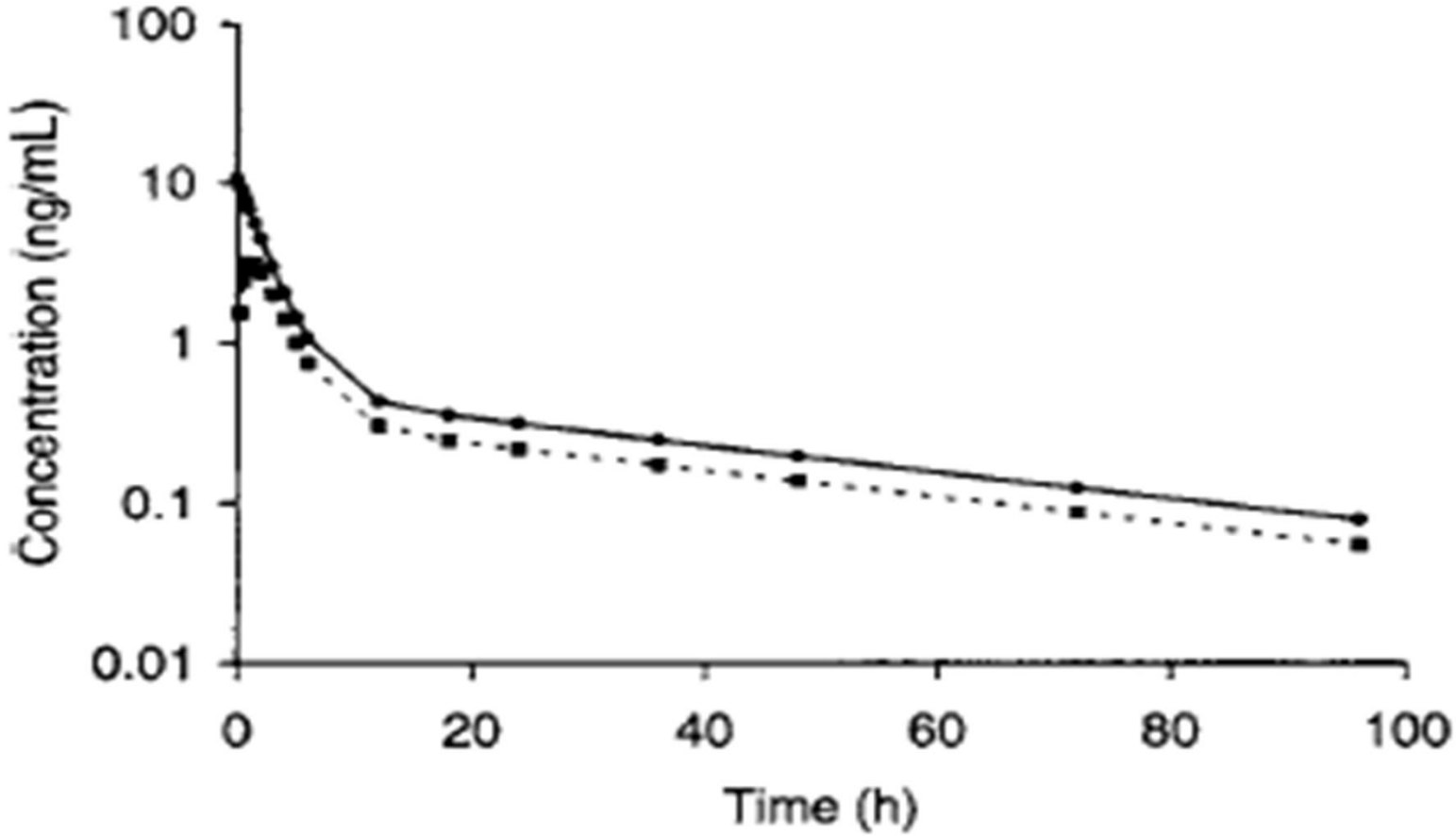
Digoxin

- Digoxin is the primary cardiac glycoside in clinical use and it is used for the treatment of

1. congestive heart failure (CHF) because of its inotropic effects on the myocardium and

2. for the treatment of atrial fibrillation because of its chronotropic effects on the electrophysiological system of the heart.

