محاضرة: lec 13

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Urinary data post extravascular route of administration

PK theory lec.13

Analysis of Urinary data following oral administration-Sigma minus method

- Similar to the analysis of urinary data following IV administration, the urinary data following oral data can be analyzed via sigma minus method or rate method.
- Based on sigma minus method the amount of the drug excreted in the urine can be expressed as:

$$Xu = \frac{KrKaFXo}{K}\left[\frac{1}{Ka} + \frac{e^{-Kt}}{(K-Ka)} - \frac{Ke^{-Kat}}{Ka(K-Ka)}\right]........(1)$$

- At t=infinity

$$Xu^{\infty} = \frac{KrFXo}{K}........(2)$$

Analysis of Urinary data following oral administration-Sigma minus method

- Substitution with Xu^∞ from the second equation in the first equation and rearrangement yields

$$(Xu^\infty - Xu) = \frac{Xu^\infty}{Ka-K}\left[K_a e^{-Kt} - K e^{-Kat}\right]$$

- When Ka>>K

$$(Xu^\infty - Xu) = \frac{Xu^\infty}{Ka-K}\left[K_a e^{-Kt}\right]$$

$$Log(Xu^\infty - Xu) = Log\frac{Xu^\infty K_a}{Ka-K} - \left[\frac{Kt}{2.303}\right]$$

slope

intersept

Sigma minus method

In summary potting the logarithm of the amount remaining to be eliminated ((Xu$^\infty$ - Xu) versus time will yield a curvilinear plot with terminal segment representing elimination rate constant (slope = -K/2.303)

* The residual line representing the absorption rate constant (slope = -Ka/2.303) and **vice versa in flip-flop.**

Practically, collection of sufficient number of urine samples during the absorption phase to enable a pharmacokinetics analysis of this phase **is generally not possible unless the absorption half-life is long.**

A serious shortcoming for this approach is manifested by the need to collect the urine for a long period of time (seven t$_{1/2}$), and also that samples cannot be skipped.

* في الـ Sigma method الـ intercept بتاعها residual الـ والـ terminal تقطع وتلاقي، ، الـ residual دائماً أعلى من سـ الـ terminal

Table C.3 Application of the Method of Residuals to Urinary Excretion Data Obtained After Oral Administration of a Drug

Time (h)	X_u[a] (mg)	$X_u^\infty - X_u$ (mg)	Extrapolated $X_u^\infty - X_u$ (mg)	Residual $X_u^\infty - X_u$ (mg)
1.0	0.36	49.64	65.8	16.16
2.0	1.32	48.68	61.5	12.82
3.0	3.70	47.30	57.3	10.0
4.0	4.37	45.63	53.5	7.87
6.0	8.23	41.77	46.5	4.73
8.0	12.35	37.65	40.5	2.85
12.0	20.24	29.76		
18.0	29.82	20.18		
24.0	36.65	13.45		
36.0	44.11	5.90		
∞	50.00			

[a]Cumulative amount of drug in the urine.

Notes: The data are analyzed using the sigma-minus method. First-order absorption and a one-compartment model are assumed. $K = 0.0693$ h^{-1}, $k_a = 0.231$ h^{-1}, $V = 10$ liters, $X_0 = 500$ mg, $F = 1$.

Analysis of Urinary data following oral administration-Rate method

- The rate of drug excretion after a single oral dose of drug is given by

$$\frac{dXu}{dt} = KrXt \ldots\ldots \quad ..(a)$$

$$Xt = \frac{KaFXo}{(Ka - K)}\left[e^{-Kt} - e^{-Kat}\right]\ldots\ldots(\quad b)$$

- Substituting the value of X_t in equation b

$$\frac{dXu}{dt} = \frac{KrKaFXo}{(Ka - K)}\left[e^{-Kt} - e^{-Kat}\right]$$

Analysis of Urinary data following oral administration-Rate method

- When Ka>>K

$$\frac{dXu}{dt} = \frac{KrKaFXo}{(Ka - K)}\left[e^{-Kt}\right]$$

$$\log \frac{dXu}{dt} = \log \frac{KrKaFXo}{(Ka - K)} - \frac{Kt}{2.303}$$

intercept — slope

- T: mid point of the collection interval

Rate method

- In summary, plots of log($\Delta Xu/ \Delta t$) versus time will yield a curvilinear profile with the terminal phase representing the elimination rate constant (slope = -K/2.303) and the residual line representing the absorption rate constant (slope = - Ka/2.303).

- Drugs exhibiting flip-flop kinetics, the terminal segment of the plot drawn between log($\Delta Xu/ \Delta t$) versus time will represent the absorption rate constant (slope = - Ka/2.303) and the residual represent the elimination rate constant (slope = -K/2.303).

