TDM of Digoxin

- REFERENCE: APPLIED CLINICAL PHARMACOKINETICS
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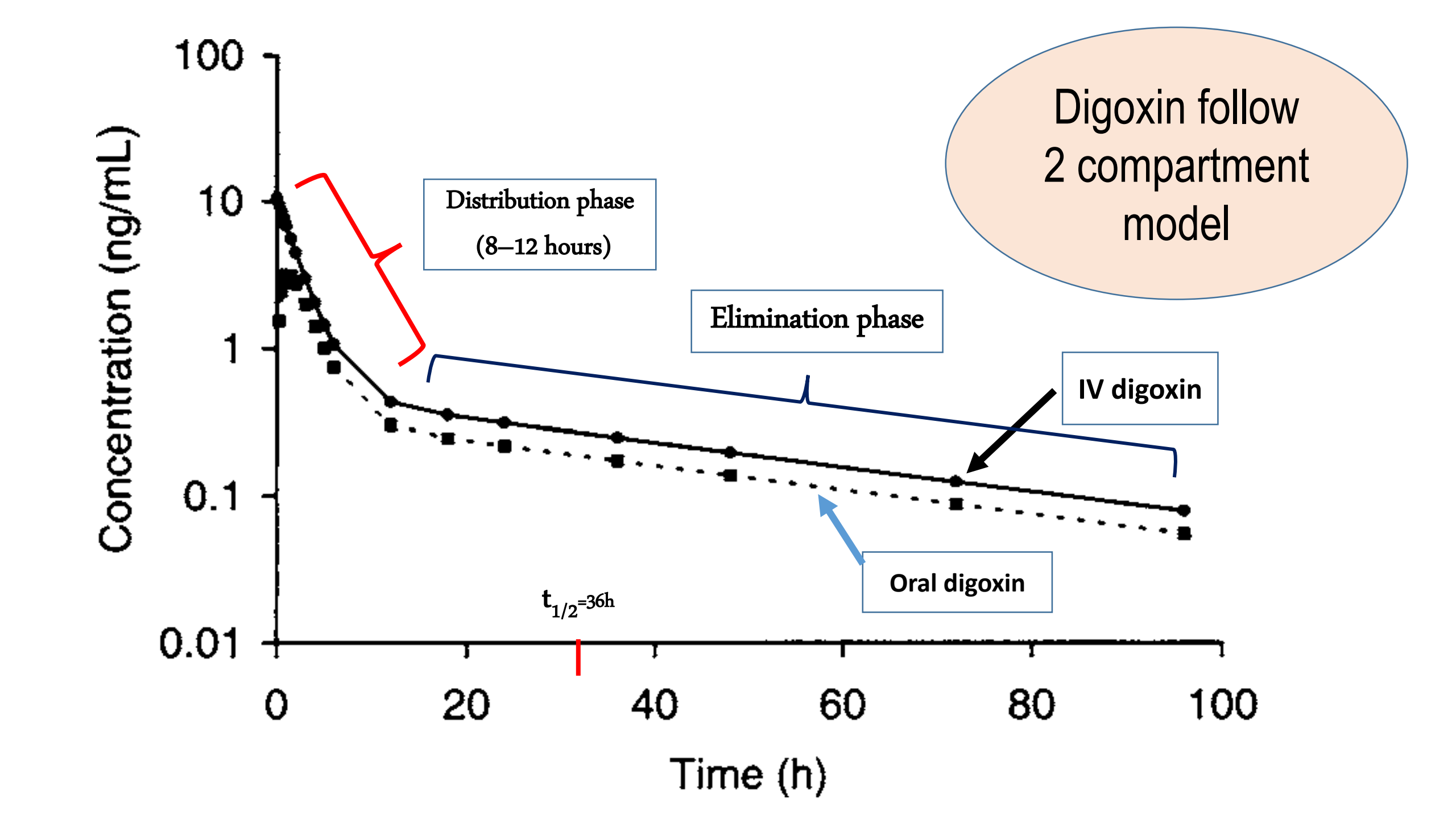
- Digoxin is the primary cardiac glycoside in clinical use.
- Digoxin is used for the treatment of congestive heart failure (CHF) because of its inotropic effects on the myocardium and atrial fibrillation because of its chronotropic effects.
- When given as oral or intravenous doses, the serum digoxin concentration–time curve follows a two-compartment model and exhibits a long and large distribution phase of 8–12 hours.


