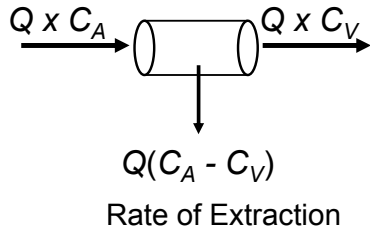


HEPATIC CLEARANCE

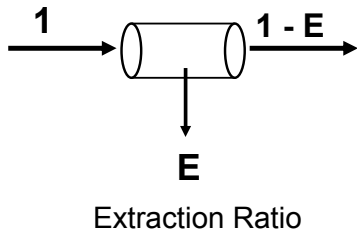
1. Mass Balance



1

HEPATIC CLEARANCE

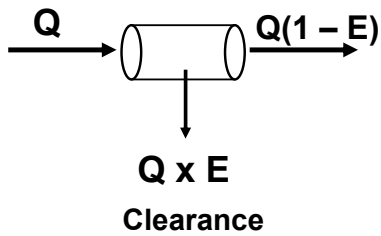
2. Mass Balance Normalized to Rate of Entry



2

HEPATIC CLEARANCE

3. Mass Balance Normalized to C_A



3

Recall that $CL = QE$; hence

$$CL_H = Q_H E$$

CL_H = hepatic clearance

Q_H = hepatic blood flow

E = hepatic extraction ratio

Q_H - from 1.0 to 1.5 L/min

E - ranges from 0 to 1

4

Recall that $CL = QE$; hence

$$CL_H = Q_H E$$

Thus, if the non-renal clearance of a drug exceeds Q_H , some form of non-renal and non-hepatic elimination must take place.

5

Example: (labetalol)

$$CL_T = 2.344 \text{ L/min}$$

$$CL_R = 0.08 \text{ L/min}$$

$$V_{ss} = 685 \text{ L}$$

$$t_{1/2} = 6 \text{ hr}$$

Can the nonrenal clearance be attributed solely to hepatic elimination?

6

$$CL_H = Q_H E$$

Suggests that

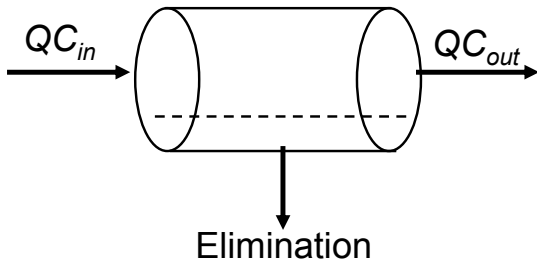
$$CL_H \sim Q_H$$

Actually

$$\uparrow Q_H = \downarrow E$$

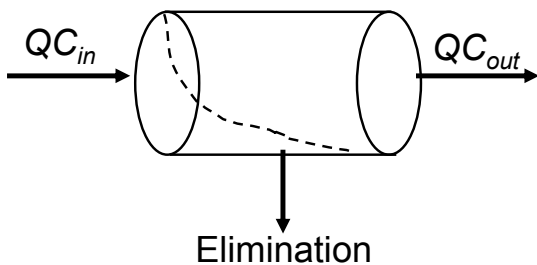
7

VENOUS EQUILIBRIUM MODEL



8

SINUSOIDAL MODEL



9

$$E = \frac{CL_{\text{int}}}{Q_H + CL_{\text{int}}}$$

Intrinsic hepatic clearance: The ability of the liver to remove xenobiotic from the blood in the absence of other confounding factors (e.g., Q_H).

10

$$E = \frac{CL_{\text{int}}}{Q_H + CL_{\text{int}}}$$

Since

$$CL_H = Q_H E$$

11

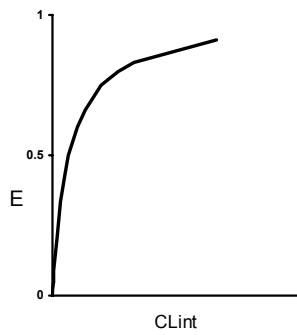
$$CL_H = \frac{Q_H CL_{\text{int}}}{Q_H + CL_{\text{int}}}$$

12

Quantitative Assessment of Hepatic Clearance Assuming the Venous Equilibrium Model

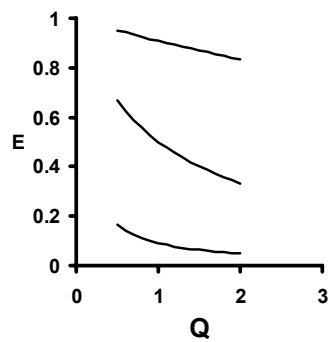
13

Assuming Q constant at 1 L/min



14

CL_{int} of 0.1, 1.0, and 10.0 L/min



15

Limits:

When $Q_H \gg CL_{int}$, then $E \rightarrow \frac{CL_{int}}{Q_H}$

Because $E = \frac{CL_{int}}{Q_H + CL_{int}} \approx \frac{CL_{int}}{Q_H}$

16

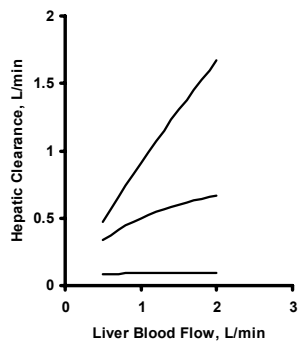
Limits:

