Digoxin

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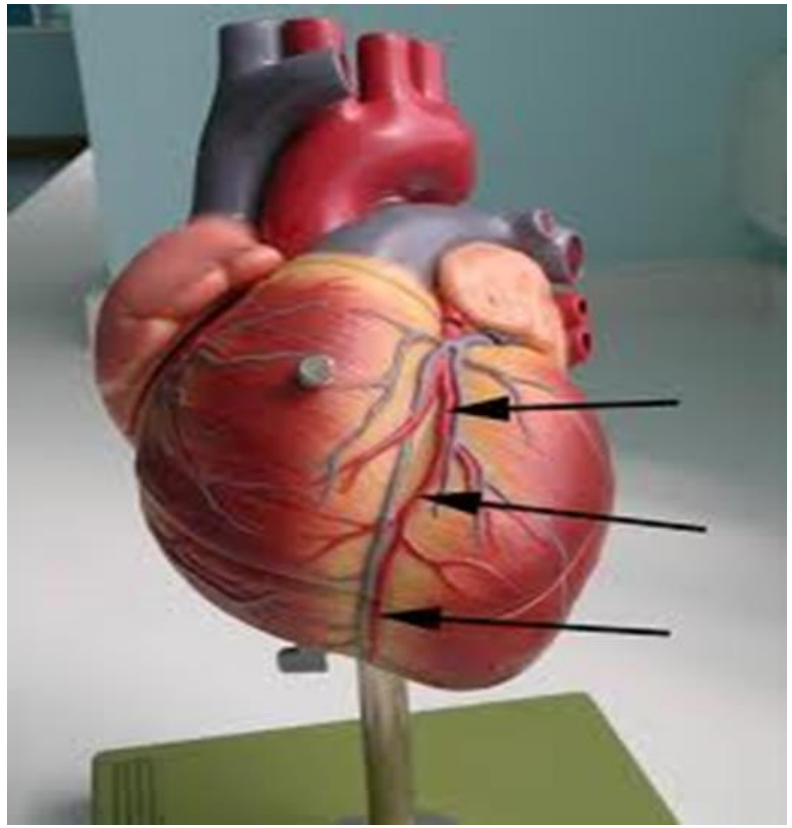
Introduction

- Digoxin is the primary cardiac glycoside in clinical use.

- Digoxin is used for the treatment of
    - congestive heart failure (CHF) because of its inotropic effects on the myocardium.
    - atrial fibrillation because of its chronotropic effects.



Therapeutic and toxic concentrations

- Inotropic Effects of digoxin are generally achieved at steady-state serum concentrations of

