Drug Therapy

Remark

Phamarcokinetic-phamarcodynamic modeling and Simulation:

- 인체에 투여한 약물의 농도와 효과의 변화를 정량적으로 계량하고 예측하는 학문
- 신약 개발 과정을 단축할 수 있고, 약물을 환자 개개인의 특성에 맞게 적정(titration) 할 수 있다.
- Nonlinear mixed effects model : 약물 반응의 개인차(inter-individual variability)를 반영하면서도 각 개인당 적은 수의 관측 값만으로도 분석이 가능하여 주로 사용되는 모형이다.
- Software : NONMEM® 혼합효과모형(mixed effects model)을 구현할 수 있게 해주는 프로그램 – 훈련기관-서울아산병원 참조

Introduction

- Patients with Asthma have constriction of the airways in the lungs and consequent difficulty in breathing out.
- This aliment can be alleviated by introducing the drug theophylline into the bloodstream.
- This is done by injecting another drug, aminophylline, which the body quickly convert theophylline.
- Once present in the blood, however, the drug is steadily excreted from the body via the kidneys. That is, the system leaks and unless there is replenishment the quantity of drug in the blood will fall.

Experiments

- Theophylline has hardly any therapeutic effect if its concentration in the bloodstream is below 5(mg/l)
- Theophylline is toxic if its concentration in the bloodstream is above 20 (mg/l).
- How to administer the drug in such a way that the concentration remains within the therapeutic range between 5(mg/l) and 20(mg/l)

Problem

- How to administer the drug in such a way that the concentration remains within the therapeutic range between 5(mg/l) and 20(mg/l).
  1. We need a model for the concentration of the drug in the body
  2. We need to find a way to administer the drug which satisfies our need.

Some assumptions and a model for drug concentration in the body

- The rate of at which the drug removed by the kidney is proportional to the amount of the drug in the body:
- ✓ Need to obtain a differential equations which describes the concentration c(t) at any time t: find the solution of the equation and apply the answer to the data given above to see how well the model agrees with reality.

Experimental Data 1

- Inject a dose (300 mg) of theophylline into a patient
- Check the concentration of the drug at regular intervals

Initial quantity = 300 (mg)	
Concentration (mg/l)	**Time (hours)**
10.0	1
7.0	3
5.0	5
3.5	7
2.5	9
2.0	11
1.5	13
1.0	15
0.7	17
0.5	19

Experimental Data 2

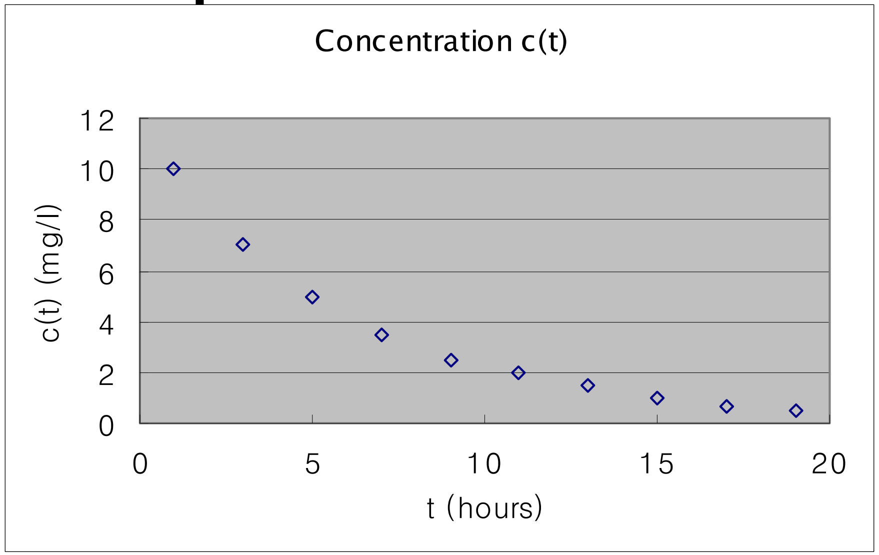
- The apparent volume of distribution (*V* litres) and the patient's weight (*W* kg)