When $Q_H \ll CL_{int}$, then $E \rightarrow 1$

Because $E = \frac{CL_{int}}{Q_H + CL_{int}} \approx 1$

17

CL_{int} of 10, 1.0, and 0.1 L/min



18

Limits:

When $Q_H \gg CL_{int}$,
then $CL_H \rightarrow CL_{int}$

$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}} \approx CL_{int}$$

19

Limits:

When $Q_H \ll CL_{int}$,
then $CL_H \rightarrow Q_H$

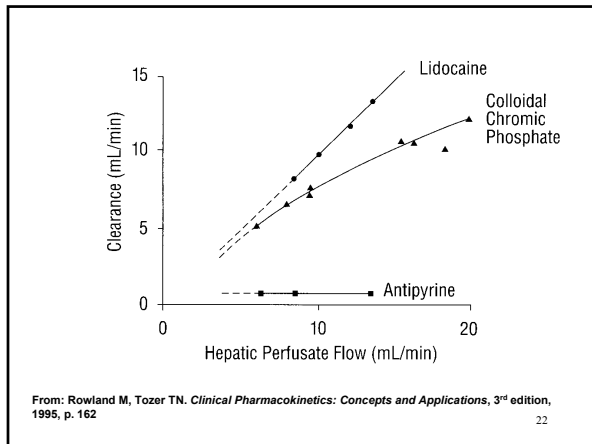
$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}} \approx Q_H$$

20

$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}} \approx Q_H$$

Compounds with a high CL_{int} are said to exhibit perfusion rate-limited elimination.

21



HEPATIC EXTRACTION RATIO OF REPRESENTATIVE DRUGS

<p>Low (<0.3)</p> <p>Antipyrine Diazepam Phenylbutazone Theophylline Tolbutamide Warfarin</p>	<p>High (>0.7)</p> <p>Lidocaine Meperidine Propoxyphene Propranolol Verapamil</p>
<p>Intermediate: Quinidine</p>	

23

Consider the case of administering a constant infusion of a drug with the following conditions:

$CL_{int} = 7.0 \text{ L/min}$, $Q_H = 1.0 \text{ L/min}$
 $K_o = 1.0 \text{ mg/min}$

Assuming drug is eliminated completely via hepatic metabolism, what would the steady-state concentration be?

$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}}$$

24

$$CL_H = \frac{1.0 \text{ L/min} \times 7.0 \text{ L/min}}{1.0 \text{ L/min} + 7.0 \text{ L/min}} = 0.875 \text{ L/min}$$

$$C_{ss} = \frac{K_0}{CL_H}$$

$$= \frac{1.0 \text{ mg/min}}{0.875 \text{ L/min}}$$

$$= 1.14 \text{ mg/L}$$

25

What if the pt developed CHF resulting in a 25% reduction in Q_H ?

$$CL_H^* = \frac{Q_H^* \times CL_{int}}{Q_H^* + CL_{int}}$$

$$= \frac{0.75 \text{ L/min} \times 7.0 \text{ L/min}}{0.75 \text{ L/min} + 7.0 \text{ L/min}}$$

$$= 0.677 \text{ L/min}$$

$$C_{ss}^* = \frac{K_0}{CL_H^*} = \frac{1.0 \text{ mg/min}}{0.677 \text{ L/min}} = 1.48 \text{ mg/L}$$

26

In contrast, suppose we administer a low CL_{int} ?

**$CL_{int} = 0.01 \text{ L/min}$, $Q_H = 1.0 \text{ L/min}$
 $K_0 = 0.1 \text{ mg/min}$**

$$CL_H = \frac{1.0 \text{ L/min} \times 0.01 \text{ L/min}}{1.0 \text{ L/min} + 0.01 \text{ L/min}} = 0.0099 \text{ L/min}$$

$$C_{ss} = \frac{0.1 \text{ mg/min}}{0.0099 \text{ L/min}} = 10 \text{ mg/L}$$

27

What if Q_H were reduced by 25%

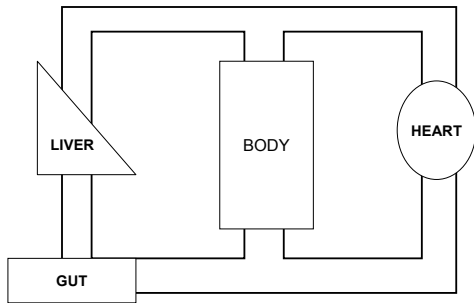
$$CL_H^* = \frac{0.75 \text{ L/min} \times 0.01 \text{ L/min}}{0.75 \text{ L/min} + 0.01 \text{ L/min}} = 0.0099 \text{ L/min}$$