Digoxin follow
2 compartment
model
Distribution phase
(8–12 hours)
Elimination phase
IV digoxin
Oral digoxin
$t_{1/2}$=36h
Concentration (ng/mL)
100
10
1
0.1
0.01
0
20
40
60
80
100
Time (h)

Therapeutic and Toxic Concentrations

- **Inotropic Effects** of digoxin are generally achieved at steady-state serum concentrations of **0.5 - 1ng/mL (0.8)**.
- **Chronotropic Effects** usually require higher digoxin steady-state serum concentrations of **0.8 – 1.5 ng/mL (1.2)**.
- **Adverse drug reactions** increase at steady-state digoxin serum concentration above **2 ng/mL**
- **Digoxin toxicity** increase at serum concentration of **2.5 ng/mL** or above

Basic Clinical Pharmacokinetic Parameters

- Digoxin elimination from the body occurs by two routes:

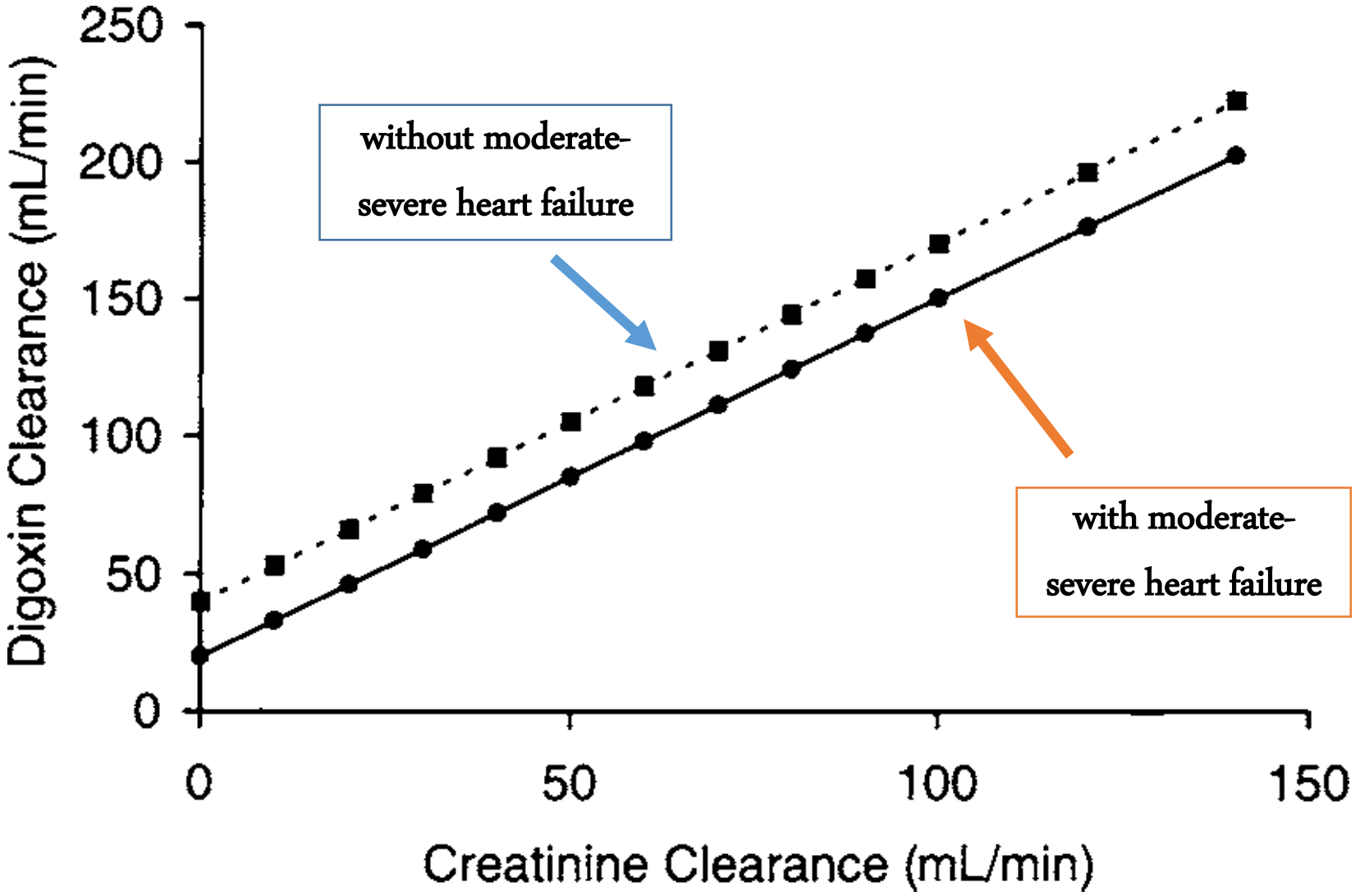
1. **~75%** via **kidney** (by glomerular filtration and active tubular secretion)
2. **~25% via hepatic** metabolism or biliary excretion

- Plasma protein binding is **~25%** for digoxin.
- Average bioavailability constants (F) for the: **tablet=0.7,**

elixir=0.8,

capsule =0.9.