- 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.


100
10
1
0.1
0.01
Concentration (ng/mL)
0
20
40
60
80
100
Time (h)

- Clinically beneficial inotropic effects of digoxin are generally achieved at steady-state serum concentrations of 0.5–1 ng/mL.

- Increasing steady-state serum concentrations to 1.2–1.5 ng/mL may provide some minor, additional inotropic effect.

- Chronotropic effects usually require higher digoxin steady-state serum concentrations of 0.8–1.5 ng/mL.

- Additional chronotropic effects may be observed at digoxin steady-state serum concentrations as high as 2 ng/mL.

- Because of pharmacodynamic variability, clinicians should consider these ranges as initial guidelines and rely heavily on patient response to monitor digoxin therapy.

- 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

- Most digoxin side effects involve the **gastointestinal tract**, **central nervous system**, or **cardiovascular system**.

- Gastrointestinal-related adverse effects include anorexia, nausea, vomiting, diarrhea, abdominal pain, or constipation.

- Central nervous system side effects are headache, fatigue, insomnia, confusion, or vertigo.

- Visual disturbances can also occur and are manifested as blurred vision and changes in color vision or colored halos around objects often times involving the yellow-green spectrum.

- Cardiac side effects commonly include second or third degree atrioventricular block, atrioventricular dissociation, bradycardia, premature ventricular contractions, or ventricular tachycardia.

- In the case of life-threatening digoxin overdose, digoxin antigen binding fragments or digoxin immune Fab (Digibind) are portions of digoxin-specific antibodies that can be used to rapidly reverse the adverse symptoms.

Basic Clinical Pharmacokinetic 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 remainder removed by hepatic metabolism or biliary excretion. Enterohepatic recirculation of digoxin occurs.

- Digoxin is given as an IV injection or orally as a tablet, capsule, or elixir. When given intravenously, doses should be infused over at least **5-10** minutes.

- Average bioavailability constants (F) for the tablet, capsule, and elixir are 0.7, 0.9, and 0.8. Digoxin is not usually administered IM due to erratic absorption and severe pain at the injection site.

- Plasma protein binding is ~25%.

- Usual digoxin doses for adults are 250 µg/d (range: 125–500 µg/d) in patients with good renal function (creatinine clearance ≥80 mL/min) and 125 µg every 2–3 days in patients with renal dysfunction (creatinineclearnace ≤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.

- **Drug Interactions**
- **Quinidine** decreases both the renal and nonrenal clearance of digoxin and also decreases the Vd of digoxin.
- **Verapamil**, **diltiazem**, and **bepridil** inhibit digoxin clearance and increase mean digoxin steady-state concentrations by various degrees.
- **Amiodarone** is antiarrhythmic agents that decrease digoxin clearance. In addition to this drug interaction mechanism, amiodarone also simultaneously increases digoxin oral bioavailability.

- **Metoclopramide** and **cisapride** decreases oral digoxin bioavailability by decreasing gastrointestinal transit time.

Pharmacokinetic Dosing Method

- Clearance Estimate:

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

- Where: Cl is the digoxin clearance in mL/min, CrCl is creatinine clearance in mL/min, and Cl_{NR} is digoxin nonrenal clearance.

- A digoxin nonrenal clearance value of **40 mL/min** is used for patients without heart failure or who have only mild signs and symptoms of heart failure

- Patients with moderate or severe heart failure have significant decreases in cardiac output which leads to a reduction in liver blood flow and digoxin hepatic clearance . In these cases, digoxin nonrenal clearance is set to equal **20 mL/min** in the equation.

- For example, the estimated digoxin clearance for an individual with a creatinine clearance of 10 mL/min is ……. mL/min if the patient has no or mild symptoms of heart failure
- [Cl = 1.303(10 mL/min) + 40 = 53 mL/min]

- Or ….. mL/min if the patient has moderate-to-severe symptoms of heart failure
- [Cl = 1.303 (10 mL/min) + 20 = 33 mL/min].
- Taking the patient's renal function into account when deriving initial doses of digoxin is the single most important characteristic to assess.

