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Review on "Analyzing the Therapeutic Potential of Digoxin"

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***Abstract*-- Digoxin is one of the oldest medications still in use today in cardiovascular care, both domestically and internationally. This medication is called a cardiac glycoside and is used to treat heart conditions including congestive heart failure, atrial fibrillation or flutter, and certain cardiac arrhythmias. Digoxin is a medicine used to cardiac problems, although its therapeutic index is relatively restricted. Even though ACE inhibitors and β-blockers have been shown to improve survival, digoxin still seems to have a role in the management of heart failure and atrial fibrillation after 230 years of usage. Digoxin therapy is a well-researched, reasonably priced, and potentially very cost-effective treatment. The only oral administered inotrope that lowers the mortality rate in heart failure is patients, particularly if low doses are being approach.Digoxin was the first medication used to treat heart failure, and studies have shown that it lowers hospital admission rates.**

***Keywords*--Digoxin, Digoxin mechanism of action, Digoxin toxicity, Digoxin clinical effects, Cardiac glycosides, Digoxin pharmacokinetics, Adverse impact of digoxin etc**

I. Introduction

Digitalis lanata, sometimes known as white foxglove, is the source of the cardiac glycoside digoxin. It has been used rather extensively in the treatment of a number of cardiac conditions, such as congestive heart failure, atrial fibrillation or flutter, and certain cardiac arrhythmias. You are aware that digoxin is one of the most often used medications in cardiology. Given that the majority of medications are derived from the digitalis (foxglove) plant, digoxin is frequently referred to as digitalis or digitalis glycosides.

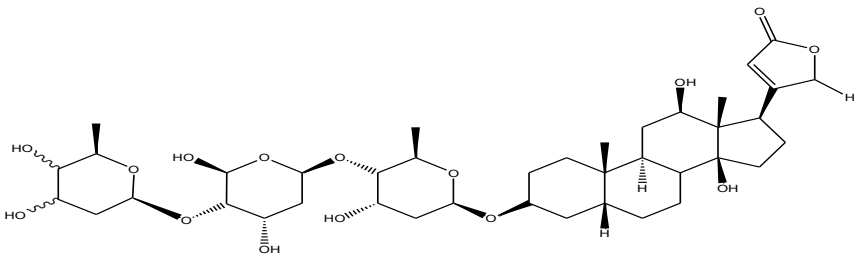
These are a class of somewhat related chemicals that work by making the myocardial cell more contractile; as a result, they are mostly used to treat heart failure. With very little difference between a therapeutic dose and hazardous or even deadly levels, cardiac glycosides have a poor therapeutic index.

II. Chemistry

In 1930, digoxin was first discovered in D. lanata, I believe, a foxglove plant. The prototype, digoxin, consists of a sequence of sugars at carbon 3 of the nucleus and a steroid nucleus connected to a lactone ring at position 17. You understand that their solubility is not pH-dependent as they do not have a readily ionizable group.Digoxin (12β-hydroxy digitoxin, digoxin, Lanoxin) has;

- CAS Number: - 20830−75-5
- Molecular Formula: - C_{41} H_{64} O_{14}
- Molecular Weight: - 780.949 g/mol
- IUPAC Name: - 3-[(3S,5R,8R,9S,10S,12R,13S,14S,17R)-3-[(2R,4S,5S,6R)-5-[(2S,4S,5S,6R)-5-[(2S,4S,5S,6R)-4,5-dihydroxy-6-methyloxan-2-yl]oxy-4-hydroxy-6-methyloxan-2-yl]oxy-4-hydroxy-6-methyloxan-2-yl]oxy-12,14-dihydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]-2H-furan-5-one).