Digoxin clearance is proportional to creatinine clearance for patients with or without moderate-severe heart failure.



Usual Digoxin Doses for Adult Patients:

- **250 µg/day** (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 clearnace ≤15 mL/min).

Disease States and Conditions that alter Digoxin Pharmacokinetics

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.

$$t_{1/2} = \frac{0.693V}{Cl}$$

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.

$$t_{1/2} = \frac{0.693V}{Cl}$$

Initial Dosage Determination Methods

1-The pharmacokinetic dosing method

2- Jelliffe method

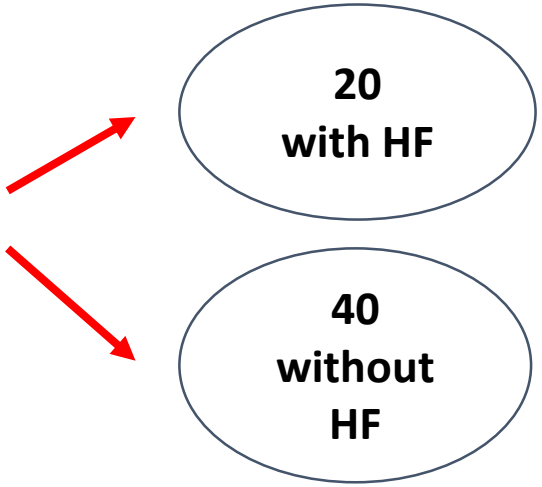
The pharmacokinetic dosing method

- The most flexible technique.
- It allows individualized target serum concentrations for a patient,
- Each pharmacokinetic parameter can be customized to reflect specific disease states and conditions present in the patient.

Calculations steps:

1- Estimate digoxin clearance

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



- **Cl is the digoxin clearance in mL/min,**
- **CrCl is creatinine clearance in mL/min, and**
- **Cl_{NR} is digoxin non-renal clearance.**

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

2- Estimate digoxin volume of distribution

V= 7 L/kg

If obese use **IBW**

- In renal dysfunction (creatinine clearance $\leq$30 mL/min) USE:

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

3-Steady-State Concentration Selection

- For heart failure ……. Css = **0.5–1 ng/mL**

  Target digoxin concentration equal to 0.8 ng/mL

- For atrial fibrillation …… Css = **0.8–1.5 ng/mL**

  Target digoxin concentration of 1.2 ng/mL

Note:

ng/mL = µg/L

4-Selection of Appropriate Model and Equations

- $D = (Css \cdot Cl \cdot \tau) / F$
- $Css = [F (D/\tau)] / Cl$ τ = 1 day
- $LD = (Css \cdot V) / F$

- D is the digoxin dose in μg,
- τ is the dosage interval in days, and
- Cl is digoxin clearance in L/d.
- F is the bioavailability fraction for the oral dosage form (F = 1 for intravenous digoxin)

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute an **intravenous digoxin** dose for this patient to control **ventricular rate**.

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:

$$\text{CrClest} = [(140 - \text{age})\text{BW}] / (72 \cdot \text{SCr})$$

$$= [(140 - 50\ \text{y})70\ \text{kg}] / (72 \cdot 0.9\ \text{mg/dL})$$

$$\text{CrClest} = 97\ \text{mL/min}$$

2. Estimate clearance.

$$Cl = 1.303\,(CrCl) + Cl_{NR}$$

$$= 1.303\,(97\ mL/min) + 40\ mL/min$$

$$= 167\ mL/min$$

the patient does not have moderate to severe heart failure

3. Css for atrial fibrillation= 1.2 ng/mL

F=1 for IV route

To covert unit of Cl from ml/min to L/day

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

$$= (1.2\ \mu g/L \cdot 167\ mL/min \cdot 1440\ min/d) / (1 \cdot 1000\ mL/L) / 1$$

$$= 288\ \mu g/d, \text{ round to } 250\ \mu g/d$$

4. Use loading dose equation to compute digoxin loading dose

$V = 7\ L/kg \cdot 70\ kg = 490\ L$

$LD = (Css \cdot V) / F$

$= (1.2\ \mu g/L \cdot 490\ L) / 1$

$= 588\ \mu g$ rounded to $500\ \mu g$

- ***Note***

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 250 μg would be given initially, followed by two additional intravenous doses of 125 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.

Jelliffe method

- This method depend on the amount of digoxin in the body that produces the desired effect, which is known at the **total body stores (TBS)** of digoxin.
- **In normal renal function**,

- Digoxin TBS = 8–12 µg/kg required to cause inotropic effects,
- Digoxin TBS = 13–15 µg/kg needed to cause chronotropic effects.