Volume Of Distribution Estimate:

- The average volume of distribution for patients without disease states and conditions that change this parameter is 7 L/kg.

- Because obesity does not change digoxin volume of distribution, the weight factor used in this calculation is ideal body weight (IBW) for patients that are significantly overweight (>30% over IBW).

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

STEADY-STATE CONCENTRATION SELECTION

- Digoxin steady-state concentrations are selected based on the cardiovascular disease being treated.

- For heart failure, steady-state serum concentrations of 0.5–1 ng/mL are usually effective

- For initial dosing purposes, a target digoxin concentration equal to 0.8 ng/mL is reasonable.

- For patients with atrial fibrillation, steady-state serum concentrations of 0.8–1.5 ng/mL are usually needed to control the ventricular rate to 100 beats/min or less.

- An initial target digoxin concentration of 1.2 ng/mL is reasonable for patients with this disease state.

- Pharmacokinetics Models
- Very simple pharmcokinetic equation that computes the average digoxin steady-state serum concentration (Css in ng/mL = µg/L) is widely used and allows maintenence dosage calculation:
- $Css = [F(D/\tau)] / Cl$
- $D/\tau = (Css * Cl) / F$
- $LD = (Css * V) / F$

- **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.

- *Estimate creatinine clearance.*
- Cockcroft-Gault equation
- CrClest = [(140 – age)BW] / (72 · SCr) =

- [(140 – 50 y)70 kg] / (72 · 0.9 mg/dL) CrClest =

- 97 mL/min

- *Estimate clearance.*
- Cl = 1.303 (CrCl) + ClNR
- ClNR = 40 mL/min since the patient does not have moderateto- severe heart failure

- 1.303(97 mL/min) + 40 mL/min = 167 mL/min

- *Use average steady-state concentration equation to compute digoxin maintenance dose*
- For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/mL.

- A serum concentration equal to 1.2 ng/mL will be chosen for this patient, and intravenous digoxin will be used (F = 1).
- 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).

- $D/\tau = (Css \cdot Cl) / F =$
- $(1.2\ \mu g/L \cdot 167\ mL/min \cdot 1440\ min/d) / (1 \cdot 1000\ mL/L) =$
- 288 µg/d, round to 250 µg/d

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

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

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

- $(1.2\ \mu g/L \cdot 490\ L) / 1 = 588\ \mu g$ rounded to $500\ \mu g$

- 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.