  $$V = \frac{1}{2}W$$

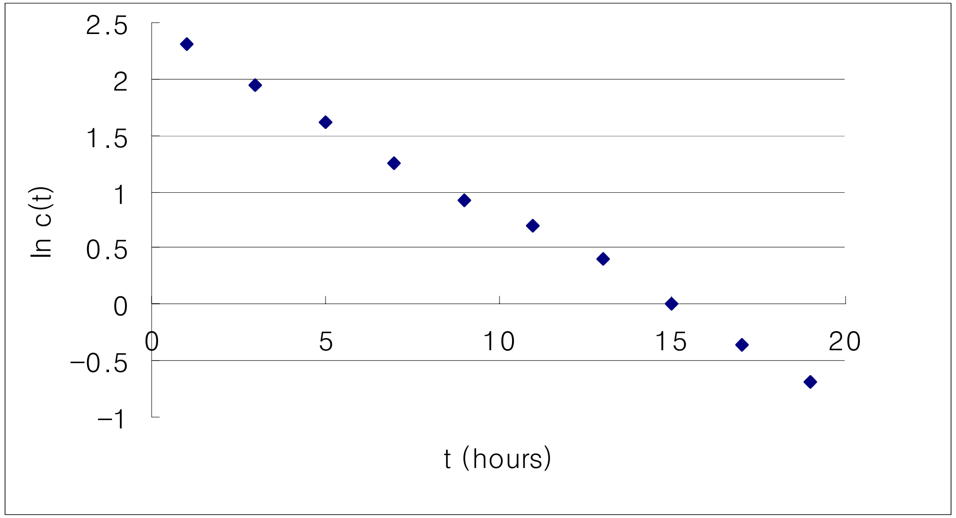
- The dose necessary to achieve a required initial theophylline concentration can be inferred from the patient's weight alone:
  - ✓ The dose D (mg) to obtain a 12 (mg/l) concentration in a 50 (kg) patient is obtained from D/V =12

    $$D = 12V = 6W = 300 \text{ (mg)}$$

Data Plots:



Concentration c(t)
c(t) (mg/l)
12
10
8
6
4
2
0
0
5
10
15
20
t (hours)



ln c(t)
2.5
2
1.5
1
0.5
0
−0.5
−1
0
5
10
15
20
t (hours)

Governing equation and solution

- $y(t)$: the amount of drug present at time t
- The governing equation

$$\frac{dy}{dt} = -ky \Rightarrow c(t) = \frac{y(t)}{V} \Rightarrow \frac{dc}{dt} = -kc$$