III. Structure Of Digoxin



Digoxin

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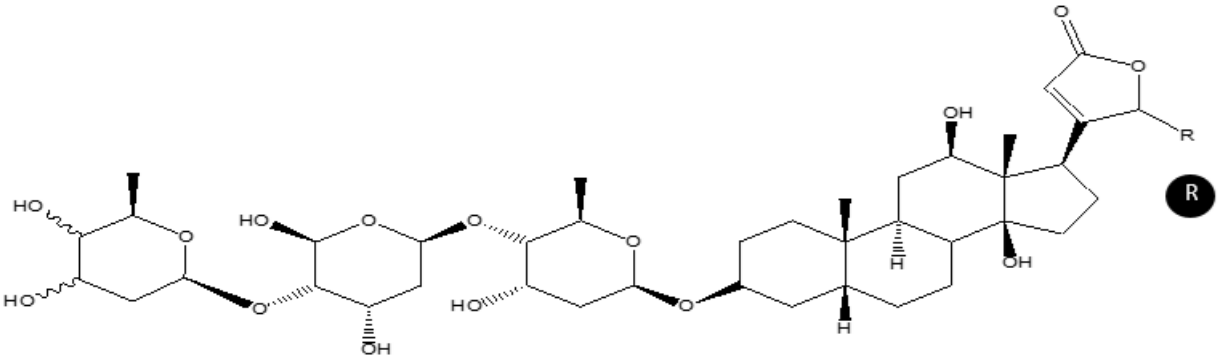
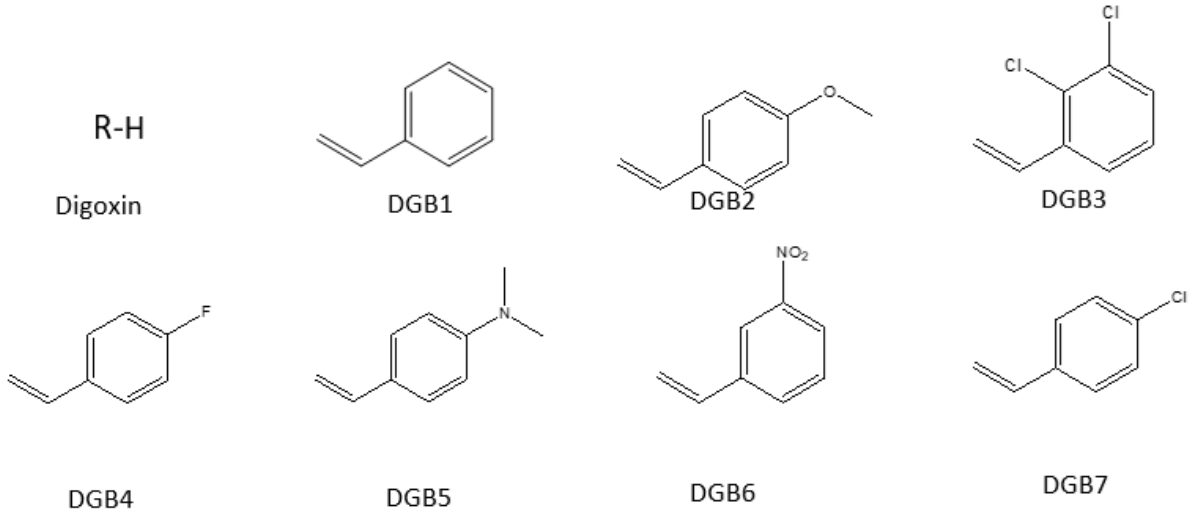
Derivatives Of Digoxin

The tested digoxin compounds are likely to be—DBG1, DGB2, DGB3, DGB4, DGB5, DGB6, and DGB7 were synthesized by Alves et al. (2015) given below:



Common Structure of Digoxin



IV. Properties

Appearance: - Powder & white crystalline in nature

Melting Point: - 239° C (Decompose)

Solubility: - Slightly soluble in water

Partition Co-efficient: - Log P (OCTANOL-WATER) = 1.26

V. Pharmacokinetics

All cardiac glycosides have comparable therapeutic effects on the heart, although they differ significantly in terms of their pharmacokinetic characteristics. Each glycoside's lipophilic characteristic leaves a lasting impression on the moiety.

More lipophilic cardiac glycosides are often absorbed more quickly and, as a result, have longer half-lives due to sluggish renal excretion rates.Digoxin, the sole cardiac glycoside used in the United States, is absorbed in the gastrointestinal system 65–80% of the time after oral and injectable forms are administered. Other glycosides absorb differently, ranging from 0% to over 100%. All cardiac glycosides are extensively transported throughout tissues, including the central nervous system, once they are in the circulation. The reason for its wide distribution volume is that it accumulates in muscles. Compared to other cardiac glycosides, kind of digoxin has a longer half-life of 30 to 40 hours. Urine is the primary way that the kidneys get rid of it.