0.5 - 1ng/mL

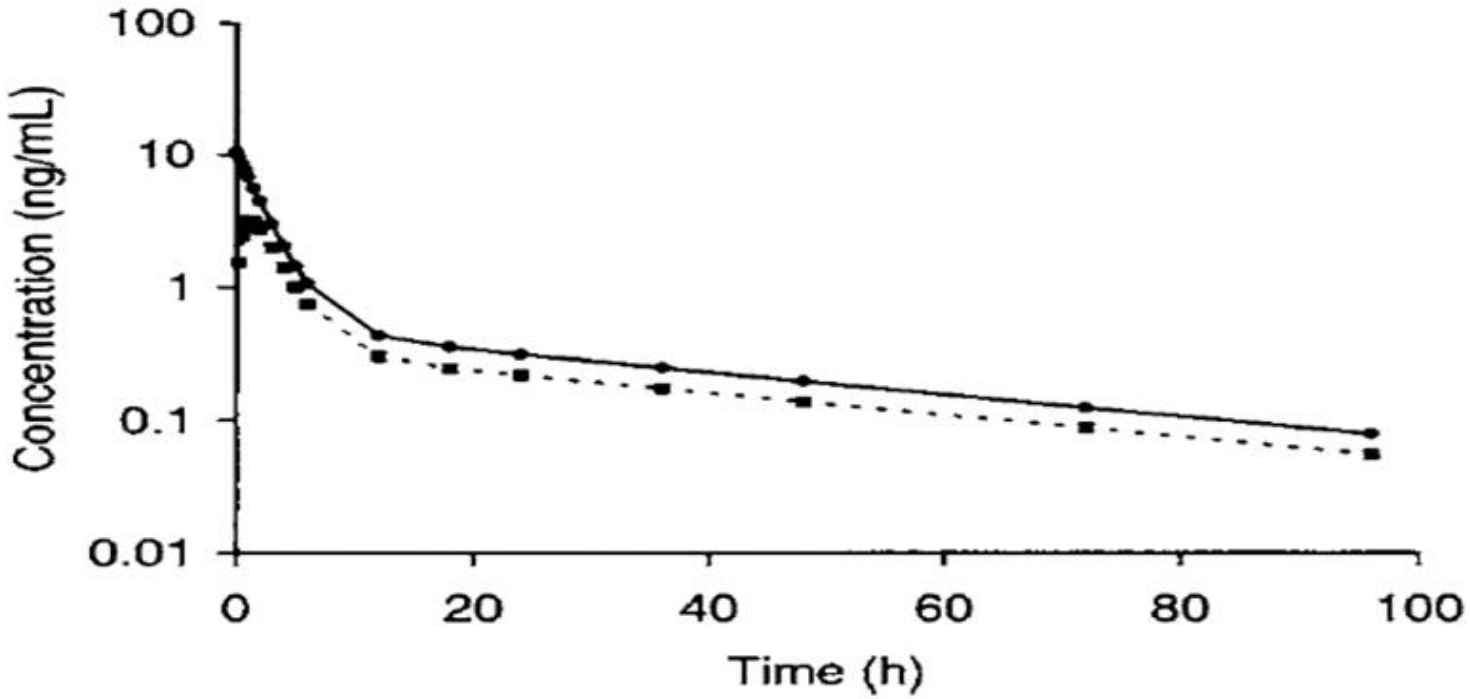
- Chronotropic Effects usually require higher digoxin steady-state serum concentrations of

0.8 – 1.5 ng/mL

- Steady-state digoxin serum concentrations above **2 ng/mL** are associated with an increased incidence of **adverse drug reactions**.

Therapeutic and toxic concentrations

- When given as oral or intravenous doses, the serum digoxin concentration–time curve follows a two-compartment model and exhibits a long and large **distribution phase** of **8–12 hours**.



Basic and clinical pharmacokinetics parameters

- The primary route of digoxin elimination from the body is by the:
- **Kidney** via glomerular filtration and active tubular secretion of unchanged drug (~75%)
- **Hepatic** metabolism or biliary excretion (~25%).
- Plasma protein binding is **~25%** for digoxin.
- Average bioavailability constants (F) for the tablet, elixir, and capsule are 0.7, 0.8, and 0.9.

Usual Digoxin Doses For Adult Patients

- Patients with good renal function (creatinine clearance≥80 mL/min).

  250 µg/d (range: 125–500 µg/d)

- Patients with renal dysfunction (creatinine clearance ≤15 mL/min)

  125 µg every 2–3 days

TABLE 6-2 Disease States and Conditions that Alter Digoxin Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	VOLUME OF DISTRIBUTION	COMMENT
Adult, normal renal function	36 hours or 1.5 days (range: 24–48 hours)	7 L/kg (range: 5–9 L/kg)	Usual dose 250 µg/d (range: 125–500 µg/d) resulting in total body stores of 8–12 µg/kg for heart failure or 13–15 µg/kg for atrial fibrillaton. Digoxin is eliminated ~75% unchanged renally/~25% nonrenally.
Adult, renal failure	120 hours or 5 days	4.5 L/kg $V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right) \times (Wt / 70)$ where V is digoxin volume of distribution in L/70 kg, Wt is body weight in kg (use ideal body weight if >30% overweight) and CrCl is creatinine clearance in mL/min.	Renal failure patients have decreased digoxin clearance and volume of distribution. As a result, half-life is not as long as might be expected [$t_{1/2}$ = (0.693V) / Cl]. Digoxin total body stores decrease to 6–10 µg/kg because of reduced volume of distribution.