Thus $\quad c(t) = c_0 e^{-kt}$

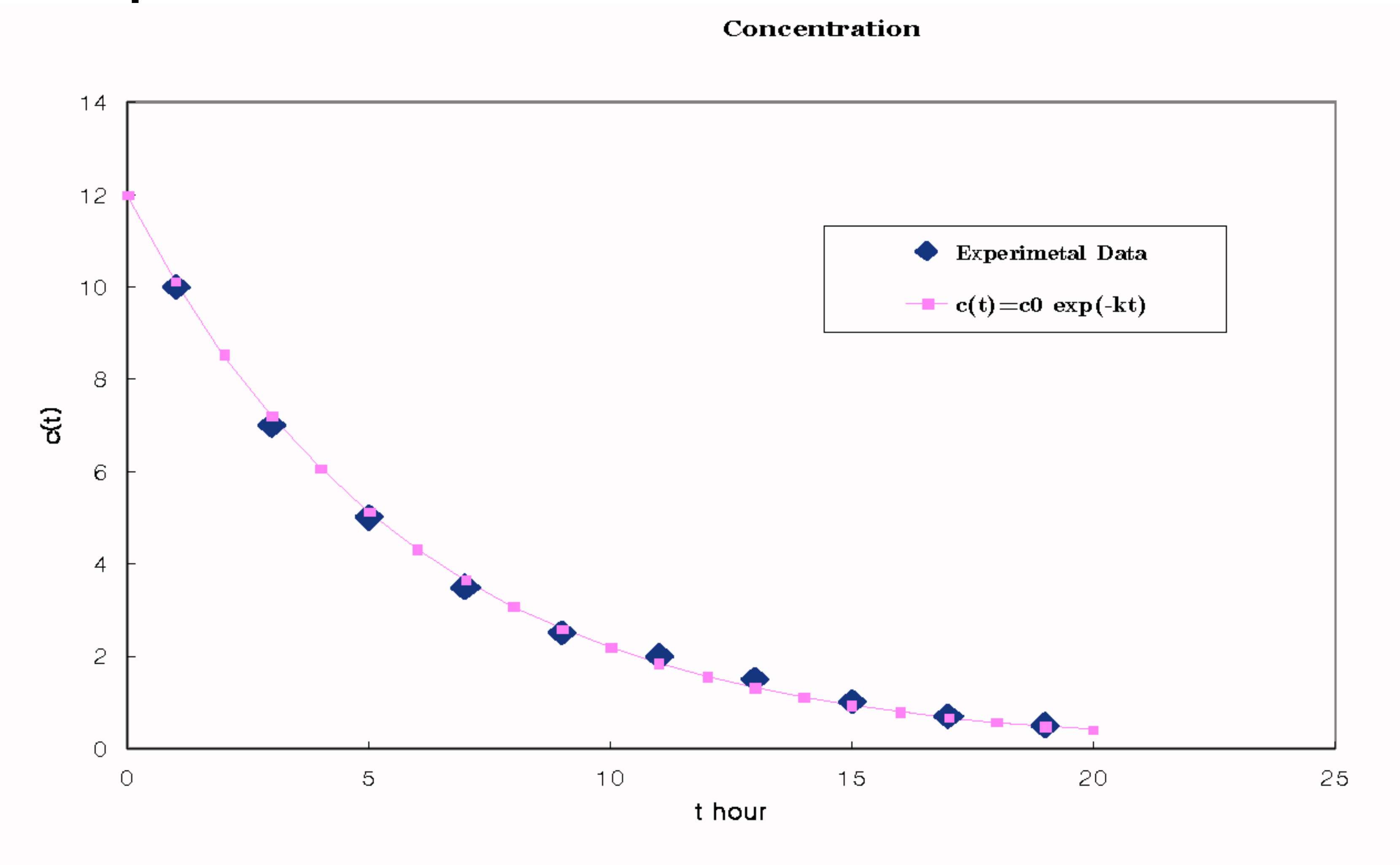
- To obtain c_0 and k, use the figure: log plot

$\ln c(t) = \ln c_0 - kt$ (use the least square to obtain k)

$c_0 = 12$ mg/l, $k = 0.17$ / hour (These are not from LS for given data!)

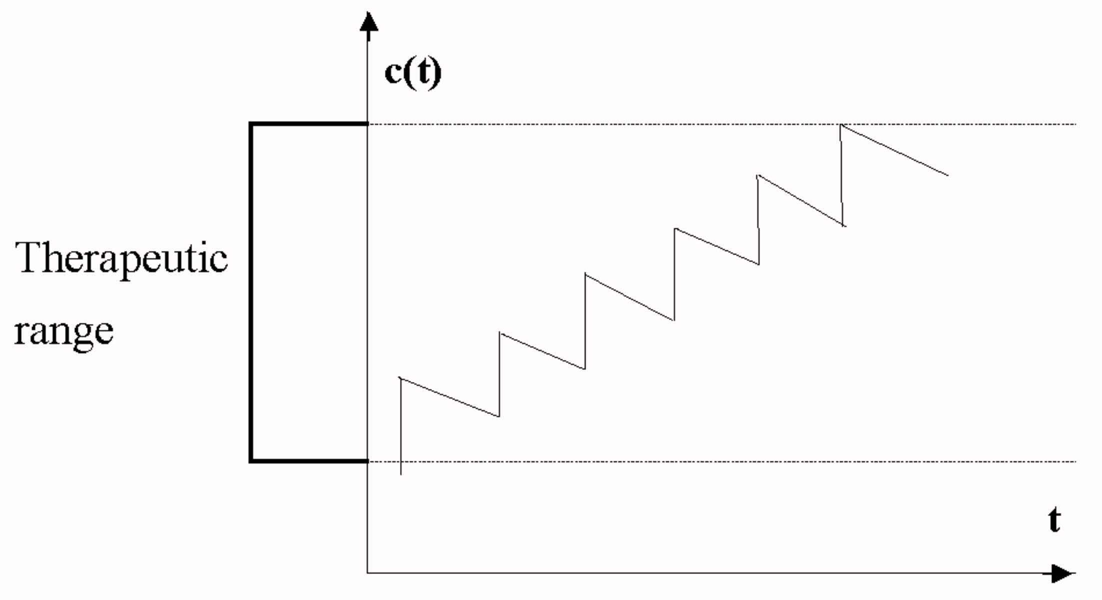
- $c(t) = 12 \exp(-0.17\, t)$ for 50 (kg) patient with D = 300mg dose
- What if we do not use the least square method to obtain k?