$$C_{ss}^* = \frac{0.1 \text{ mg/min}}{0.0099 \text{ L/min}} = 10 \text{ mg/L}$$

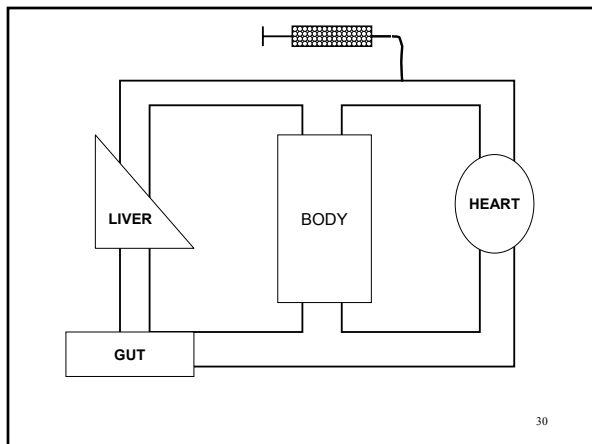
$$C_{ss} = 10 \text{ mg/L}$$

28

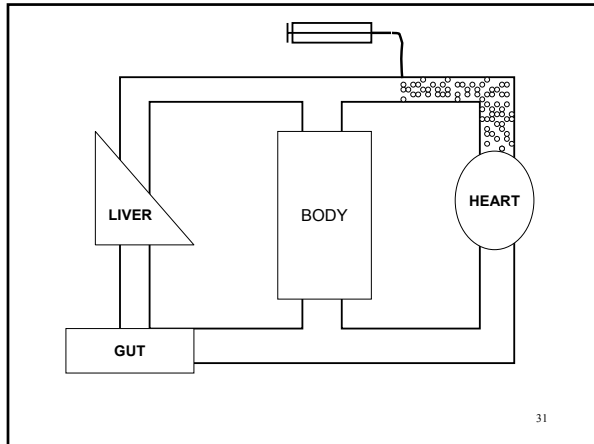
FIRST-PASS EFFECT

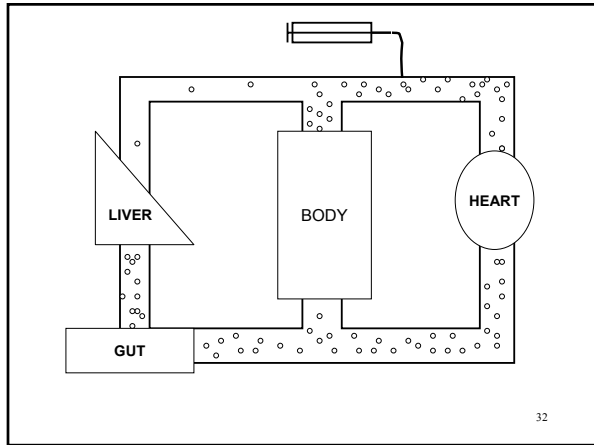


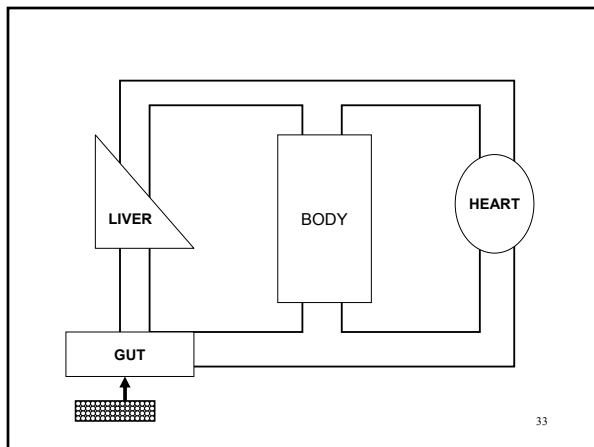
29

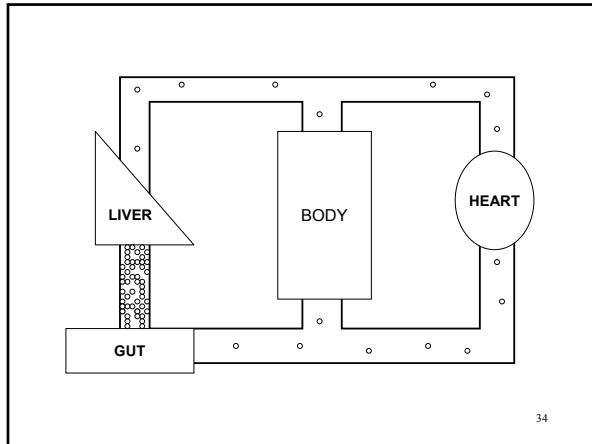


30









If a drug is completely absorbed after oral administration, the fraction of the oral dose that reaches the systemic circulation (F) is given as

