Program S-2 Ilmu Kefarmasian
Universitas Pancasila

Model Farmakokinetika

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Model Farmakokinetik

- Model digunakan untuk menggambarkan dan menginterpretasikan data yang diperoleh dari ekperimen.
- Model di dalam farmakokinetika adalah struktur hipotetik yang dapat digunakan untuk memberi gambaran nasib obat dalam tubuh, yang diberikan dengan cara dan bentuk sediaan tertentu.
- Dibuat dengan menggunakan data pengukuran kadar obat dalam tubuh

Kegunaan Model Farmakokinetika

1. Estimasi kadar obat dalam plasma, jaringan dan urine pada berbagai regimen dosis.
2. Menghitung regimen dosis optimum untuk tiap penderita secara individual.
3. Menghubungkan konsentrasi obat dengan aktivitas farmakologik dan toksikologik.
4. Estimasi kemungkinan akumulasi obat dan atau metabolit.
5. Menilai perbedaan kecepatan atau tingkat availabilitas antar formulasi (bioekivalensi).
6. Menggambarkan perubahan faal atau penyakit yang mempengaruhi absorbsi, distribusi atau eliminasi obat.
7. Menjelaskan interaksi obat.

Model Kompartemen

- Tubuh merupakan suatu susunan / sistem dari kompartemen-kompartemen yang berhubungan secara timbal balik satu dengan lainnya.
- Model kompartemen tubuh merupakan model kompartemen terbuka.
- Kegunaan:
  1. Merumuskan persamaan differensial untuk menggambarkan perubahan konsentrasi obat dalam masing-masing kompartemen.
  2. Memberikan suatu gambaran nyata dari kecepatan proses.
  3. Menunjukkan berapa banyak tetapan farmakokinetik yang diperlukan untuk menggambarkan suatu proses secara memadai.

Macam-macam Model Kompartemen

1. **Model Mammillary**
   - Model terdiri atas satu atau lebih kompartemen perifer yang dihubungkan dengan kompartemen sentral
   - Paling umum digunakan dalam farmakokinetika

   Contoh:

   a. Model kompartemen satu terbuka injeksi intravena
   b. Model kompartemen satu terbuka ekstravaskular
   c. Model kompartemen dua terbuka injeksi intravena
   d. Model kompartemen dua terbuka ekstravaskuler

2. **Model Caternary**
   - Model terdiri atas kompartemen-kompartemen yang bergabung satu dengan yang lain menjadi deretan kompartemen

3. **Model Fisiologik/Model Aliran darah/Model Perfusi**
   - Model yang didasarkan atas data anatomi dan fisiologi yang diketahui.

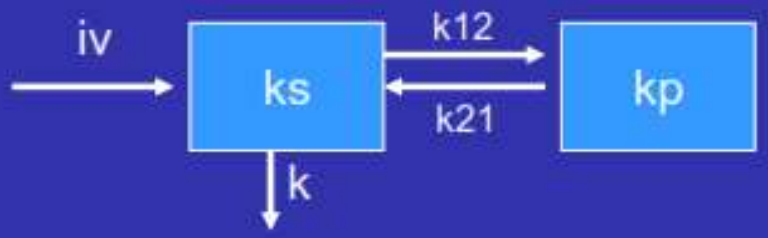
Model Mammillary

- Model yang terdiri atas satu atau lebih kompartemen perifer yang dihubungkan dengan kompartemen sentral
- Paling umum digunakan dalam farmakokinetika

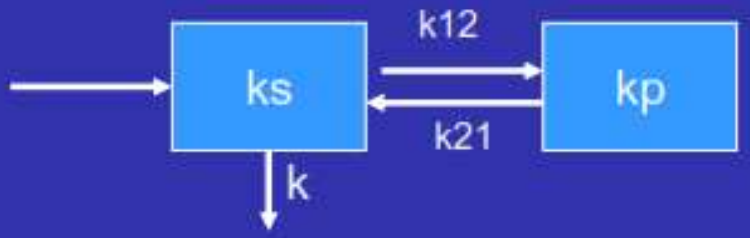
Contoh:

Model Komp. Satu terbuka iv

Model Komp. Satu terbuka ev



Model Komp. dua terbuka iv



Model Komp. dua terbuka ev

Model Caternary

- Model yang terdiri atas kompartemen-kompartemen yang bergabung satu dengan yang lain menjadi satu deretan kompartemen.