Moderate/severe heart failure	See comments	7 L/kg	Heart failure patients (NYHA III–IV) have decreased cardiac output, which causes decreased liver blood flow and digoxin hepatic clearance. In patients with good renal function (creatinine clearance >80 mL/min), the effect on digoxin total clearance is negligable. But in patients with poor renal function, (creatinine clearance <30 mL/min) nonrenal clearance is a primary elimination pathway.
Obesity (>30% over IBW) with normal renal function	36 hours or 1.5 days	7 L/kg IBW	Digoxin does not distribute to adipose tissue, so volume of distribution calculations should be conducted with ideal body weight (IBW).
Hyperthyroidism with normal renal function	24 hours or 1 day	7 L/kg	Hyperthyroid patients are hypermetabolic and have higher digoxin renal and nonrenal clearances.

Initial Dosage Determination Methods

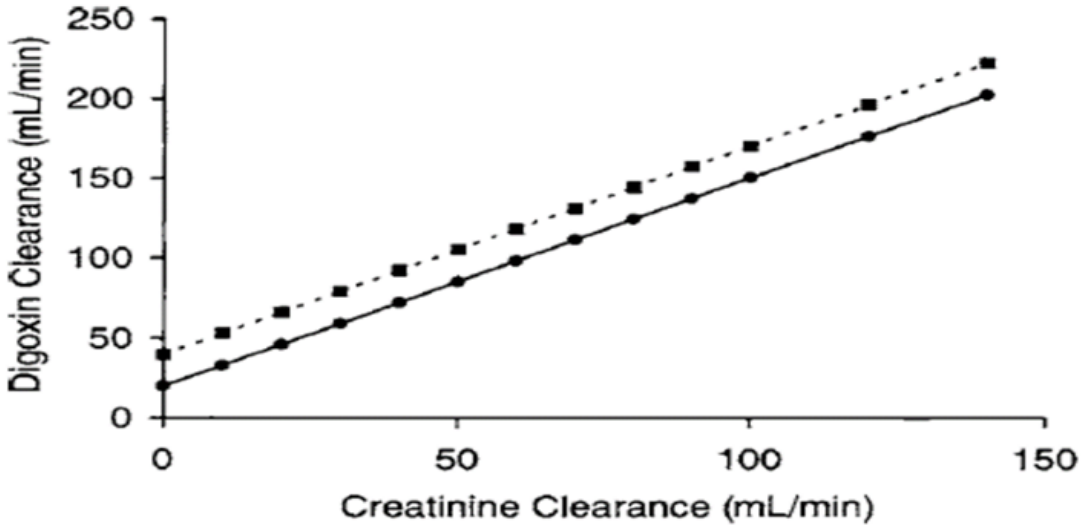
1. ***The pharmacokinetic dosing method***

2. ***Jelliffe method***

The pharmacokinetic dosing method

1. **Estimate digoxin clearance**

$$Cl\ (ml/\ min) = 1.303\ [CrCl\ (ml/min)] + Cl_{NR}$$



Cl_{NR} is digoxin clearance by nonrenal routes of elimination;

40 mL/min without or mild heart failure (NYHA CHF class I or II)

20 mL/min with moderate or severe heart failure (NYHA CHF classes III or IV)

The pharmacokinetic dosing method

- Note : only in patient with **hyperthyroid** which is a disease state known to increase digoxin metabolism and shorten half-life use this equation to calculate the CL by using

$$Cl = keV$$

Where

$t_{1/2}$ = 1 d

ke = $0.693/t_{1/2}$

= 0.693 / 1 d = 0.693 d^{-1}

Note: Digoxin Cl must be converted from (ml/min) to (L/d) by multiplying the result by (60* 24)/ 1000 or 1.44

The pharmacokinetic dosing method

2. Estimate digoxin volume of distribution

- V= 7 L/kg If obese use IBW

- It is likely that digoxin is displaced from tissue binding sites by an unknown substance or substances present in patients with renal dysfunction.

