DIGOXIN

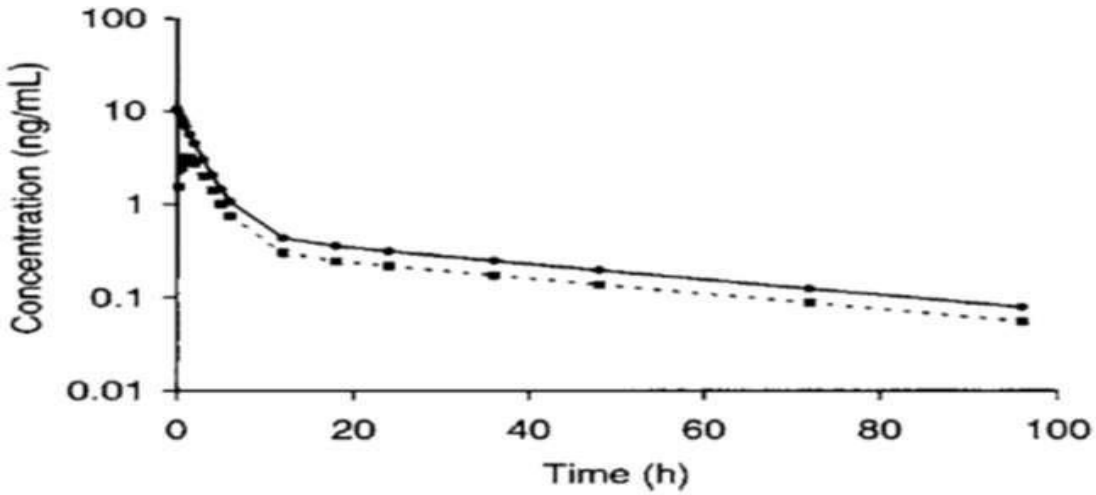
- Digoxin is the primary cardiac glycoside in clinical use
- Digoxin is used for the treatment of
  - congestive heart failure (CHF) because of its inotropic effects on the myocardium
  - atrial fibrillation because of its chronotropic effects

Therapeutic and Toxic Concentrations

- Inotropic effects of digoxin are generally achieved at steady-state serum concentrations of **0.5 – 1 ng/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. At digoxin concentrations of 2.5 ng/mL or above ~50% of all patients will exhibit some form of digoxin toxicity.

Basic and clinical pharmacokinetics parameters

- 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%). The primary transporter involved in active tubular secretion and biliary excretion is **p-glycoprotein.** Enterohepatic recirculaton of digoxin occurs.
  - Hepatic metabolism or biliary excretion (~25%).

- Plasma protein binding is ~25% for digoxin.
- Bioavailability (F) = 0.7 for tablets , 0.8 for elixir , 0.9 for capsule
- Usual digoxin doses for adult patients:
  - **250 µg/d** (range: 125–500 µg/d) in patients with good renal function (creatinine clearance≥80 mL/min)
  - **125 µg** every 2–3 days in patients with renal dysfunction (creatinine clearance ≤15 mL/min)

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

1) Calculate the estimated pharmacokinetic parameter
2) Steady-state concentration selection
3) Select pharmacokinetic model and equations

2. Jelliffe method

Based on total body stores (TBS) and the percent of drug that is lost on a daily basis

The pharmacokinetic dosing method

1. Calculate the estimated pharmacokinetic parameter

i. Estimate digoxin clearance

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

where **Cl_{NR}** is non-renal clearance and equals **20 mL/min** in patients with moderate-severe heart failure and **40mL/min** in patients with no or mild heart failure.

Cl_{NR} is **lower** for patients with moderate-severe heart failure because reduced cardiac output results in decreased liver blood flow and digoxin hepatic clearance

ii. 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 substances present in patients with renal dysfunction.

↓V = VB + (fB / ↑fT) VT

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

2. Steady-State Concentration Selection

For heart failure Target digoxin concentration equal to 0.8 ng/mL

For patients with atrial fibrillation Target digoxin concentration of 1.2 ng/mL

3. Selection of Appropriate Model and Equations

$D = (Css \cdot Cl \cdot \tau) / F$ $\tau = 1$ day

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

Example: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with NYHA class III moderate heart failure. His current serum creatinine is 3.5 mg/d indicating renal impairment and it has been stable over the last 5 days since admission. Compute digoxin dose for this patient.

1. *Estimate creatinine clearance.*

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$

$$CrCl_{est} = 25\ mL/min$$

2. *Estimate clearance.*

The drug clearance versus creatinine clearance relationship is used to estimate the digoxin clearance for this patient ($Cl_{NR} = 20$ mL/min since the patient has moderate heart failure):

$$Cl = 1.303\ (CrCl) + Cl_{NR} = 1.303(25\ mL/min) + 20\ mL/min = 53\ mL/min$$

3. *Use average steady-state concentration equation to compute digoxin maintenance dose.*

For a patient with heart failure the desired digoxin concentration would be 0.5–1 ng/mL. A serum concentration equal to 0.8 ng/mL will be chosen for this patient, and oral digoxin will be used (F = 0.7). Note that for concentration units ng/mL = µg/L, and this conversion will be made before the equation is used. Also, conversion factors are needed to change milliliters to liters (1000 mL/L) and minutes to days (1440 min/d).

$D/\tau = (Css \cdot Cl)/F = (0.8\ \mu g/L \cdot 53\ mL/min \cdot 1440\ min/d)/(0.7 \cdot 1000\ mL/L)$
$= 87\ \mu g/d$, or 174 µg every 2 days ($87\ \mu g/d \cdot 2\ d = 174\ \mu g$ every 2 days)
This oral tablet dose would be rounded to 125 µg every other day.