Model Fisiologik/Model aliran/ Model Perfusi

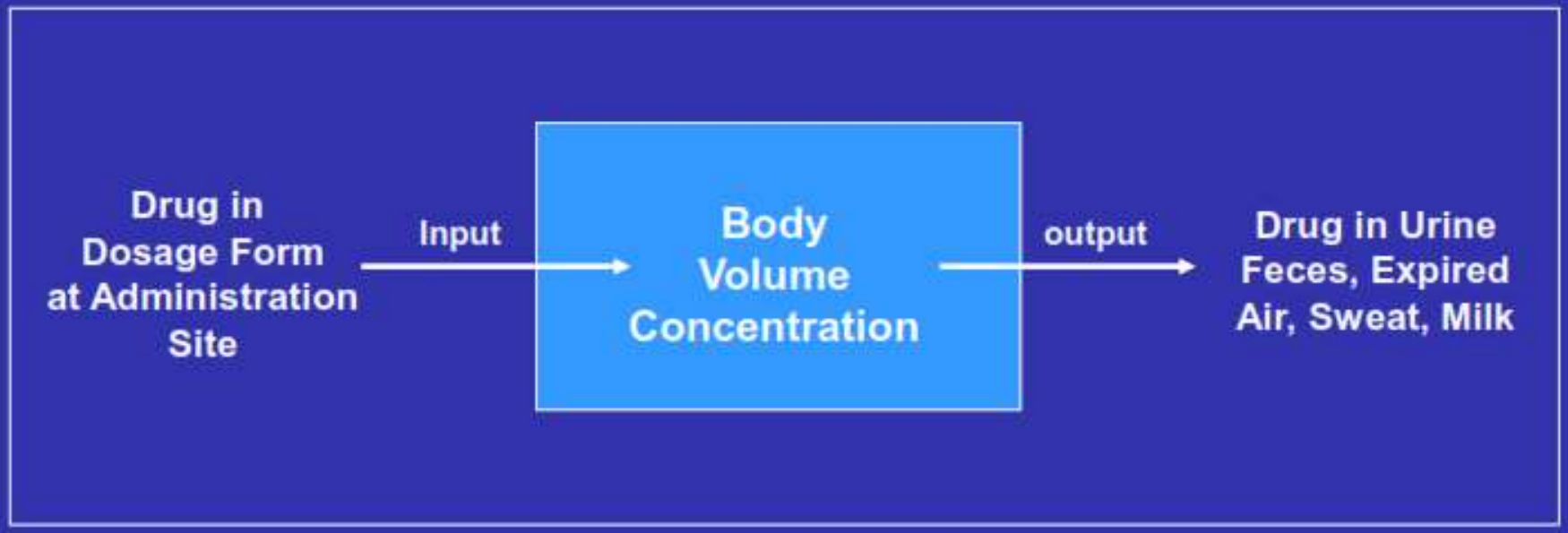
- Model yang didasarkan atas data anatomi dan fisiologis yang diketahui