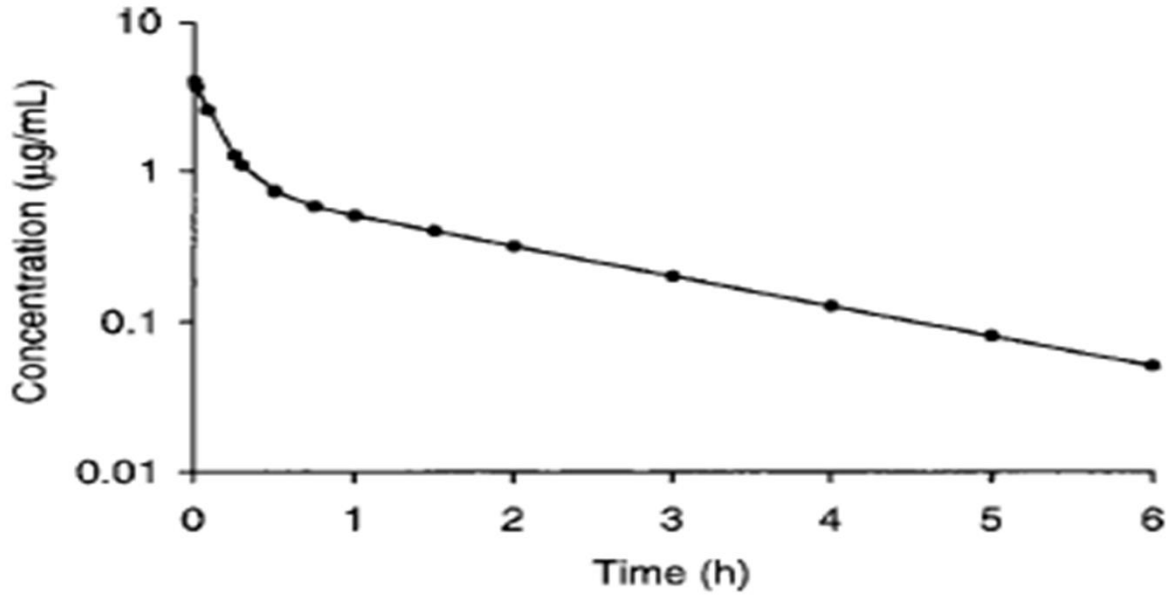
LIDOCAINE

- Lidocaine is a local anesthetic agent that also has antiarrhythmic effects.

- It is classified as a type IB antiarrhythmic agent and is a treatment for ventricular tachycardia or ventricular fibrillation

Basic Clinical Pharmacokinetic Parameters

- When given intravenously, the serum lidocaine concentration/time curve follows a two compartment model.



- This is especially apparent when initial loading doses of Lidocaine are given as rapid intravenous injections over 1–5 minutes (maximum rate: 25–50 mg/min) and a distribution phase of 30-40 minutes is observed after drug administration.

- Unlike digoxin, the myocardium responds to the higher concentrations achieved during the distribution phase because lidocaine moves rapidly from the blood into the heart, and the onset of action for lidocaine after a loading dose is within a few minutes after completion of the intravenous injection.

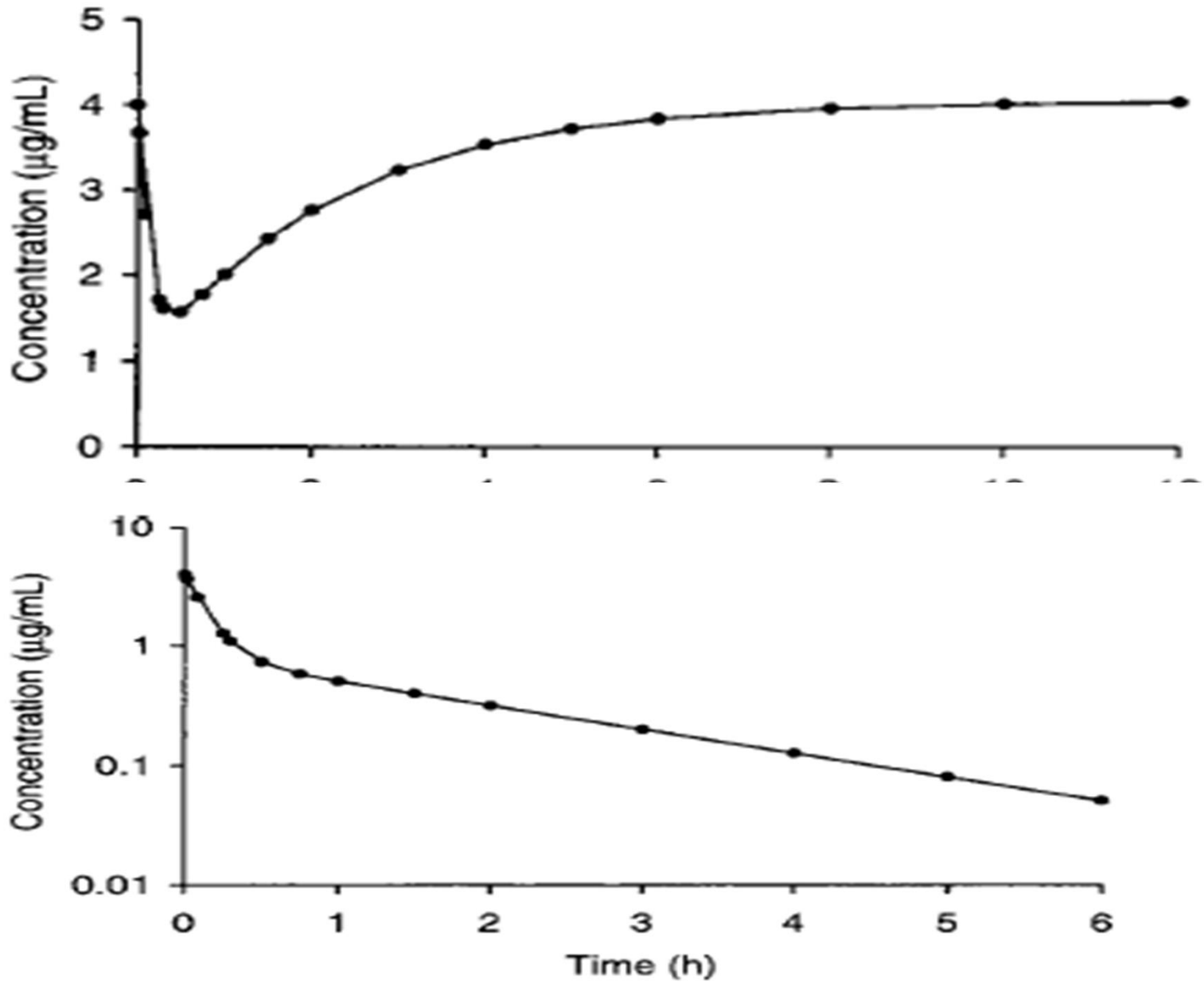
- The generally accepted therapeutic range for lidocaine is **1.5-5** µg/mL.