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VI. Absorption Of Digoxin

Digoxin is absorbed in the duodenum, the first section of the gut, to a degree of 70–80%. Between 50 and 90 percent of an oral dosage is bioavailable. On the other hand, digoxin in oral gelatine capsules is said to have 100% bioavailability. Tmax, or the amount of time needed to attain the maximum digoxin level in plasma, was found to be 1.0 hour in a clinical research including healthy participants who received 0.25 mg digoxin and a placebo. The maximum concentration in plasma, or Cmax, was determined to be 1.32 ± 0.18 ng/ml-1 and the area under the curve, or AUC, to be 12.5 ± 2.38 ng/ml-1 in the same investigation. Digoxin absorption will be delayed if it is taken after meals, but the overall quantity absorbed won't alter. Digoxin may not be absorbed as well if consumed with a fibrous food like oats.

VII. Elimination

Clearance of digoxin is proportional to the total dose and follows the order of onset. After intravenous (IV) administration to healthy volunteers, 50-70% of the dose is excreted in the urine as unchanged digoxin. Approximately 25% to 28% of

VIII. Volume Of Distribution

The medication is known to penetrate both the placenta and the blood-brain barrier and is extensively dispersed throughout the body. Digoxin has a known volume of dispersion of 475–500 L. It should be noted that as people age, their muscle mass frequently declines and their distribution of digoxin may also diminish.

IX. Metabolism

A healthy person metabolizes around 13% of a digoxin medication. Digoxin has several urine metabolites, such as digoxin and dihydro digoxin. Hydrolysis, oxidation, and conjugation reactions are hypothesized to create their glucuronidated and sulfated conjugates. Digoxin metabolism is not significantly influenced by the cytochrome P-450 system, and the medication has no effect on or inhibition of any of the system's enzyme digoxin is excreted outside by the kidney. Bile excretion appears to be more important than renal excretion.

X. Pharmacodynamics

The cardiac glycoside belonging to the digitalis type is called digoxin. It acts directly on the smooth muscle vascular and myocardium, and it also has a favorable inotropic effect indirectly by, sort of, raising the force of cardiac contraction. It works positively chronotropically (slows heart rate) and antiarrhythmically (lowers conductivity of the AV node), which is fantastic.

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	Atrium	Purkinje Ventricle	AV Fiber	SA Node	Node
Contractility	↑	↑	—	—	—
Excitability	0	Variable	↑	—	—
Conductivity	↑	↑	↓	↓	—
Refractory period	↓	↓	↑	↑	—
Automaticity	—	—	↑	—	↓

AV, atrioventricular; SA, sinoatrial; ↑ increased action; ↓ decreased action; 0, no action; —, no data available.

XI. Pharmacological, Actions

- *Cardiac actions*

  Digitalis has direct and indirect actions on the heart.

  1. Direct action by inhibiting Na $^{+}K^{+}$ ATPase.
  2. Indirect action by stimulating vagus (vagomimetic effect).
     - Myocardial contractility
     - Electrophysiological actions
     - Heart Rate
- ECG
- *Extracardiac actions*

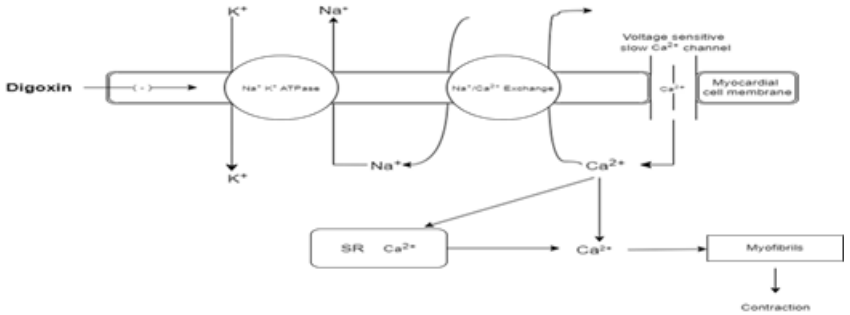
1. *Gastrointestinal tract (GIT):* Digitalis can produce anorexia, nausea, vomiting and occasionally diarrhoea due to stimulation of chemoreceptor trigger zone (CTZ) and a direct action on the gut.
2. *Kidney:* In patients with CCF, digitalis causes diuresis (increased urine output).

Central nervous system (CNS): In high doses, it can cause central sympathetic stimulation, confusion, blurring of vision, disorientation, etc.