Q = kecepatan perfusi darah ke jaringan

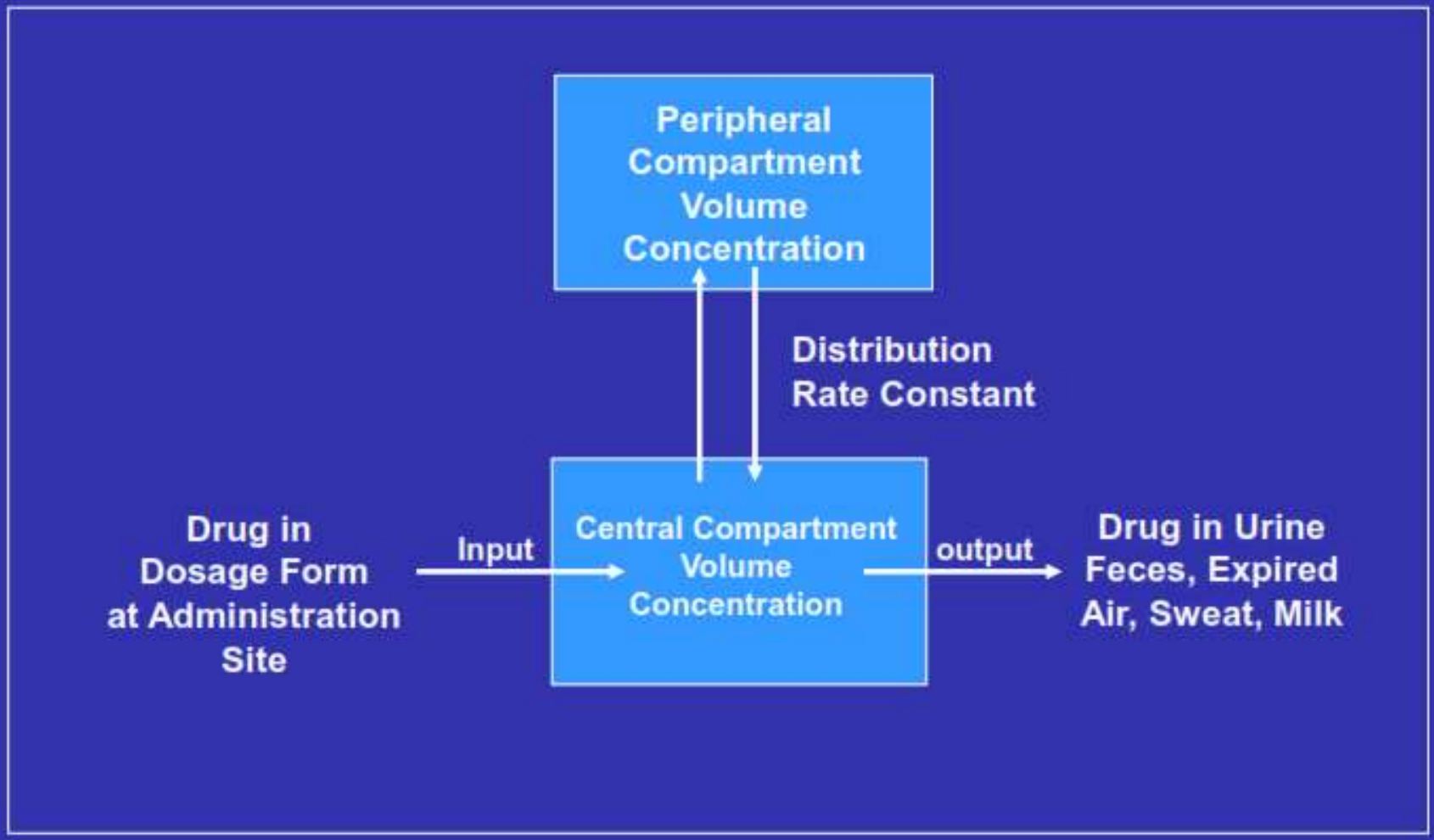
SET = Slowly Equilibrating Tissue (Jaringan yang berkeseimbangan dengan lambat

RET = Rapidly Equilibrating Tissue

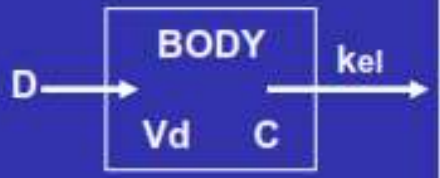
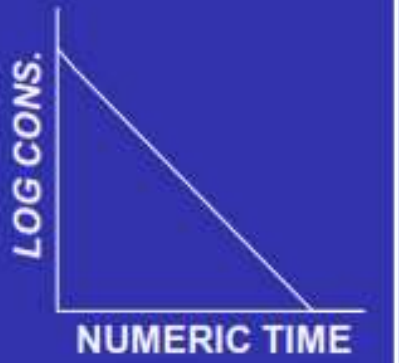
Concept of Open One-Compartment Model



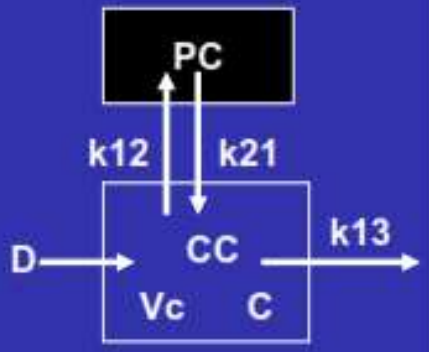
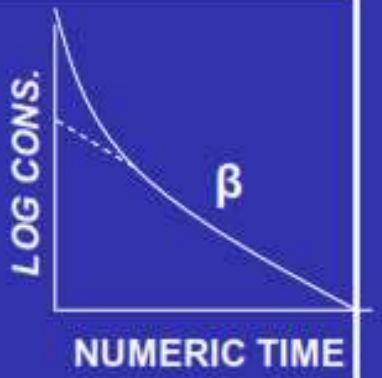
Concept of Open Two-Compartment Model