$$F = 1 - E$$

Remembering that

$$E = \frac{CL_{int}}{Q_H + CL_{int}}$$

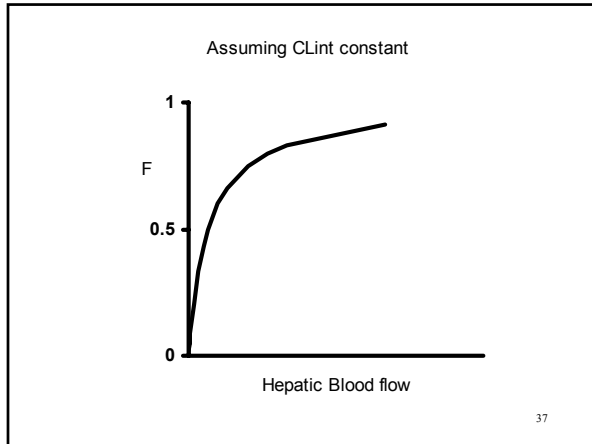
35

$$F = 1 - \frac{CL_{int}}{Q_H + CL_{int}}$$

$$F = \frac{Q_H}{Q_H + CL_{int}}$$

$Q_H \gg CL_{int} \quad F \rightarrow 1$
 $Q_H \ll CL_{int} \quad F \rightarrow 0$

36



Determination of CL_{int} after oral dosing:

Assumes:

- Drug is completely absorbed
- No extrahepatic metabolism
- System is stationary

38

Determination of CL_{int} after oral dosing:

$$CL_H = \frac{F \cdot D_o}{AUC_o}$$

$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}} \qquad F = \frac{Q_H}{Q_H + CL_{int}}$$

39

Determination of CL_{int} after oral dosing:

$$\frac{Q_H \times CL_{int}}{Q_H + CL_{int}} = \frac{Q_H}{Q_H + CL_{int}} \times \frac{D_o}{AUC_o}$$

$$CL_{int} = \frac{D_o}{AUC_o}$$

40

Estimated in this fashion the CL_{int} is often referred to as the oral clearance (CL_o)

For a high CL_{int} drug:

$$\frac{D_{iv}}{AUC_{iv}} = CL_H \quad \frac{D_o}{AUC_o} = CL_{int}$$

41

Estimated in this fashion the CL_{int} is often referred to as the oral clearance (CL_o)

For a low CL_{int} drug:

$$\frac{D_{iv}}{AUC_{iv}} = \frac{D_o}{AUC_o} = CL_H = CL_{int}$$

42

Consider a high clearance drug (e.g., propranolol) after oral and IV dosing:

$$CL_{int} = 10 \text{ L/min}, Q_H = 1.5 \text{ L/min}$$

$$CL_H = \frac{Q_H \times CL_{int}}{Q_H + CL_{int}}$$

$$CL_H = \frac{1.5 \text{ L/min} \times 10 \text{ L/min}}{1.5 \text{ L/min} + 10 \text{ L/min}}$$

$$CL_H = 1.304 \text{ L/min}$$

43

$$CL_H = 1.304 \text{ L/min}$$

What would happen to CL_H if Q_H were reduced to 1.0 L/min?

$$CL_H = \frac{1.0 \text{ L/min} \times 10 \text{ L/min}}{1.0 \text{ L/min} + 10 \text{ L/min}} = 0.909 \text{ L/min}$$

What if drug were administered orally under these conditions?

44

$$E = \frac{CL_{int}}{Q_H + CL_{int}}$$

$$E = \frac{10 \text{ L/min}}{1.5 \text{ L/min} + 10 \text{ L/min}}$$

$$E = 0.869$$

$$F = 1 - E = 1 - 0.869 = 0.13$$

45

$$F = 1 - E = 1 - 0.869 = 0.13$$

How would a decrease in Q_H affect this?

$$E^* = \frac{10 \text{ L/min}}{1.0 \text{ L/min} + 10 \text{ L/min}}$$

$$E^* = 0.909$$

$$F^* = 1 - 0.909 = 0.091$$

46

But what happens to AUC?

$$CL_H = \frac{D_o F}{AUC_o} \quad \text{or} \quad AUC_o = \frac{D_o F}{CL_H}$$

For control conditions:

$$AUC_o = \frac{100 \text{ mg} (0.13)}{1.304 \text{ L/min}} = 10 \text{ mg} \cdot \text{min/L}$$

When Q_H is decreased:

$$AUC_o = \frac{100 \text{ mg} (0.091)}{0.091 \text{ L/min}} = 10 \text{ mg} \cdot \text{min/L}$$

47

IMPACT OF PROTEIN BINDING

$$CL_{int} = f_{ub} CL_{uint}$$

$$E = \frac{f_{ub} CL_{uint}}{Q_H + f_{ub} CL_{uint}}$$

$$CL_H = \frac{Q_H \times f_{ub} CL_{uint}}{Q_H + f_{ub} CL_{uint}}$$

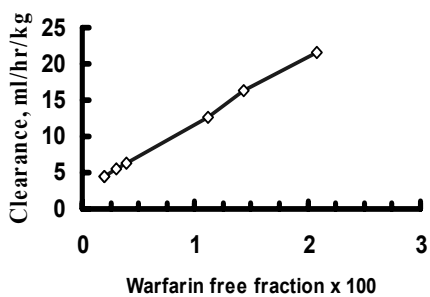
48

$$CL_H = \frac{Q_H \times f_{ub} CL_{u\text{int}}}{Q_H + f_{ub} CL_{u\text{int}}}$$