XII. Mechanism Of Action Of Digoxin.

Digoxin has two principal mechanisms of action, which are selectively employed depending on the indication, like, you know: Positive Inotropic:

By reversibly blocking the myocardial Na+-K+ ATPase pump, an enzyme that regulates the flow of ions into the heart, it strengthens the contraction force of the heart. Digoxin raises the intracellular sodium level, which stimulates the myocardial cell's calcium influx and increases myocyte contractility. Ventricular output decreases with an increase in cardiac output.



Ref. Fig.: - Shanbagh T.V., S. Smita, Pharmacology for Medical Graduates, Elsevier

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AV Node inhibition:

Digoxin affects the AV node in a vagomimetic manner. It lowers heart rate by slowing electrical transmission in the atrioventricular node, which is achieved by, you know, activating the parasympathetic nervous system. The extension of phase 0 and phase 4 of the action potential caused by an increase in calcium in myocytes lengthens the AV node's refractory period. Reduced ventricular response is conveyed by slower AV node conduction.

XIII. Digoxin Dosing In Cardiac Arrest

Given the unclear aetiology of the medical emergency, bigger dosages that would somewhat attain complete neutralization are appropriate in the case of (imminent) cardiac arrest owing to ventricular tachyarrhythmias and ventricular fibrillation. Empirically determined dosages of 400–800 mg for adults and children with acute poisoning and 240 mg for adults (patients > 20 kg) or 40 mg for children (< 20 kg) with chronic poisoning are advised in the event that the estimated digoxin dose or serum digoxin levels are unavailable.

XIV. Digoxin Dosing In Acute Poisoning

Patients using digoxin or those who have been taken it for some time may experience acute toxicity. Since complete tissue distribution has not yet taken place, the first plasma digoxin concentration in patients who arrive prematurely (within 6 hours after intake) may be extremely high and overestimate the overall body burden/load. Digoxin has a sluggish beginning of action, so it might take several hours before all of the harmful consequences are apparent. Complete neutralization is not essential, and in fact, it may be desired in people on therapeutic digoxin, since it may exacerbate underlying medical issues, as a therapeutic dose of digoxin will have minimal impact on a digoxin-naive individual.

XV. Digoxin Dosing In Chronic Poisoning

When a patient routinely takes more medicine than is advised or when the body's capacity to metabolize the drug changes—for example, due to renal impairment—even when the patient takes the proper amount, long-term poisoning may result. The majority of digoxin users are elderly, have co-morbid conditions such as diabetes, hypertension, atrial fibrillation, congestive heart failure, and beta-adrenoceptor blockers, and frequently use diuretics, calcium antagonists, and beta-adrenoceptor blockers as co-medication. Diagnosing chronic digoxin toxicity might be difficult since there are several possible causes of the symptoms associated with it. Rather from being the result of acute toxicity, elevated blood digoxin levels frequently point to underlying problems such renal impairment. As a result, there are less precise guidelines for prescription digoxin. However, digoxin-Fabs must be administered very away in situations of cardiac arrest and ventricular tachyarrhythmia. Digoxin has already permeated the whole body in chronic digoxin poisoning cases, with significant concentrations seen outside the circulation. Since most individuals have been taken digoxin for medicinal purposes, full neutralization is not essential and may even be undesirable since it might exacerbate pre-existing conditions such as atrial fibrillation or congestive heart failure. Digoxin 40 mg should be given, and patients should be closely watched for a clinical response.

XVI. Digoxin-Drugs Interactions

Digitalis poisoning is frequently caused by digoxin-drug interactions. Digoxin-quinidine interaction has been well-documented, and it has been shown recently that the P-gp-dependent renal tubular release of digoxin has therapeutic implications. Digoxin interacts with various medications, some of which are listed below: -

