Fab, was introduced in the 1970s and is indicated for the treatment of life-threatening or potentially life-threatening digoxin toxicity or overdose[23,24].The two products currently available in the U.S.A. are DigiBind and DigiFab. They are ovine in origin, collected and purified from sheep and immunized using human albumin conjugated with digoxin. Digoxin molecules bind to the antibody-fragments, making them unavailable for binding to their receptors. The digoxin-antibody complexes are then renally eliminated[25].For both brands of digoxin immune Fab, one vial of the product will bind approximately 0.5 mg of digoxin. Therefore, the dose of digoxin immune Fab is based on the amount of excess digoxin believed to be present in the patient. In some cases, this amount is known, such as in the cases of suicide attempts with deliberate overdoses or unintentional ingestion by a child. However, in cases of chronic ingestion, this may be more difficult to ascertain, especially as the toxicity may have developed over time with changes in renal function.

The clinical conditions indicating the need for these products as defined in their package inserts include the following: acute ingestion of greater than 10 mg of digoxin in adults or 4 mg of digoxin in children, acute ingestion of digoxin leading to a serum level of more than 10 ng/mL, chronic ingestion of digoxin leading to a serum level higher than 6 ng/mL in adults or 4 ng/mL in children, or manifestations of life-threatening digoxin toxicity, such as severe ventricular arrhythmias, progressive bradycardia, second- or third-degree heart block not responsive to atropine, or serum potassium levels exceeding 5 mEq/L in adults or 6 mEq/L in children with rapidly progressive signs and symptoms of digoxin toxicity[24].Digibind has also been suggested and used in the treatment of poisoning with oleander, bufadienolide-containing aphrodisiacs, digitoxin, and foxglove extract[26].

An understanding of both digoxin and digoxin-immune Fab pharmacokinetics is crucial to developing a therapeutic dosing regimen. The volume of distribution for digoxin immune Fab is approximately 0.35 L/kg, indicating penetration into the extracellular space[24].The volume of distribution for digoxin immune Fab is approximately 0.35 L/kg, indicating penetration into the extracellular space[24].However, this volume is much smaller than that of digoxin, signifying that shifts from deeper tissue stores of digoxin may occur as the antibody complexes with digoxin in the central circulation as well as more accessible tissue stores[23].The costs associated with digoxin toxicity should be considered. It has been shown that the mean overall cost associated with digoxin toxicity is approximately $4,000 per episode.This cost may be somewhat variable with the use of digoxin immune Fab, especially in the treatment of patients with renal dysfunction and a serum digoxin concentration of 2.3 ng/mL or higher. In such cases, the use of digoxin immune Fab can result in a reduction in length of stay and overall lower treatment costs[27].The benefit of using this product in such patients should be weighed against the risks, and as a safety measure, treatment for anaphylaxis should be readily available[24].

Summary

Digoxin poisonousness can happen because of numerous circumstances, including drug cooperations, electrolyte unsettling influences, changes in renal capacity, intense ingestion of a lot of digoxin, or incessant ingestion of dosages bigger than should be expected for restorative impacts. Doctors should screen patients for the indications of digoxin harmfulness while using preventive measures. Such preventive measures ought to incorporate fitting digoxin serum fixation estimations, assessment of pharmacotherapy regimens for potential medication communications, evaluation of electrolytes, and digoxin routine assurance dependent on pharmacokinetic boundaries. In the event that digoxin poisonousness happens, treatment ought to be executed dependent on the patient's clinical condition. With suitable consideration, digoxin can be an adequate, safe, and cost-effective treatment.

REFERENCES

1.C.K. Kokate ,A.P. Purohit, S.B. Gokhale, Niraliprakashan advancement of knowledge, 55th Edition ,Page no.9.35-9.38

2. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012;28(2):125–36. Erratum in: *Can J Cardiol*2012:28(3)396.

3. Malcom J, Arnold O, Howlett JG, Ducharme A, Ezekowitz JA, Gardner M, et al. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure—2008 update: best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. Can J Cardiol. 2008;24(1):21–40.

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–327. Epub 2013 Jun 5.

5. 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.

6. Winter ME. Digoxin. In M. E. Winter, ME. (Ed.), Basic clinical pharmacokinetics (4th ed.). Baltimore:Lippincott Williams & Wilkins, 2004, 183-221.

7. Clausen T. The Na+, K+ pump in skeletal muscle:quantification, regulation and functional significance.ActaPhysiologicaScandinavica. 2014; 156:227-235.

8. Winter ME. Digoxin. In: Winter ME. *Basic Clinical Pharmacokinetics*. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2004:183-221.

9. Hirata S, Izumi S, Furukubo T, et al. Interactions between clarithromycin and digoxin in patients with end-stage renal disease. *Int J ClinPharmacolTher*. 2005;43:30-36.

10.Mutnick AH. Digoxin. In: Schumacher GE, ed. *Therapeutic Drug Monitoring*. Norwalk: Appleton & Lange; 1995:469-491.

11. Gault MH, Charles JD, Sugden DI, et al. Hydrolysis of digoxin by acid. *J Pharm Pharmacol*. 1980;29:27-32.

12. Gault MH, Karla J, Ahmed M, et al. Influence of gastric pH on digoxin biotransformation. I. Intragastric hydrolysis. *ClinPharmacolTher*. 1980;27:16-21.

13. Winter ME. Digoxin. In: Winter ME. *Basic Clinical Pharmacokinetics*. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2004:183-221.

14. Maury P, Rollin A, Galinier M, Juilliére Y. Role of digoxin in controlling the ventricular rate during atrial fibrillation: a systematic review and rethinking. Research Reports in Clinical Cardiology. 2014;5:93–101.

15. Chaggar PS, Shaw SM, Williams SG. Is foxglove effective in heart failure? CardiovascTher. 2015;33:236–241.

16. Eichhorn EJ, Gheorghiade M. Digoxin. Prog Cardiovasc Dis. 2002;44:251–266.

17. Stucky MA, Goldberger ZD. Digoxin: its role in contemporary medicine. Postgrad Med J. 2015;91:514–518.

18. Rang HP, Dale MM, Ritter JM, Gardner P.Pharmacology. New York: Churchill Livingstone,2006.

19.Prybys KM. Deadly drug interactions in emergency medicine. *Emerg Med Clin North Am*. 2004;22:845-863.

20. Parker RB, Patterson JH, Johnson JA. Heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:219-260.

21.Rang HP, Dale MM, Ritter JM, Gardner P. *Pharmacology*. New York: Churchill Livingstone; 1995:283-284.

22. Fee WH. Activated charcoal safe and effective for digoxin toxicity [letter]. American Journal of Medicine. 200 8; 116 :430.

23. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev*. 2004;23:135-143.

24. Facts & Comparisons 4.0. DigoxinimmuneFab.Availableat:online.factsandcomparisons.com. Accessed December 12, 2005.

25. Facts & Comparisons 4.0. (n.d.). Digoxin immune Fab. Retrieved December 12, 2005, from online.factsandcomparisons.com

26. Jortani SA, Valdes R Jr. Digoxin and its related endogenous factors. *Crit Rev Clin Lab Sci*. 1997; 34:225-274.

27. DiDomenico RJ, Walton SM, Sanoski CA, Bauman JL. Analysis of the use of digoxin immune fab for the treatment of non-life-threatening digoxin toxicity. *J CardiovascPharmacolTher*. 2000;5:77-85.