When $Q_H \gg f_{ub} CL_{u\text{int}}$, then $CL_H \cong f_{ub} CL_{u\text{int}}$

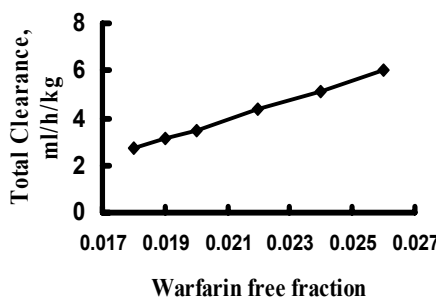
When $Q_H \ll f_{ub} CL_{u\text{int}}$, then $CL_H \cong Q_H$

49



Effect of protein binding on warfarin clearance in the rat. Data from Yacobi A, Levy G. *J Pharm Sci* 64:1660, 1975.

50



Effect of protein binding on warfarin clearance in humans. Data from Routledge et al. *Br J Clin Pharmacol* 8:243, 1979.

51

$$CL_{u_{int}} = 0.25 \text{ L/min} \quad Q_H = 1.5 \text{ L/min}$$

$$f_{ub} = 0.1 \quad K_0 = 0.25 \text{ mg/min}$$

$$CL_H = \frac{Q_H \times f_{ub} CL_{u_{int}}}{Q_H + f_{ub} CL_{u_{int}}}$$

$$CL_H = \frac{1.5 \text{ L/min} \times 0.1 \times 0.25 \text{ L/min}}{1.5 \text{ L/min} + (0.1 \times 0.25 \text{ L/min})}$$

$$CL_H = 0.0246 \text{ L/min}$$

52

$$CL_{u_{int}} = 0.25 \text{ L/min} \quad Q_H = 1.5 \text{ L/min}$$

$$f_{ub} = 0.1 \quad K_0 = 0.25 \text{ mg/min}$$

$$CL_H = 0.0246 \text{ L/min}$$

$$C_{ss} = \frac{K_0}{CL_H}$$

$$C_{ss} = \frac{0.25 \text{ mg/min}}{0.0246 \text{ L/min}}$$

$$C_{ss} = 10.2 \text{ mg/L}$$

53

What if $f_{ub} = 0.2$?

$$CL_H^* = \frac{Q_H \times f_{ub}^* CL_{u_{int}}}{Q_H + f_{ub}^* CL_{u_{int}}}$$

$$CL_H^* = \frac{1.5 \text{ L/min} \times 0.2 \times 0.25 \text{ L/min}}{1.5 \text{ L/min} + (0.2 \times 0.25 \text{ L/min})}$$

$$CL_H^* = 0.0484 \text{ L/min}$$

54

What if $f_{ub} = 0.2$?

$$CL_H^* = 0.0484 \text{ L/min}$$

$$C_{ss}^* = \frac{K_0}{CL_H}$$

$$C_{ss}^* = \frac{0.25 \text{ mg/min}}{0.0484 \text{ L/min}}$$

$$C_{ss}^* = 5.16 \text{ mg/L}$$

55

$$C_{ss} = 10.2 \text{ mg/L}$$

$$C_{ss}^* = 5.16 \text{ mg/L}$$

What happens to free concentration?

Control

$$C_{ss_{fub}} = C_{ss} \times f_{ub} = 10.2 \text{ mg/L} \times 0.1 = 1.02 \text{ mg/L}$$

Change

$$C_{ss_{fub}}^* = C_{ss}^* \times f_{ub}^* = 5.16 \text{ mg/L} \times 0.2 = 1.03 \text{ mg/L}$$

56

What about oral administration?

$$F = 1 - \frac{f_{ub} CL_{u\text{int}}}{Q_H + f_{ub} CL_{u\text{int}}}$$

$$F = 1 - \frac{0.1 \times 0.25 \text{ L/min}}{1.5 \text{ L/min} + (0.1 \times 0.25 \text{ L/min})}$$

$$F = 0.98$$

$$F^* = 1 - \frac{0.2 \times 0.25 \text{ L/min}}{1.5 \text{ L/min} + (0.2 \times 0.25 \text{ L/min})}$$

$$F^* = 0.97$$

57

Consider a high clearance drug iv:

$$CL_{uint} = 30 \text{ L/min} \quad Q_H = 1.5 \text{ L/min}$$
$$f_{ub} = 0.25 \quad K_0 = 2 \text{ mg/min}$$

$$CL_H = \frac{Q_H f_{ub} CL_{uint}}{Q_H + f_{ub} CL_{uint}}$$

$$CL_H = \frac{1.5 \text{ L/min} \times 0.25 \times 30 \text{ L/min}}{1.5 \text{ L/min} + (0.25 \times 30 \text{ L/min})}$$

$$CL_H = 1.25 \text{ L/min}$$

58

Consider a high clearance drug iv:

$$CL_{uint} = 30 \text{ L/min} \quad Q_H = 1.5 \text{ L/min}$$
$$f_{ub} = 0.25 \quad K_0 = 2 \text{ mg/min}$$

$$CL_H = 1.25 \text{ L/min}$$

$$C_{ss} = \frac{K_0}{CL_H} = \frac{2 \text{ mg/min}}{1.25 \text{ L/min}} = 1.6 \text{ mg/L}$$

$$C_{ss_{fub}} = C_{ss} \times f_{ub} = 1.6 \text{ mg/L} \times 0.25 = 0.4 \text{ mg/L}$$