- Unbound digoxin molecules displaced from tissue binding sites move into the blood causing the decreased volume of distribution

$$\downarrow V = VB + (f_B / \uparrow f_T)\, VT$$

The pharmacokinetic dosing method

- In renal failure

$$V = \left(226 + \frac{298 \cdot \mathrm{CrCl}}{29.1 + \mathrm{CrCl}}\right)(\mathrm{Wt} / 70)$$

The pharmacokinetic dosing method

3. Steady-state concentration selection

- For heart failure…….0.5–1 ng/mL

  Target digoxin concentration equal to 0.8 ng/mL

- For patients with atrial fibrillation……0.8–1.5 ng/mL

  Target digoxin concentration of 1.2 ng/mL

The pharmacokinetic dosing method

4. **Selection of appropriate model and equations**

$$D = (Css \cdot Cl \cdot \tau) / F$$

$$Css = [F (D/\tau)] / Cl$$

τ = 1 day

Jelliffe Method

1. The amount of digoxin in the body that produces the desired effect is known at the total body stores (TBS) of digoxin.

- For patients with creatinine clearance values >30 mL/min, digoxin total body stores of 8–12 µg/kg are usually required to cause inotropic effects.
- While 13–15 µg/kg are generally needed to cause chronotropic effects.
- Ideal body weight (IBW) for obese patients.
- Since renal disease (creatinine clearance <30 mL/min) decreases digoxin volume of distribution, initial digoxin total body stores of 6–10 µg/kg.

Jelliffe Method

2. The percent of drug that is lost on a daily basis (%lost/d) is related to renal function according to the following equation

$$\%lost/d = 14\% + 0.20\,(CrCl)$$

Where 14% is the percent of digoxin eliminated per day by non-renal routes and CrCl is creatinine clearance in mL/min

Jelliffe Method

3. The maintenance dose (D in µg/d)

$$D = [TBS \cdot (\%lost/d)] / F$$

Combining the two equations produces the initial digoxin maintenance dose

$$D = \{TBS \cdot [14\% + 0.20(CrCl)]\} / (F \cdot 100)$$

$$LD = TBS / F$$

Use of digoxin serum concentrations to alter dosages

1. ***Linear Pharmacokinetics Method***

2. ***Pharmacokinetic Parameter Method***

Linear pharmacokinetics method

$$D_{new} = (Css_{new}/Css_{old})D_{old}$$

Pharmacokinetic parameter method

- This method calculates the patient-specific drug clearance by using the obtained Css

$$Cl = [F\,(D/\tau)] / Css$$

Cl is digoxin clearance in L/d

- Then use this actual clearance to calculate new dose

$$D = (Css \cdot Cl \cdot \tau) / F$$

Use of digoxin booster doses to immediately increase serum concentrations

- If a patient has a subtherapeutic digoxin serum concentration in an acute situation, it may be desirable to increase the digoxin concentration as quickly as possible.

- A modified loading dose equation is used to accomplish computation of the booster dose (BD) which takes into account the current digoxin concentration present in the patient

$$BD = [(C_{desired} - C_{actual})\ V] / F$$

Example 1

BN is a 52-year-old, 85-kg (6 ft. 2 in) male with atrial fibrillation who is receiving therapy with intravenous digoxin. He has normal liver and renal function. After receiving an initial loading dose of digoxin (1000 µg) and a maintenance dose of 250 µg/d of digoxin for 5 days, his digoxin concentration is measured at 0.6 ng/mL immediately after pulse rate increased to 200 beats/min. Compute a booster dose of digoxin to achieve a digoxin concentration equal to 1.5 ng/mL?

Example 1

Answer

1. Estimate volume of distribution according to disease states and conditions present in the patient.

- In the case of digoxin, the population average volume of distribution equals 7 L/kg and this will be used to estimate the parameter for the patient.

- The patient is non-obese, so his actual body weight will be used in the computation:

$$V = 7\ L/kg \cdot 85\ kg$$

$$= 595\ L$$

Example 1

2. Compute booster dose

- The booster dose is computed using the following equation:

$$BD = [(C_{desired} - C_{actual})\ V]/F$$

$$= [(1.5\ \mu g/L - 0.6\ \mu g/L)\ 595\ L] / 1$$

$$= 536\ \mu g, \text{ rounded to } 500\ \mu g \text{ of digoxin.}$$

Conversion of patient doses between dosage forms

$$D_{IV} = D_{PO} \cdot F$$

- D_{IV} is the equivalent digoxin intravenous dose in µg
- D_{PO} is the equivalent digoxin oral dose
- F is the bioavailability fraction appropriate for the oral dosage form (F = 0.7 for tablets, 0.8 for elixir, 0.9 for capsules)

Example 2

YT is a 67-year-old, 60-kg (5 ft. 5 in) male with atrial fibrillation receiving 200 µg of intravenous digoxin daily which produces a steady-state digoxin concentration of 1.3 ng/mL. Compute an oral tablet dose that will maintain steady-state digoxin concentrations at approximately the same level?