Comparison: Data and Analytic solution
(for the patient 50 kg and D=300 mg)



Therapeutic range

- In order that the concentration $c(t)$ remains inside the therapeutic range, a series of injections must be given and the desired concentration pattern may be as in Fig.

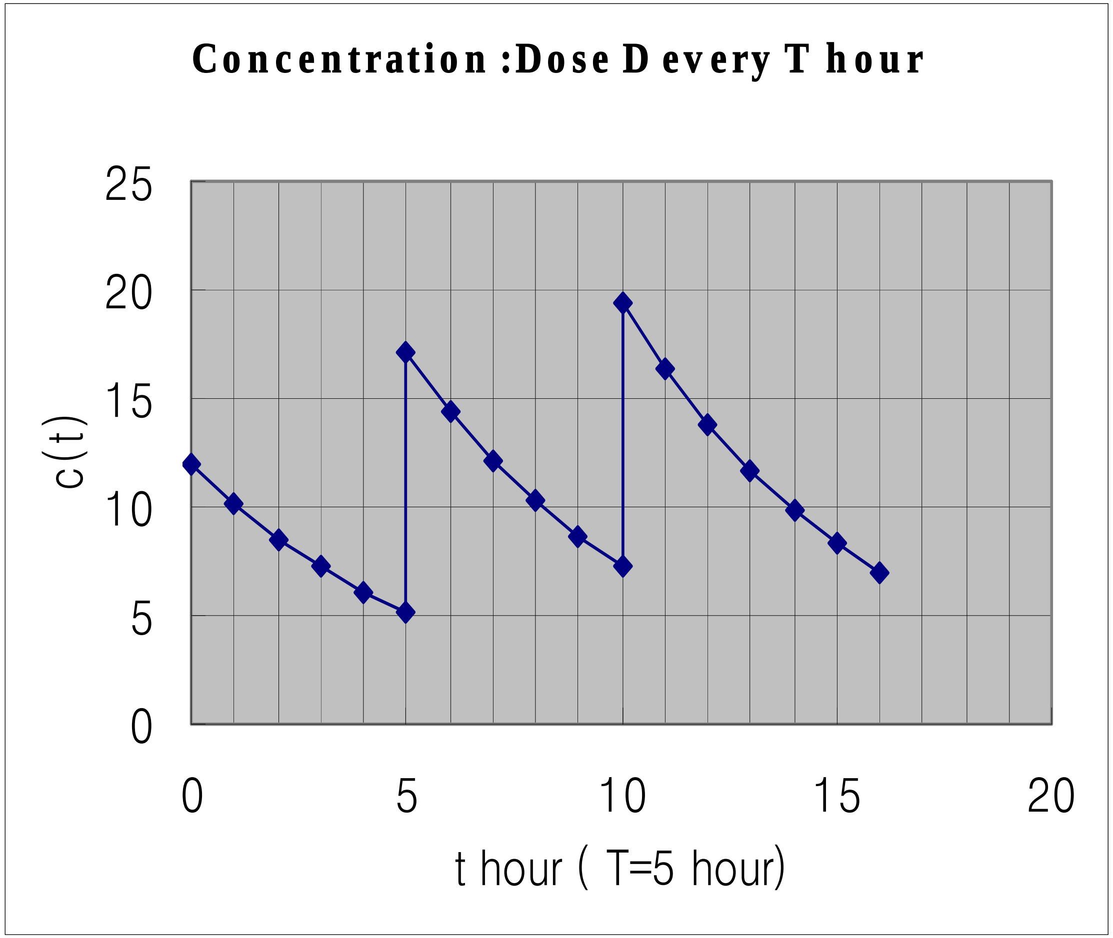


Some questions

- Equal sized dose D (mg) are to be administered at equal interval of time T hours

1. Is it possible to achieve a saturation as in the Fig.
2. Is it possible to choose the dose D and the interval T to remain in the therapeutic range?
3. What would you advise for the patient?
4. Is there any advantage in giving a larger dose initially and then a series of dose of size D as above?