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AGENTS NAME	MODE OF INTERACTION
Potassium-depletion diuretics	Low potassium levels which enhance the digoxin toxicity and increase in the potential for lethal cardiac arrhythmias
Quinidine	Quinidine can do increase in the serum concentrations of digoxin.
Verapamil	Verapamil can do increase in the serum concentrations of digoxin.
Alprazolam	Alprazolam can do increase in the serum concentrations of digoxin.
Amiodarone	Amiodarone can do increase in the serum concentrations of digoxin.
Propafenone	Propafenone can do increase in the serum concentrations of digoxin.
Indomethacin	Indomethacin can do increase in the serum concentrations of digoxin.
Itraconazole	Itraconazole can do increase serum in the concentrations of digoxin.
Spironolactone	Spironolactone can do increase serum concentrations of digoxin
Macrolide and Tetracycline antibiotics	Macrolide and tetracycline antibiotics can do alteration in slow metabolism of digoxin by altering gastrointestinal flora.
Antacids	Antacids can do interfere with the absorption of digoxin.
Kaolin-pectin	Kaolin-pectin can do interfere with the absorption of digoxin.
Metoclopramide	Metoclopramide can do interfere with the absorption of digoxin.
Neomycin	Neomycin can do interfere with the absorption of digoxin.
Sulfasalazine	Sulfasalazine can do interfere with the absorption of digoxin.
Chemotherapy/radiation	Chemotherapy/radiation can do interfere with the absorption of digoxin.
Colestipol	Colestipol can do interfere with the absorption of digoxin.
Cholestyramine	Cholestyramine can do interfere with the absorption of digoxin.
Rifampin	Rifampin can do decrease in the serum concentrations of digoxin.
Sympathomimetic agents	The use of sympathomimetics and digoxin increases in the potential for cardiac arrhythmias.
Succinylcholine	Succinylcholine potentiates the conduction effects of digoxin, increases the ventricular irritability, and can-do precipitate cardiac arrhythmias.

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XVII. Adverse Impact Of Digoxin

Inappropriate treatment for digoxin intoxication can be lethal. Digestion symptoms including cramping in the abdomen, vomiting, and diarrhea are frequently the first indications of digoxin poisoning. Further visual abnormalities that patients may encounter include seeing green or yellow halos and seeing "fuzzy shadows," which are similar to the feeling of driving at night while wearing excessively filthy glasses. With prolonged poisoning, confusion and yellow vision might happen, followed by bradycardia, ventricular arrhythmias, and atrioventricular blockage.

Hypokalemia aggravates digoxin toxicity as wellDue to its binding to the K+ site of the Na+/K+-ATPase pump, digoxin lowers serum potassium levels, which raises the possibility of digoxin poisoning. On the other hand, digoxin is less effective in cases of hyperkalemia. Digoxin poisoning is more common in elderly people, who frequently have conditions including potassium imbalances and renal difficulties. This is due to the possibility that their bodies will have trouble correctly metabolizing and excreting the medicine. It is essential to regularly monitor their status and modify the dosage as needed to prevent negative consequences.Digoxin's margin of safety is quite limited. During digitalis medication, it is crucial to monitor serum digoxin, electrolyte levels, and electrocardiogram (ECG)..

	New Digoxin Users (n = 779) Rate* (Events)	**Matched Control Participants† (n = 2, 337) Rate* (Events)**	**HR (95% CI) Digoxin Versus No Digoxin**	**p Value**
Death	8.13 (79)	5.11 (151)	1.78 (1.37–2.31)	<0.0001
CV death	3.71 (36)	2.31 (68)	1.60 (1.07–2.38)	0.0218
Sudden cardiac death	1.34 (13)	0.61 (18)	2.14 (1.11–4.12)	0.0230
Non-CV death	3.19 (31)	1.93 (57)	1.67 (1.12–2.49)	0.0121
HF hospitalization	4.22 (33)	2.52 (62)	1.69 (1.15-2.49)	0.0083

XVIII. Clinical Impact Of Digoxin

Digoxin is presently being administered to over 1.7 million individuals in the US for heart failure and/or atrial fibrillation. Digoxin's hemodynamic effects, neurohormonal effects, or both may be responsible for the positive outcomes observed in individuals with HF and impaired systolic function. However, the rapidity of a patient's decline upon digoxin discontinuation implies that its hemodynamic effects are significant.New Digoxin user. the 12,703 patients who did not start taking digoxin at the beginning, 873 (6.9%) became new digoxin users throughout follow-up. Approximately 790 patients and 2,340 approximately control volunteers were matched (1:3). After five patient couples were eliminated from the study because the same control was matched to a case, there were around 780 patients and 2,340 control participants in total.