Use IBW in obese patients

- **In renal dysfunction**,

- Digoxin TBS = 6–10 µg/kg

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

$$\%\text{lost/d} = 14\% + 0.20(\text{CrCl})$$

the percent of digoxin eliminated per day by non-renal routes

CrCl is creatinine clearance in mL/min

The maintenance dose and loading dose

➢ The maintenance dose:

$$MD\ (\mu g/d) = [TBS \cdot (\%lost/d)] / F$$

Substitute with **[14% + 0.20(CrCl)]**

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

➢ The loading dose:

$$LD = TBS / F$$

A conversion factor to convert the percentage to a fraction

Example 1 MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute an **intravenous** digoxin dose for this patient to control **ventricular rate**.

1. ***Estimate creatinine clearance****....* CrClest = 97 mL/min

2. ***Estimate total body store (TBS)***

The patient has good renal function and is non-obese. Digoxin total body stores of 13–15 μg/kg are effective in the treatment of atrial fibrillation. A digoxin dose of 14 μg/kg is chosen for this patient:

$$\mathbf{TBS = 14\ \mu g/kg \cdot 70\ kg = 980\ \mu g}$$

3. *Calculate maintenance dose (D).*

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

$$= \{980\ \mu g \cdot [14\% + 0.20(97\ mL/min)]\} / (1 \cdot 100)$$

$$= 328\ \mu g/d, \text{ round to } 375\ \mu g/d$$

4. *Calculate loading dose*

$$LD = TBS/\ F = 980\ \mu g\ /\ 1 = 980\ \mu g, \text{ round to } 1000\ \mu g$$

USE OF DIGOXIN SERUM CONCENTRATIONS TO ALTER DOSAGES

1-Linear Pharmacokinetics Method

- The advantages of this method are that it is quick and simple.

- The disadvantages are steady-state concentrations are required.

$$D_{new} = (C_{ss,new}/C_{ss,old})D_{old}$$

Example 1 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.

1. Check if digoxin conc. reach to steady state.. (CrCl+Vd+t1/2)

2. Dnew = (Css,new/Css,old)Dold

= (0.9 ng/mL / 0.6 ng/mL) 250 µg/d

= 375 µg/d

انتبـه..
يجب اولا
التأكد من
وصول التركيز
الـى حالـــة
steady
state

2-Pharmacokinetic Parameter Method

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

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

where Cl is digoxin clearance in L/d

- Then use this actual clearance to calculate new dose:

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

Example 1 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.

1. *Compute drug clearance.*

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

2. Compute new dose to achieve desired serum concentration.

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

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.

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

$$\mathbf{V = 7\ L/kg \cdot 85\ kg = 595\ L}$$

2. *Compute booster dose.*

BD = [(Cdesired– Cactual) V]/F = [(1.5 μg/L – 0.6 μg/L) 595 L] / 1

= 536 μg, rounded to 500 μg of digoxin.

Conversion of Patient Doses Between Dosage Forms

- When patients are switched between digoxin dosage forms, differences in **bioavailability** should be accounted, using the following equation:

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

D_{IV} is the equivalent digoxin intravenous dose in μg,

D_{PO} is the equivalent digoxin oral dose, and

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 1 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.*

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

- **Css new = Css old(Drounded/Dcomputed) = 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
- Improvements in digoxin adverse effects can be seen within **30 minutes** of digoxin immune Fab administration.

Use of Digoxin Immune Fab in Digoxin Overdoses

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, if necessary).

2. To treat chronic digoxin overdoses, 6 vials are usually needed for adults and older children while 1 vial is usually adequate for children under the weight of 20 kg

3. Chronic Overdose or Acute Overdose 8–12 Hours After Ingestion

- In these cases, a postabsorption, postdistribution 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 (ng/mL)][body weight (kg)] / 100

Example 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.

Digibind dose (in vials) = [digoxin concentration (ng/mL)][body weight (kg)]/100

= (4.1 ng/mL · 80 kg)/100

= 3.3 vials, rounded up to 4 vials

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:

$$\text{TBS} = F\,(\#\text{ dosage units})\,(\text{dosage form strength (mg)})$$

#dosage units: is the number of tablets or capsules

- 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:

$$\text{Digibind dose} = \text{TBS}/\,(0.5\ \text{mg/vial})$$

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.

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

  = 0.7 (50 tablets · 0.25 mg/tablet)

  = 8.75 mg

- **Digibind dose = TBS/ (0.5 mg/vial)**

  = 8.75 mg / (0.5 mg/vial)

  = 17.5 vials ==== 18


ANY
Questions?