Answer:

1. Convert current digoxin dose to the equivalent amount for the new dosage form/route.

$D_{PO} = D_{IV} / F$

= 200 µg / 0.7 = 286 µg digoxin tablets, round to 250 µg

Example 2

2. Estimate change in digoxin steady-state concentration due to rounding of dose.

- The oral tablet dose of 286 µg would have produced a steady-state concentration similar to the intravenous dose of 200 µg.

- However, the dose had to be rounded a dose that could be given as a tablet.

Example 2

- The expected digoxin steady-state concentration from the rounded dose would be proportional to the ratio of the rounded dose and the actual computed dose:

$$Css_{new} = Css_{old} (D_{rounded}/D_{computed})$$
$$= 1.3 \text{ ng/mL } (250 \text{ µg} / 286 \text{ µg})$$
$$= 1.1 \text{ ng/mL}$$

Use of digoxin immune fab in digoxin overdoses

- Digoxin immune Fab (Digibind) are digoxin antibody molecule segments that bind and neutralize digoxin which can be used in digoxin overdose situations

1. If a digoxin serum concentration or an estimate of the number of tablets ingested are **not available** 20 vials of Digibind are usually adequate to treat most life-threatening acute overdoses in children and adults.

- In less emergent situations, 10 vials may be initially given, patient response monitored, and an additional 10 vials administered.

Use of digoxin immune fab in digoxin overdoses

2. TO TREAT CHRONIC DIGOXIN OVERDOSES

- Six vials are usually needed for adults and older children while 1 vial is usually adequate for children <20 kg.

3. CHRONIC OVERDOSE OR ACUTE OVERDOSE 8–12 HOURS AFTER INGESTION

- In these cases, a post absorption, post distribution digoxin concentration can be used to estimate the necessary dose of Digibind for a patient using the following formula:

Digibind dose (vials) = (Digoxin concentration ng/mL) (Body weight in kg)/100

Example 3

HY is a 72-year-old, 80-kg (5 ft. 7 in) male who has accidently been taking twice his prescribed dose of digoxin tablets. The admitting digoxin serum concentration is 4.1 ng/mL. Compute an appropriate dose of Digibind for this patient?

Answer:

Digibind dose (vials) = (Digoxin concentration in ng/mL)(Body weight in kg)/100

$$=(4.1\ \text{ng/mL} \cdot 80\ \text{kg})/100 = 3.3\ \text{vials, rounded up to 4 vials}$$

Use of digoxin immune fab in digoxin overdoses

4. ACUTE OVERDOSE WHERE NUMBER OF TABLETS IS KNOWN OR CAN BE ESTIMATED

- For this situation, digoxin total body stores are estimated using the number of tablets ingested corrected for dosage form bioavailability:

TBS = F (# dosage units) (dosage form strength)

- # dosage units is the number of tablets or capsules, and dosage form strength is in mg (Note: 250 µg = 0.25 mg).

Use of digoxin immune fab in digoxin overdoses

- Each vial of Digibind will inactivate approximately 0.5 mg of digoxin, so the dose of Digibind (in vials) can be calculated using the following equation:

Digibind dose = TBS/ (0.5 mg/vial)

- TBS is digoxin total body stores in mg.

Example 4

DL is a 22-year-old, 85-kg (5 ft 9 in) male who took approximately 50 digoxin tablets of 0.25-mg strength about 4 hours ago. Compute an appropriate dose of Digibind for this patient.

Answer:

TBS = F (# dosage units) (dosage form strength)

= 0.8 (50 tablets · 0.25 mg/tablet) = 10 mg

Digibind dose = TBS/ (0.5 mg/vial)

= 10 mg / (0.5 mg/vial) = 20 vials


thank you!