Following the inclusion of bottom-line data and the removal of two more pairs of patients, the final analysis comprised 2,337 control individuals and 779 patients. The one variable with standardized differences more than 10% (chronic obstructive pulmonary disease) was 11.8%.Compared to matched control subjects, new digoxin users had a substantially higher overall mortality risk (adjusted HR: 1.78; 95% CI: 1.37 to 2.31; $p < 0.0001$).The results were true for both heart failure patients and non-patients. With a statistically significant rise (adjusted hazard ratio: 1.58; 95% confidence interval: 1.12 to 2.24; $p = 0.0100$) and (adjusted HR: 2.07; 95% CI: 1.39 to 3.08; $p = 0.0003$), the risk of unfavorable outcomes was increased in both groups. The median time to death for individuals who began using digoxin and died was 165 days (25th, 75th percentiles: 28, 363 days).

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The entire population and patients with or without heart failure at baseline had substantially poorer outcomes when compared to matched control individuals, according to Kaplan-Meier curves for all causes of death. Comparable outcomes were seen in the couples matched in an outpatient environment exclusively in the sensitivity analysis.The number needed to harm for all-cause death was 34 at one year (95% CI: 19 to 84) and 17 at two years (95% CI: 9 to 41). Digoxin poisoning A male patient, aged fifty, arrives to the emergency room complaining of palpitations, nausea, and dyspnea. He is on digoxin and has a history of congestive heart failure and atrial fibrillation. Due to the discomfort and frequent occurrences of palpitations, his primary care physician last week upped his digoxin dosage from 0.125 mg to 0.25 mg daily.

A 148 beats per minute pulse and a 96/52 mmHg blood pressure are examples of vital indicators. Gain more knowledge about the pharmacokinetics of digoxin, enhance blood level monitoring, and recognize significant interactions between digoxin and other medications used in combination to lessen CHF arrhythmias.. Nonetheless, distinguishing between cardiac arrhythmias and neurological or gastrointestinal symptoms in heart transplant recipients still requires understanding digoxin toxicity. Toxicology may be treated with the antibiotics digoxin anti-Fab (DIGIBIND, DIGIFAB).

Product	Absolute Bioavailability	Equivalent Doses (µg) Among Dosage Forms			
Digoxin tablets	60-80%	62.5	125	250	500
Digoxin elixir paediatric	70-85%	62.5	125	250	500
Digoxin CAPS	90-100%	50	100	200	400
Digoxin injection/IV	100%	50	100	200	400

Comparison of Digoxin and Digitoxin

	Digoxin	Digitoxin
Gastrointestinal Absorption	70-80 %	95-100 %
Average half-life	1-2 days	5-7 days
Protein binding	25-30 %	90-95 %
Enterohepatic cycling	5 %	25 %
Excretion	Kidney; Largely unchanged	Liver metabolism
Therapeutic plasma level	0.5-2.5 ng/ml	20-35 ng/ml
Digitalizing	Oral: 0.75-1.5	Oral: 0.8-1.2
Dose (mg)	IV: 0.5-1.0	IV: 0.8-1.2
Maintenance dose (oral mg)	0.125-0.5	0.05-0.2

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XIX. Pharmacokinetics Of Different Types Of Digoxin Preparation

Digitarlin, tricoside C, its partial hydrolyzate adelantoside C (desacetyl tricoside C), digolin Sin, and ouabain are among the glycosides that are purified in the manufacture of cardiac glycosides using different powdered digitalis leaves. Digoxin is the only cardiac glycoside that is currently marketed for clinical use in the US.

XX. Partition Coefficient

The lipophilicity of cardiac glycosides and their constituents is assessed by observing how they partition between chloroform and water mixed with methanol. The more lipophilic the cardiac glycoside, the greater its concentration in the chloroform phase and the drug partition coefficient.

Glycosides	Partition Coefficient ($CHCl_3$/16% aq. Me.OH)
Digoxin	81.5
Digitoxin	96.5
Lanatoside C	16.2
Acetyldigoxin	98.0
G-Strophanthin	Very low

XXI. Conclusion

In conclusion, digoxin is a useful drug that is frequently used to treat cardiac problems like heart failure and atrial fibrillation. It is not without risk, though, since its dosage must be well watched to prevent toxicity, which can result in dangerous symptoms that are not connected to the heart. Digoxin is used safely and efficiently by doctors when they are aware of its pharmacokinetics and pharmacodynamics—the ways in which it affects and passes through the body. Its primary duties include regulating specific bodily substances and enhancing cardiac function. However, overindulging may result in toxicity. To ensure digoxin is used properly, it is imperative that patients and clinicians are aware of these dangers and collaborate Digoxin is a formidable instrument and possible risk in the field of cardiac medicine, emphasizing the need for cautious handling and education.

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