59

What if $f_{ub} = 0.5$?

$$CL_H^* = \frac{Q_H f_{ub}^* CL_{uint}}{Q_H + f_{ub}^* CL_{uint}}$$

$$CL_H^* = \frac{1.5 \text{ L/min} \times 0.5 \times 30 \text{ L/min}}{1.5 \text{ L/min} + (0.5 \times 30 \text{ L/min})}$$

$$CL_H^* = 1.36 \text{ L/min}$$

60

What if $f_{ub} = 0.5$?

$$CL_H^* = 1.36 \text{ L/min}$$

$$C_{ss}^* = \frac{K_0}{CL_H^*} = \frac{2 \text{ mg/min}}{1.36 \text{ L/min}} = 1.47 \text{ mg/L}$$

$$C_{ss} = 1.6 \text{ mg/L}$$

$$C_{ss_{fub}}^* = C_{ss}^* \times f_{ub}^* = 1.47 \text{ mg/L} \times 0.5 = 0.73 \text{ mg/L}$$

$$C_{ss_{fub}} = 0.4 \text{ mg/L}$$

61

What about oral administration?

$$E = \frac{f_{ub} CL_{u\text{int}}}{Q_H + f_{ub} CL_{u\text{int}}}$$
$$E = \frac{0.25 \times 30 \text{ L/min}}{1.5 \text{ L/min} + (0.25 \times 30 \text{ L/min})} = 0.83$$

$$AUC_o = \frac{D_o(1-E)}{CL_H}$$
$$AUC_o = \frac{500 \text{ mg}(1-0.83)}{1.25 \text{ L/min}} = 66.67 \text{ mg} \cdot \text{min/L}$$
$$AUC_{o_{fub}} = 16.67 \text{ mg} \cdot \text{min/L}$$

62

What if $f_{ub} = 0.5$?

$$E^* = \frac{f_{ub}^* CL_{u\text{int}}}{Q_H + f_{ub}^* CL_{u\text{int}}}$$
$$E^* = \frac{0.5 \times 30 \text{ L/min}}{1.5 \text{ L/min} + (0.5 \times 30 \text{ L/min})} = 0.091$$

$$AUC_o^* = \frac{D_o(1-E^*)}{CL_H^*}$$
$$AUC_o^* = \frac{500 \text{ mg}(1-0.091)}{1.36 \text{ L/min}} = 30.9 \text{ mg} \cdot \text{min/L}$$
$$AUC_{o_{fub}}^* = 15.54 \text{ mg} \cdot \text{min/L}$$

63

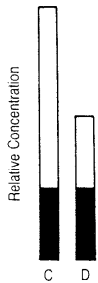
What if $f_{ub} = 0.5$?

$AUC_o = 66.67 \text{ mg} \cdot \text{min/L}$
 $AUC_{o_{fub}} = 16.67 \text{ mg} \cdot \text{min/L}$

$AUC_o^* = 30.9 \text{ mg} \cdot \text{min/L}$
 $AUC_{o_{fub}}^* = 15.54 \text{ mg} \cdot \text{min/L}$

64

Low Extraction

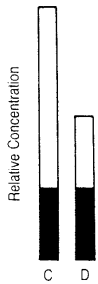


Effect of displacement (D) of plasma protein binding on total and unbound concentrations of drug