- In the upper end of the therapeutic range (>3 µg/mL), some patients will experience minor side effects including drowsiness, dizziness, paresthesias, or euphoria.

- Lidocaine serum concentrations above the therapeutic range can cause muscle twitching, confusion, agitation, dysarthria, psychosis, seizures, or coma.

- Cardiovascular adverse effects such as atrioventricular block, hypotension, and circulatory collapse have been reported at lidocaine concentrations above 6 µg/mL, but are not strongly correlated with specific serum levels.

- For dose adjustment purposes, lidocaine serum concentrations are best measured at steady state after the patient has received a consistent dosage regimen for 3–5 drug halflives.
- Lidocaine half-life varies from 1–1.5 hours in normal adults to 5 hours or more in adult patients with liver failure.


Concentration (µg/mL)
5
4
3
2
1
0
Concentration (µg/mL)
10
1
0.1
0.01
0
1
2
3
4
5
6
Time (h)

- After a lidocaine loading dose is given, serum concentrations from this dose rapidly decline due to distribution from blood to tissues, and serum concentrations due to the infusion are not able to increase rapidly enough to avoid a temporary decline or dip in lidocaine concentrations.

- The decline may be severe enough that ventricular arrhythmias which were initially suppressed by lidocaine may recur due to subtherapeutic antiarrhythmic concentrations.

- Because of this dip in concentrations due to distribution of drug after the intravenous loading dose, an additional dose (50% of original loading dose) can be given 20–30 minutes after the original loading dose or several additional doses.

- (33–50% of original loading dose) can be given every 5–10 minutes to a total maximum of 3 mg/kg