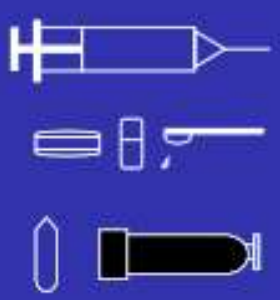
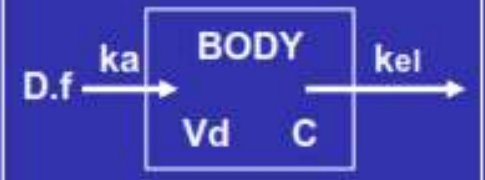
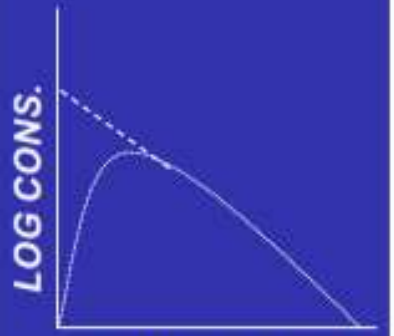
Characteristic of the Open One-Compartement Model (1)

Application	Characteristics	Model	Blood Level vs. Time Curve
Intravaskuler 	• No absorption, all injected drug is in system circulation, rapid distribution of drug between blood stream and tissue; • equilibrium (steady state) is instantly ob tained; • fall of drug concentration depends on excretion and metabolism	 D = Dose administered Vd = Volume of Distribution C = drug concentration in plasma Kel = elimination rate constant	

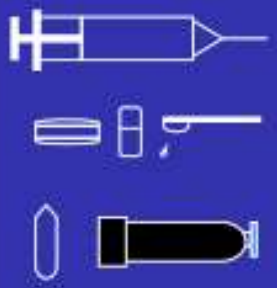
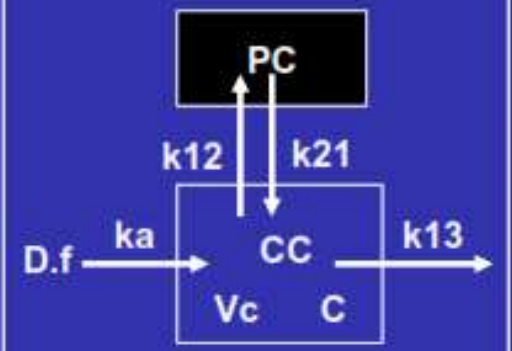
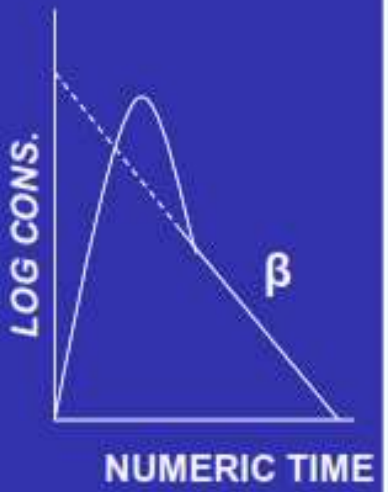
Characteristic of the Open Two-Compartement Model (1)

Application	Characteristics	Model	Blood Level vs. Time Curve
Intravaskuler 	• No absorption, all injected drug is in the systemic circulation, slow distribution of drug between blood stream and tissue; • equilibrium (steady state) is obtained some later time after administration; • steep fall of first part of blood level curve due to distribution; • decline of second part of blood level curve depends on back-distribution of drug from tissue to blood, excretion and metabolism.	 D = Dose administered CC = Central Compartment PC = peripheral Compartment K12,k21= distribution rate constant K31 = elimination rate constant from central compartment Vc = Volume of central compartment C = drug concentration in central compartment B = overall elimination rate constant	

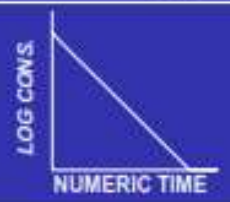
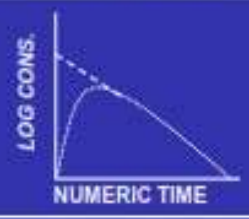
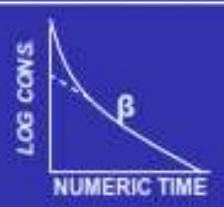
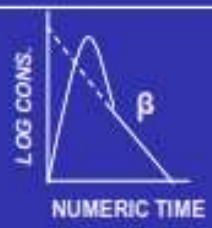
Characteristic of the Open One-Compartement Model (2)