From: Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3rd edition 65

Low Extraction

High Extraction



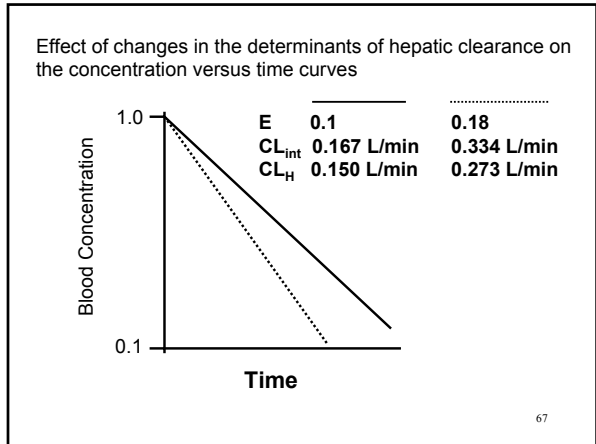
Intravenous

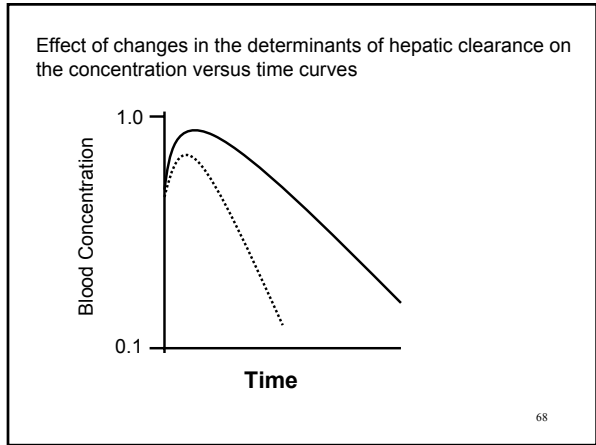


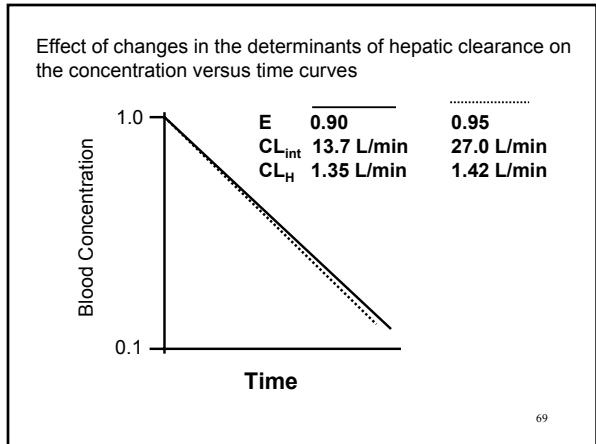
Oral



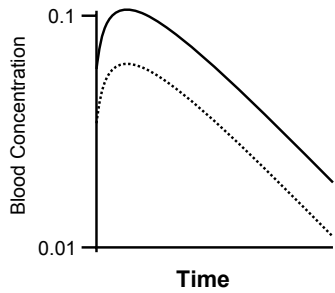
From: Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3rd edition 66



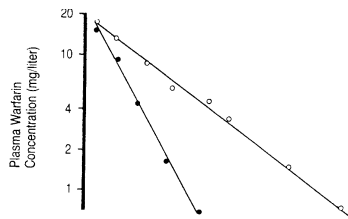




Effect of changes in the determinants of hepatic clearance on the concentration versus time curves

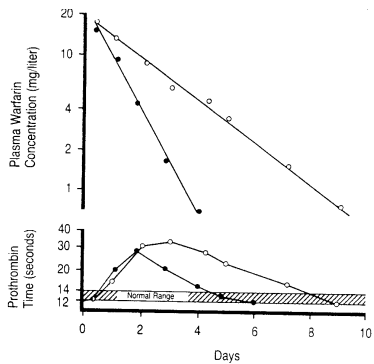


70

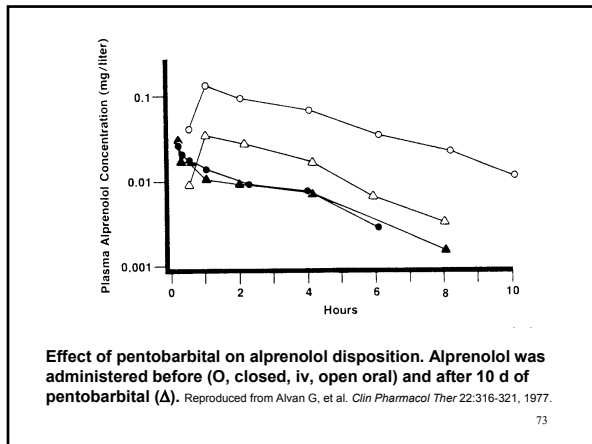


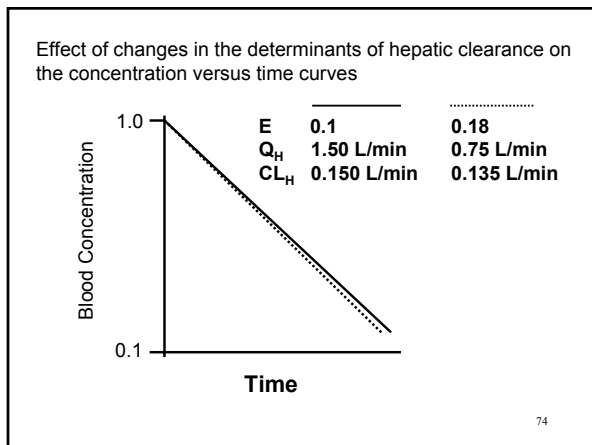
Effect of rifampin on the kinetics of warfarin after a single dose before (open circles) and after (closed circles) treatment with rifampin 600 mg/day. From: O'Reilly RA. Interaction of sodium warfarin and rifampin. *Ann Intern Med* 81:337-40, 1974.