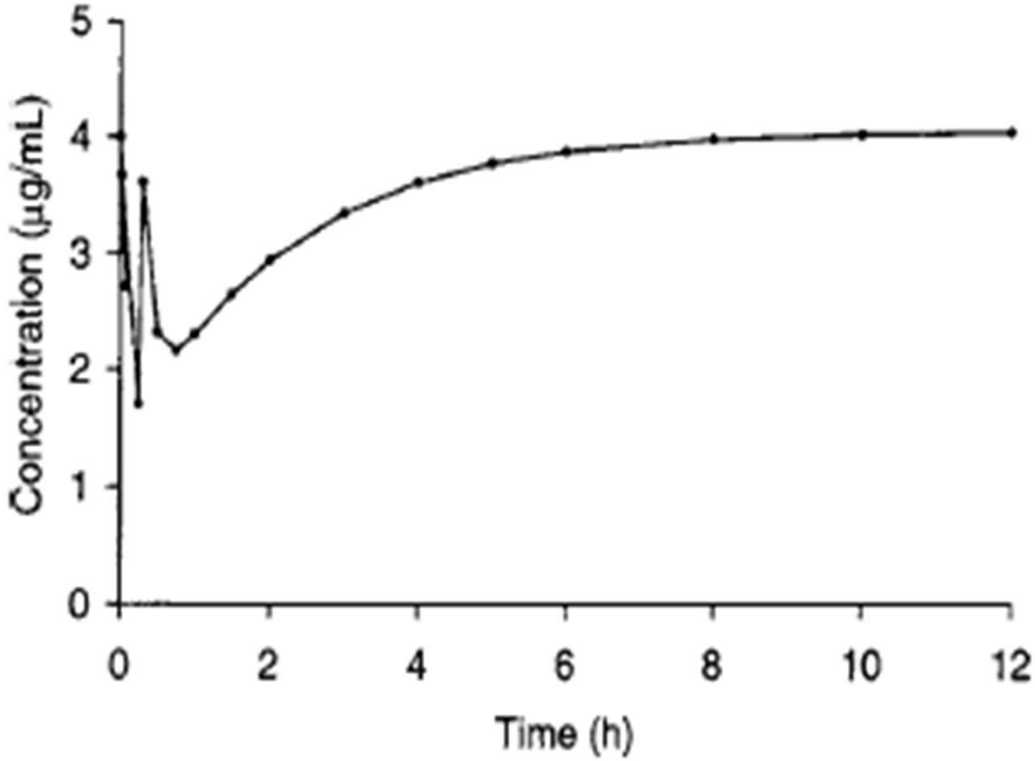


FIGURE 7-4 Since the dip in serum lidocaine concentrations below therapeutic amounts can allow previously treated arrhythmias to recur, a supplemental loading or "booster" dose is typically given 20–30 minutes after the initial loading dose. This prevents lidocaine serum concentrations from declining too far during the distribution phase of the intravenous bolus dose and before serum concentrations from the intravenous infusion have had an opportunity to attain therapeutic concentrations.

CLINICAL MONITORING PARAMETERS

- The electrocardiogram (ECG) should be monitored to determine the response to lidocaine in patients with ventricular tachycardia or fibrillation.

- The goal of therapy is suppression of ventricular arrhythmias and avoidance of adverse drug reactions.

- Lidocaine therapy is often discontinued after 6–24 hours of treatment so the need for long term antiarrhythmic drug use can be reassessed, although longer infusions may be used in patients with persistent tachyarrhythmias.

- Because lidocaine is usually given for a short duration (<24 hours), it is often not necessary to obtain serum lidocaine concentrations in patients receiving appropriate doses who currently have no ventricular arrhythmia or adverse drug effects.

- However, lidocaine serum concentrations should be obtained in patients who have a recurrence of ventricular tachyarrhythmias, are experiencing possible lidocaine side effects, or are receiving lidocaine doses not consistent with disease states and conditions known to alter lidocaine pharmacokinetics

- Serum concentration monitoring can aid in the decision to increase or decrease the lidocaine dose.

- For instance, if the ventricular arrhythmia reappears and the lidocaine serum concentration is <5 µg/mL, increasing the lidocaine dose is a therapeutic option.

- However, if the lidocaine serum concentration is over 5 µg/mL, it is unlikely a dosage increase will be effective in suppressing the arrhythmia and there is an increased likelihood that drug side effects may occur.

- Similarly, if a possible lidocaine adverse drug reaction is noted in a patient and the lidocaine serum concentration is <3–5 μg/mL, it is possible that the observed problem may not be due to lidocaine treatment and other sources can be investigated

- Patients receiving lidocaine infusions for longer than 24 hours are prone to unexpected accumulation of lidocaine concentrations in the serum and should be closely monitored for lidocaine side effects.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

- Lidocaine is almost completely eliminated by hepatic metabolism (>95%).

- Hepatic metabolism is mainly via the CYP3A enzyme system.

- Lidocaine metabolites have some antiarrhythmic activity and have also been implicated as the cause of some adverse effects attributed to lidocaine therapy.