Application	Characteristics	Model	Blood Level vs. Time Curve
Ekstravakuler 	• Absorption proceeding according to drug liberation and absorption mechanism; at time 0 no drug is in systemic circulation; • as absorption proceeds drug concentration in systemic circulation increase to peak and then decreases according to elimination (excretion and metabolism); • not necessarily all of the administered drug is absorbed.	 D = Dose administered f = percent of drug absorbed ka = absorption rate constant Vd = Volume of Distribution C = drug concentration in plasma Kel = elimination rate constant	

Characteristic of the Open Two-Compartement Model (2)

Application	Characteristics	Model	Blood Level vs. Time Curve
Ekstravaskuler 	• Absorption proceeding according to drug liberation mechanism; • at time 0 there is no drug in systemic circulation, as absorption proceeds drug concentration in systemic circulation rises to a peak, followed by a steep fall due to slow distribution until equilibrium (steady state) is obtained; • mono exponential decline of curve depends on back distribution of drug from tissue to blood excretion and metabolism.	 D = Dose administered CC = Central Compartment PC = peripheral Compartment ka = absorption rate constant K12,k21= distribution rate constant K31= elimination rate constant from central compartment Vc = Volume of central compartment C = drug concentration in central compartment B = overall elimination rate constant	

Summary of Compartment Models, Route of Administration and Blood, Serum or Plasma Concentration Equations

BLOOD LEVEL (on semi-log paper)	ROUTE OF ADMINISTRATION	COMPARTMENT MODEL	BLOOD LEVEL EQUATION (µg/ml)
	Intravascular (intravenous, intra cardiac, intra-arterial)	Open one	$Ct = Co \cdot e^{-kel \cdot T}$
	Extra vascular (oral, per oral, rectal, intramuscular, subcutaneous, intracutaneous)	Open one	$Ct = B \cdot e^{-kel \cdot t} - A \cdot e^{-ka \cdot t}$
	Intravascular (intravenous, intra cardiac, intra-arterial)	Open two	$Ct = B \cdot e^{-\beta \cdot t} + A \cdot e^{-\alpha \cdot t}$
	Extra vascular (oral, per oral, rectal, intramuscular, subcutaneous, intracutaneous)	Open two	$Ct = B \cdot e^{-\beta \cdot t} + A \cdot e^{-\alpha \cdot t} - Co \cdot e^{-ka \cdot t}$

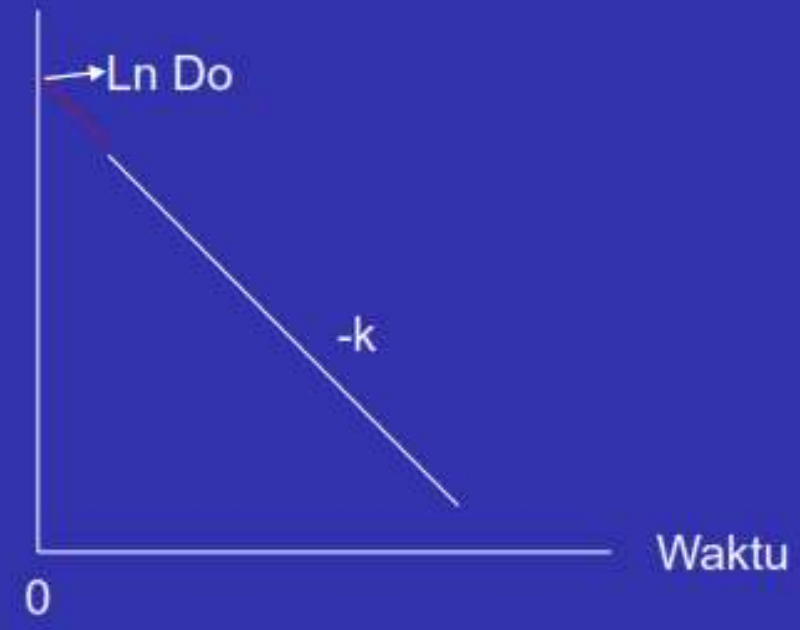
Model satu kompartemen terbuka – intravaskular (iv)