A series of dose $D=300$(mg) at every $T=5$ hour for W=50 (kg) patient: c_0=12 (mg/l)



A series of dose D of every T hours: Concentration variation

t	Concentration $c(t)$	Remarks
0	c_0	1st dose
	$c_0 e^{-kt}$	$0 \le t \le T$
T	$c_0 e^{-kT}$	
T^+	$c_0 e^{-kT} + c_0$	2nd dose at T
	$c_0(1+e^{-kT})e^{-k(t-T)}$	$T \le t \le 2T$
$2T$	$c_0(e^{-kT}+e^{-2kT})$	
$2T^+$	$c_0(1+e^{-kT}+e^{-2kT})$	3rd dose at $2T$
	$c_0(1+e^{-kT}+e^{-2kT})e^{-k(t-2T)}$	
$3T$	$c_0(e^{-kT}+e^{-2kT}+e^{-3kT})$	
$3T^+$	$c_0(1+e^{-kT}+e^{-2kT}+e^{-3kT})$	4th dose at $3T$
	$c_0(1+e^{-kT}+e^{-2kT}+e^{-3kT})e^{-k(t-3T)}$	$3T \le t \le 4T$
$\vdots$	$\vdots$	$\vdots$
nT	$c_0(e^{-kT}+e^{-2kT}+\cdots+e^{-nkT})$	
nT^+	$c_0(1+e^{-kT}+e^{-2kT}+\cdots+e^{-nkT})$	(n+1)th dose at nT
$\vdots$	$\vdots$	$\vdots$
∞	$\dfrac{c_0}{1-e^{-kT}}$	The sup of the concentration $c(t)$
Assume the drug is instantaneously dispersed throughout the body $c_0 = D/V$		

Is it possible to achieve a saturation as in the Fig.?

- Decide the dose D and the interval T to keep the concentration range $5 \le c(t) \le 20, \quad c(t) \le \dfrac{c_0}{1-e^{-kT}}$ for all t
- For W=50(kg) patient, k=0.17/hour
- We want the limit $c_0 = 20(1-e^{-kT})$
- Choose convenient values for T and obtain the corresponding dose $D = 25c_0$

Is it possible to choose the dose D and the interval T to remain in the therapeutic range?