- Because these metabolites are eliminated by the kidney, patients with renal failure should be monitored for adverse effects due to metabolite accumulation even though lidocaine serum concentrations are within the therapeutic range

- . The hepatic extraction ratio of lidocaine is about 70%, so lidocaine is typically classified as a high extraction ratio drug.

- Lidocaine is usually given intravenously but may also be given **intramuscularly**.
- After intramuscular injection, absorption is rapid and complete with maximum concentrations occurring about 1 hour after administration and 100% bioavailability as long as the patient's peripheral circulation is not compromised due to hypotension or shock.

- Plasma protein binding in normal individuals is about 70%.
- Of this value, approximately 30% is due to drug binding to albumin while 70% is due to lidocaine bound to α1-acid glycoprotein (AGP)

- AGP is classified as an acute phase reactant protein that is present in lower amounts in all individuals but is secreted in large amounts in response to certain stresses and disease states such as *trauma*, *heart failure*, and *myocardial infarction*.
- In patients with these disease states, lidocaine binding to AGP can be even larger resulting in an unbound fraction as low as 10–15%.

- AGP concentrations continuously increase during the first 12–72 hours after a myocardial infarction, and, as a result, the lidocaine unbound fraction decreases on average from about 30% to 20% during this time period.

- Patients without myocardial infarction experience ***accumulation*** of lidocaine concentrations during long-term (>24 hours) infusions due to competition for hepatic metabolism between parent drug and metabolites.

- Thus, monitoring for adverse reactions in patients receiving long-term lidocaine infusions is important, and lidocaine serum concentrations can be useful adjuncts to avoid lidocaine toxicity.

EFFECTS OF DISEASE STATES AND CONDITIONS ON LIDOCAINE PHARMACOKINETICS AND DOSING

TABLE 7-1 Disease States and Conditions that Alter Lidocaine Pharmacokinetics

DISEASE STATE/ CONDITION	HALF-LIFE	CENTRAL VOLUME OF DISTRIBUTION (Vc)	VOLUME OF DISTRIBUTION FOR ENTIRE BODY (V_{area})	COMMENT
Adult, normal liver function	1.5 hours (range: 1–2 hours)	0.5 L/kg (range: 0.4–0.6 L/kg)	1.5 L/kg (range: 1–2 L/kg)	Lidocaine has a high hepatic extraction ratio of ~70%, so liver blood flow is primary determinate of clearance rate. Accumulation of serum lidocaine concentrations can occur with long-term (>24 h) infusions.
Adult, hepatic disease (liver cirrhosis or acute hepatitis)	5 hours	0.6 L/kg	2.6 L/kg	Lidocaine is metabolized >95% by hepatic microsomal enzymes (primarily CYP3A), so

				plasma.
Adult, heart failure	2 hours	0.3 L/kg	1 L/kg	Decreased liver blood flow secondary to reduced cardiac output reduces lidocaine clearance. Volumes of distribution are smaller due to diac output.
Adult, postmyocardial infarction (<12 h)	4 hours	0.5 L/kg	1.5 L/kg	Myocardial infarction reduces cardiac output, resulting in variable reduc

DRUG INTERACTIONS

- Lidocaine has serious drug interactions with β-adrenergic receptor blockers and cimetidine
- that decrease lidocaine clearance 30% or more.

- Lidocaine clearance may be accelerated by concomitant use of phenobarbital or
- phenytoin.32 Both of these agents are known to be hepatic drug metabolizing enzyme
- inducers, and this is the probable mechanism of their drug interaction with lidocaine.

INITIAL DOSAGE DETERMINATION METHODS

- Unfortunately, there is no good way to estimate the elimination characteristics of liver metabolized drugs using an endogenous marker of liver function in the same manner that serum creatinine and estimated creatinine clearance are used to estimate the elimination of agents that are renally eliminated.

- Because of this, a patient is categorized according to the disease states and conditions that are known to change lidocaine half-life, and ***the half-life previously measured in these studies*** is used as an estimate of the current patient's half-life.