Rumus dan Latihan soal

Model 1 kompertemen iv

$Ln\ Ct = Ln\ Co - k.t$

$Ct = Co.e^{-k.t}$

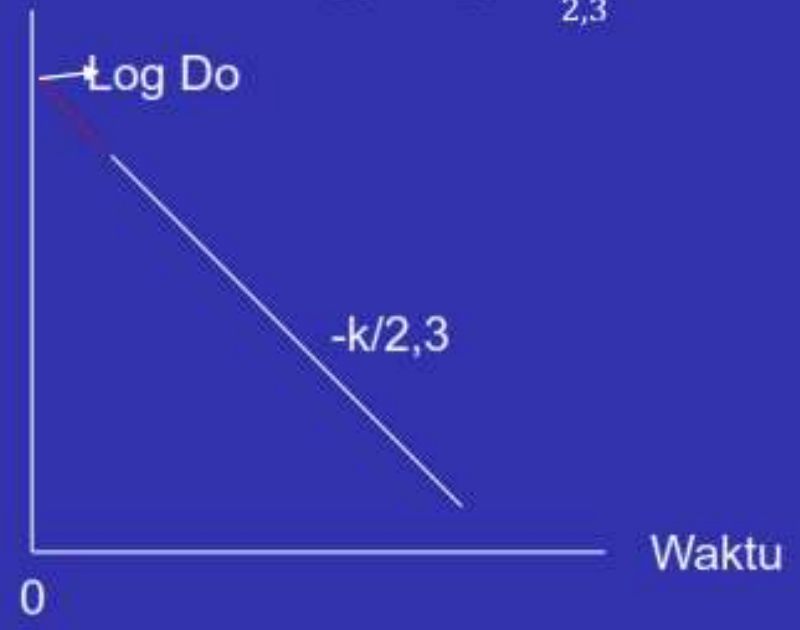


$Ln\ A = 4{,}5$

$A = e^{4,5} = 90$

$Log\ Ct = Log\ Co - \frac{k.t}{2{,}3}$

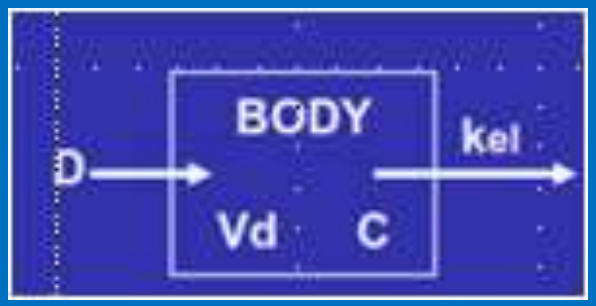
$Ct = Co - \frac{k.t}{2{,}3}$



Log A= 1,23

$A = 10^{1,23} = 17$

Model 1 kompertemen iv



$$Ct = Co.e^{-kel.t}$$

$$Log\ Ct = Log\ Co - \frac{k.t}{2,3}$$

$$Ln\ Ct = Ln\ Co - k.t$$

$$Dbt = Do.e^{-k.t}$$

$$Dbt = Vd.Ct$$

Kadar

$$Ct = Co - \frac{k.t}{2,3}$$

Log Do

-k/2,3

Waktu

0

$$Cl = \frac{Div}{AUC}$$

$$T½ = \frac{0.693}{Kel}$$

$$k = \frac{Cl}{Vd}$$

$$AUC = \frac{Co}{k}$$

KUIS MODEL KOMPARTEMEN (1)

- Seorang penderita dengan berat badan 50 kg diberi obat Dexamethason dengan dosis tunggal iv 50 mg. Kadar obat dalam plasma diukur dengan mengambil cuplikan darah pada berbagai interval waktu tertentu. Diperoleh data sebagai berikut:

Waktu (jam)	Kadar obat A (µg/ml)
0,25	9,16
0,50	8,39
1.00	7,05
2.00	4,97
4.00	2,47
6.00	1,24
8,00	0,62

Analisa data tersebut dan kemudian :

a. Ganbar data tersebut pada kertas grafik semilog, tentukan model kompartemen dan tuliskan persamaan kinetika model kompartemen!

b. Tentukan parameter farmakokinetika berikut:
   1). Waktu paruh (grafik dan rumus)
   2). Kadar obat dalam plasma mula-mula (grafik dan perhitungan)
   3). Volume distribusi obat
   4). Kliren total obat
   5). AUC (Trapezoid dan rumus)

c. Berapa kadar obat dalam darah setelah 10 jam?

d. Jika obat tidak efektif pada konsentrasi plasma 4 µg/ml. Berapa lama kerja obat?

e. Berapa lama waktu yang diperlukan untuk mengeliminasi obat 90 % dari tubuh?