4. *Use loading dose equation to compute digoxin loading dose (if needed).*

The patient has poor renal function and is nonobese. Therefore, the volume of distribution equation that adjusts the parameter estimate for renal dysfunction can be used to compute the digoxin loading dose. An intravenous loading dose (F = 1) could be given in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used to allow concentrations to accumulate over 3–5 half-lives.

$$V = \left(226 + \frac{298 \cdot CrCl}{29.1 + CrCl}\right)(Wt/70) = \left(226 + \frac{298 \cdot 25\ mL/min}{29.1 + 25\ mL/min}\right)(70\ kg/70) = 364\ L$$

$LD = (Css \cdot V)/F = (0.8\ \mu g/L \cdot 364\ L)/1 = 291\ \mu g$ rounded to 300µg

When digoxin loading doses are administered, they are usually given in divided doses separated by 4–6 hours (50% of dose at first, followed by two additional doses of 25%). In this case, an initial intravenous dose of 150 µg would be given initially, followed by two additional intravenous doses of 75 µg each. One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

i. 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 , **13–15 µg/kg** are needed to cause chronotropic effects
    - For obese patients, use ideal body weight (IBW)
- Since renal disease (creatinine clearance **<30 mL/min**) decreases digoxin volume of distribution, digoxin total body stores decreases to **6–10 µg/kg.**

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.

3. Maintenance dose (D in µg/d)

D = [TBS · (%lost/d)] / F

Combining the two equations produces the initial digoxin maintenance dose

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

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1. *Estimate creatinine clearance.*

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$$CrCl_{est} = [(140 - age)BW] / (72 \cdot S_{Cr}) = [(140 - 50\ y)70\ kg] / (72 \cdot 3.5\ mg/dL)$$
$$CrCl_{est} = 25\ mL/min$$

2. *Estimate total body store (TBS) and maintenance dose(D).*

The patient has poor renal function and is nonobese. Digoxin total body stores of 6–10 µg/kg are recommended for patients with renal dysfunction.

$$TBS = 8\ \mu g/kg \cdot 70\ kg = 560\ \mu g$$
$$D = \{TBS \cdot [14\% + 0.20(CrCl)]\} / (F \cdot 100)$$
$$= \{560\ \mu g \cdot [14\% + 0.20(25\ mL/min)]\} / (0.7 \cdot 100)$$
$$= 152\ \mu g/d, \text{ round to } 125\ \mu g/d$$

Use of Digoxin Serum Concentrations to Alter Dosages

1. **Linear pharmacokinetics method:** $D_{new} = (Css_{new}/Css_{old})D_{old}$

2. Pharmacokinetic Parameter Method

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

Cl = [F (D/τ)] / Css

where Cl is digoxin clearance in L/d then use this actual clearance to calculate new dose

D = (Css · Cl · τ) / F

Css here is the new targeted Css

Example: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with moderate heart failure. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 6 months. A digoxin dose of 250 µg/d using oral tablets was prescribed

and expected to achieve steady-state concentrations equal to 0.8 ng/mL. After a week of treatment, a steady-state digoxin concentration was measured and equalled 0.6 ng/mL. Calculate a new digoxin dose that would provide a steady-state concentration of 0.9 ng/mL

Compute drug clearance.

$$Cl = [F(D/\tau)] / Css = [0.7(250\ \mu g/d)] / 0.6\ \mu g/L = 292\ L/d$$

Compute new dose to achieve desired serum concentration.

$$D/\tau = (Css \cdot Cl) / F = (0.9\ \mu g/L \cdot 292\ L/d) / 0.7 = 375\ \mu g/d$$

The new suggested dose would be 375 µg/d given as digoxin tablets to be started at next scheduled dosing time.

Use of Digoxin Booster Doses to Immediately Increase Serum Concentration

- 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

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

$$LD = Css.\ V$$

Example: 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?

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

V= 7 L/kg = 7*85=595

BD = [(1.5 µg/L – 0.6 µg/L) 595 L] / 1

= 536 µg, rounded to 500 µg

Conversion of patient doses between dosage forms

DPO = DIV/ F

DIV is the equivalent digoxin intravenous dose in µg, DPO is the equivalent digoxin oral dose

Example 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?

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

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

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 to a dose that could be given as a tablet. 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 ng/mL (250 µg / 286 µg) = 1.1 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 respons e monitored, and an additional 10 vials administered.

- Each vial contains 40 mg of digoxin specific antibody fragments.

2. To treat chronic digoxin overdoses

- ✓ 6 vials are usually needed for adults and older children
- ✓ 1 vial is usually adequate for children under the weight of 20 kg

- Chronic digoxin toxicity may result from deteriorating renal function, dehydration, electrolyte disturbances or drug interactions.

3. Chronic overdose or acute overdose 8–12 hours after ingestion with known serum conc.

- ✓ 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 (in vials) = (Digoxin concentration in ng/mL) (Body weight in kg) / 100

4. Acute overdose where number of tablets is known or can be estimated

- ✓ 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 in mg (Note: 250 μg = 0.25 mg)

- ✓ 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

- **<u>Example</u> 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?**

chronic overdose with known serum conc.

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

= (4.1 ng/ml · 80 kg)/100 = 3.3 vials, rounded up to 4 vials

Example: 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.

Acute overdose with known no. of tablets

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

Suggested bioavailability constant for digoxin in the Digibind package insert is 0.8 for tablets and 1 for capsules which allows for variability in the fraction of the dose that was absorbed.