- Once the correct half-life is identified for the patient, it can be converted into the lidocaine elimination rate constant (k) using the following equation: $k = 0.693/t_{1/2}$.

VOLUME OF DISTRIBUTION ESTIMATE

- As with the half-life estimate, lidocaine volume of distribution values are chosen according to the disease states and conditions.

- The ***central volume of distribution*** (Vc) is used to ***compute loading doses.***

- The ***volume of distribution for the entire body*** after distribution is complete (Varea) is used to help compute lidocaine ***clearance.***

SELECTION OF APPROPRIATE PHARMACOKINETIC MODEL AND EQUATIONS

- When given by continuous intravenous infusion, lidocaine follows a two-compartment pharmacokinetic model.
- $Css = k0 / Cl$
- $k0 = Css \cdot Cl$
- $Cl = k\ Varea$
- $LD = (Css \cdot Vc)$

- Intravenous lidocaine loading doses should be given as an intravenous bolus no faster than 25–50 mg/min.

STEADY-STATE CONCENTRATION SELECTION

- The general accepted therapeutic range for lidocaine is 1.5–5 µg/mL.

- However, lidocaine therapy much be individualized for each patient in order to achieve optimal responses and minimal side effects.

- LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with **intravenous lidocaine**. He has normal liver and cardiac function. Suggest **an initial intravenous lidocaine** dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 µg/mL.

- *Estimate half-life and elimination rate constant according to disease states and conditions present in the patient.*

- The expected lidocaine half-life (t1/2) is 1.5 hours.
- The elimination rate constant is computed using the following formula: k = 0.693 / t1/2 = 0.693 / 1.5 h = 0.462 h−1.

- *Compute dosage regimen*
- Therapy will be started by administering an intravenous loading dose of lidocaine to the patient
- LD =
- $C_{ss} \cdot V_c$ =
- 3 mg/L · 38 L = 114 mg,
- An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

- A lidocaine continuous intravenous infusion will be started immediately after the loading
- dose has been administered.
- $k_0 = Css \cdot Cl =$
- $Cl = k\ Varea$
- $(3\ mg/L \cdot 52.2\ L/h)\ /(60\ min/h) =$
- 2.6 mg/min, rounded to 2.5 mg/min.

USE OF LIDOCAINE SERUM CONCENTRATIONS TO ALTER DOSES

- Because of the large amount of pharmacokinetic variability among patients, it is likely that doses computed using patient population characteristics will not always produce lidocaine serum concentrations that are expected or desirable.

- When lidocaine serum concentrations are measured in patients and a dosage change is necessary, clinicians should seek to use the simplest, most straightforward method available to determine a dose that will provide safe and effective treatment.

Linear Pharmacokinetics Method

- Because lidocaine follows linear, dose-proportional pharmacokinetics in most patients during short-term infusions (<24 hours), steady-state serum concentrations change in proportion to dose according to the following equation:
- $D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$ or
- $D_{new} = (C_{ss,new} / C_{ss,old}) D_{old}$

- OI is a 60-year-old, 85-kg (6 ft 1 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has ***liver cirrhosis*** (Child-Pugh score = 11). The current steady-state lidocaine concentration equals 6.4 µg/mL at a dose of 2 mg/min. Compute a lidocaine ***dose*** that will provide a steady-state concentration of 3 µg/mL.

Pharmacokinetic Parameter Method

- The pharmacokinetic parameter method of adjusting drug doses was among the first techniques available to change doses using serum concentrations. It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose that achieves desired lidocaine concentrations.

- **$Cl = k_0/Css,$**

- **Example 1** LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has **normal liver and cardiac function**. The current steady-state lidocaine concentration equals 2.2 µg/mL at a dose of 2 mg/min. Compute a lidocaine ***dose*** that will provide a steady-state concentration of 4 µg/mL.

- $Cl = k_0 / Css =$
- (2 mg/min) / (2.2 mg/L) = 0.91 L/min.

- *Compute lidocaine dose*
- $k_0 = Css \cdot Cl =$
- 4 mg/L · 0.91 L/min =
- 3.6 mg/min, round to 3.5 mg/min.