$$c_0 = 20(1 - e^{-kT}),\ k = 0.17$$

$$D = 25c_0$$

- We need to choose T so that

$$5 \le c_0 \le 20 \text{ and } c(T) \ge 5$$

- We have $T = 4$

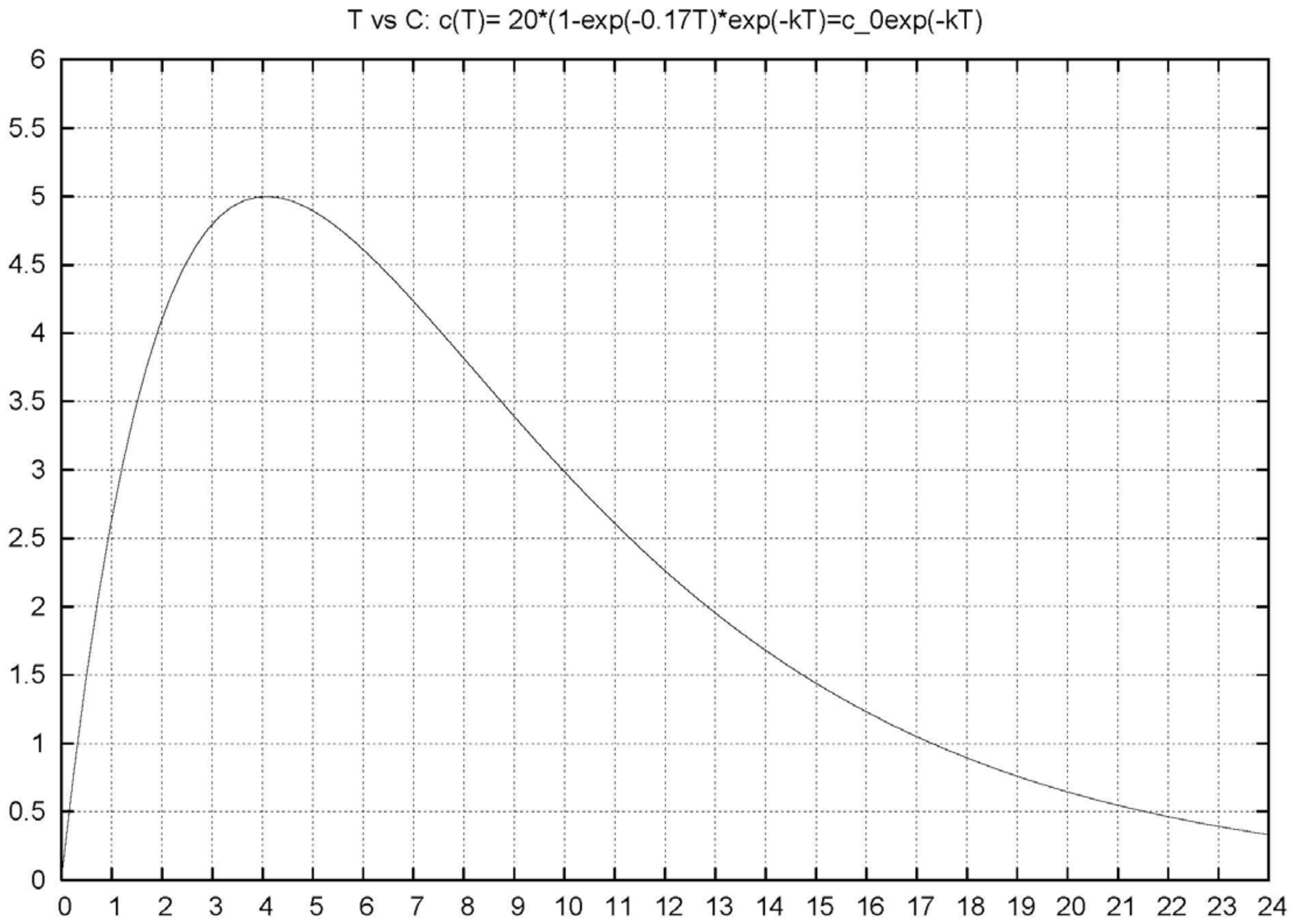
$$c_0 = 9.868 \text{ for } T = 4$$

$$c(4) = c_0\, e^{-4k} \ge 5 \text{ (mg/l)}$$

$$\frac{9.87}{1 - e^{-4k}} \le 20$$

T	c_0(mg/l)	D (mg)	$c(T)$
1	3.13	78.2	2.64
2	5.76	144	4.1
3	7.99	200	4.8
4	9.87	247	5
5	11.5	286	4.89
6	12.8	320	4.61
7	13.9	348	4.23
8	14.9	372	3.82
9	15.7	392	3.39
10	16.3	409	2.99
11	16.9	423	2.61
12	17.4	435	2.26
13	17.8	445	1.95
14	18.1	454	1.68
15	18.4	461	1.44
16	18.7	467	1.23
17	18.9	472	1.05
18	19.1	477	0.89
19	19.2	480	0.76
20	19.3	483	0.65
21	19.4	486	0.55
22	19.5	488	0.46
23	19.6	490	0.39
24	19.7	492	0.33

Graph: *T* vs. *C(T)*


T vs C: c(T)= 20*(1-exp(-0.17T)*exp(-kT)=c_0exp(-kT)
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Advice to the 50 (kg) patient

- Get the shot of a dose of 250 (mg) every 4 hours !!!

Final Comments

- Actually the value c_0 and k are not obtained by LS for gievn data.
- Check this by obtain c_0 and k using LS for given data!
- Is there any difference in your conclusion?