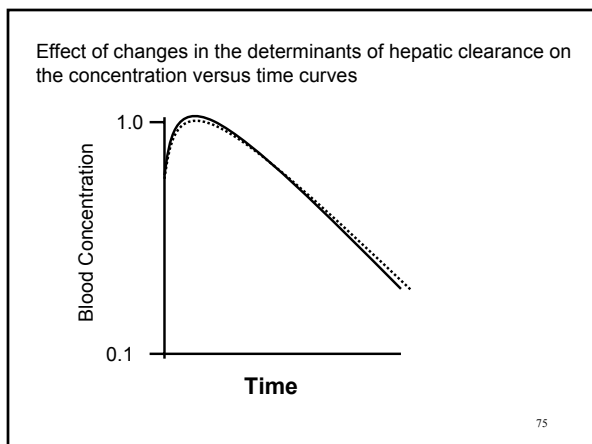
71



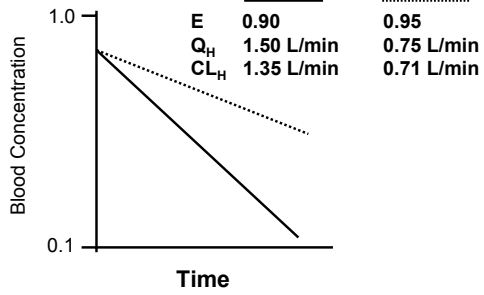
72





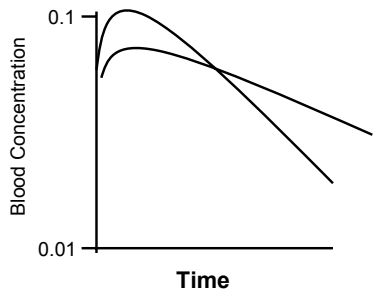


Effect of changes in the determinants of hepatic clearance on the concentration versus time curves



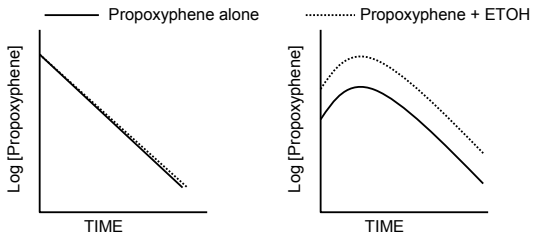
76

Effect of changes in the determinants of hepatic clearance on the concentration versus time curves



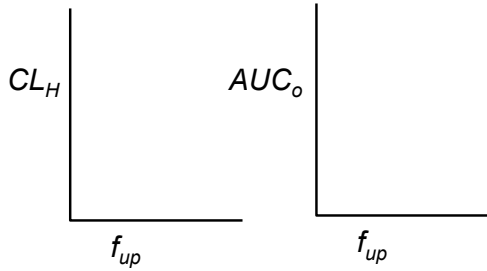
77

Propoxyphene's CNS depression is enhanced when co-administered with ethanol. To assess the contribution of a pharmacokinetic interaction to this enhancement, propoxyphene was administered iv and po, with and without ethanol. The curves below illustrate the results. What is the mechanism of interaction?



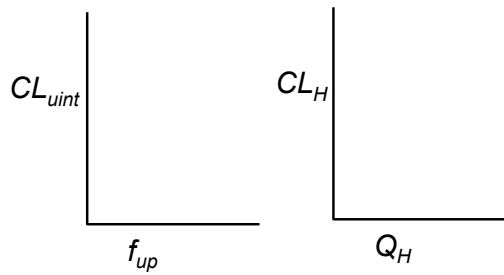
78

Complete the following graphs for a drug with a $CL_H = 20 \text{ mL/min/kg}$ and one with a $CL_H = 1 \text{ mL/min/kg}$



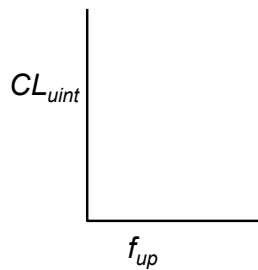
79

Complete the following graphs for a drug with a $CL_H = 20 \text{ mL/min/kg}$ and one with a $CL_H = 1 \text{ mL/min/kg}$



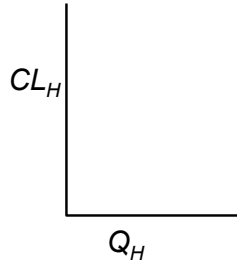
80

Complete the following graphs for a drug with a $CL_H = 20 \text{ mL/min/kg}$ and one with a $CL_H = 1 \text{ mL/min/kg}$



81

Complete the following graphs for a drug with a $CL_H = 20$ mL/min/kg and one with a $CL_H = 1$ mL/min/kg



82

E	Q_H	f_{ub}	f_{ut}	CL_T	V_{ss}	$t_{1/2}$	AUC_o
-----	-------	----------	----------	--------	----------	-----------	---------

High	↑	↔	↔				
High	↔	↓	↔				
High	↔	↔	↑				

83

E	Q_H	f_{ub}	f_{ut}	CL_T	V_{ss}	$t_{1/2}$	AUC_o
-----	-------	----------	----------	--------	----------	-----------	---------

Low	↑	↔	↔				
Low	↔	↔	↑				
Low	↔	↔		↑	↔		

84