Example: Sigma minus

- A single oral dose of an antibiotic was given to a 60-kg man at a dose level of 500mg (F=0.924). Urine samples were removed periodically and assayed for parent drug. The following data were obtained, calculate K,Kr, Ka

A	B	C	D	E	E
Time	X	Xcumulative	Xuinf-XU	Extra. Term	Residual
0.25	3.597	3.597	227.403	252.133	24.730
0.5	8.489	12.086	218.914	233.915	15.001
1	23.102	35.189	195.811	201.332	5.521
2	47.410	82.599	148.401	149.151	
4	66.561	149.160	81.840	81.856	
8	57.186	206.346	24.654	24.654	
16	22.417	228.763	2.237	2.237	
24	2.034	230.797	0.203	0.203	
32	0.184	230.982	0.018	0.018	→ terminal equation
40	0.017	230.998	0.002	0.002	
48	0.002	231.000	0.000	0.000	
56	0.000	231.000	0.000	0.000	
64	0.000	231.000	0.000	0.000	
80	0.000	231.000	0.000	0.000	

X_u^∞

Example: Sigma minus

- 1- Calculate cumulative Xu
- 2- Find Xu infinity (last cell of column C) *amount remained to be excreted*
- 3-Find ARE($Xu^{\infty} - Xu$)   *terminal* $y = 271.77e^{-0.3x}$
- 4- Plot ARE against time (upper end of the time interval), since Ka>>>k the terminal line would be
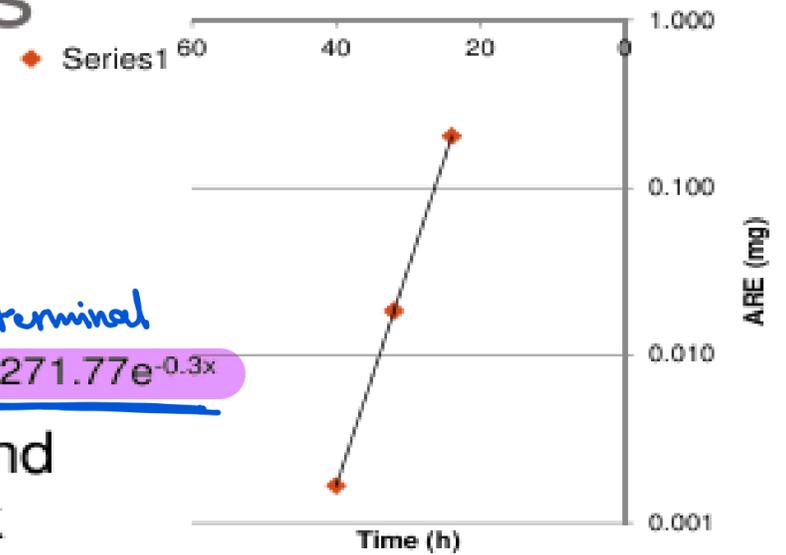
$$(Xu^{\infty} - Xu) = \frac{Xu^{\infty}Ka}{Ka-K}\left[e^{-Kt}\right]$$

- K=0.3/h

Example: Sigma minus

5- Find the early concentrations on the extrapolated line using the equation y = 271.77e$^{-0.3x}$, for example at t=0.25

Y= 252.133

6- To find the residual line Column E –Column D
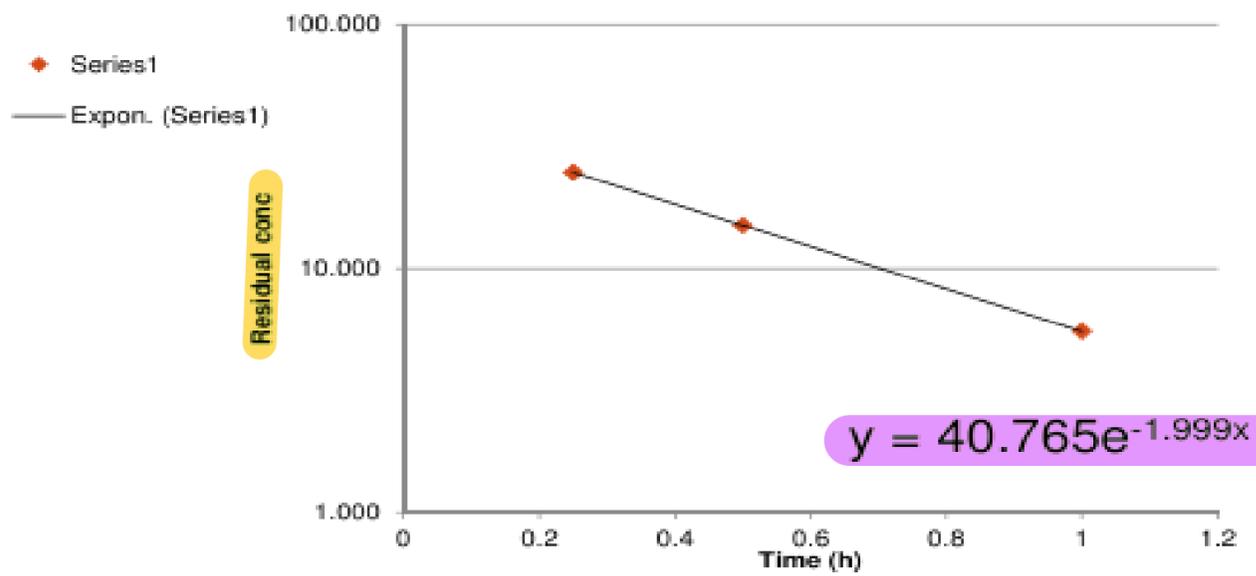
7- plot residual C Vs. Time (upper limit of the interval)

$$(Xu^{\infty} - Xu) = \frac{Xu^{\infty}K}{Ka - K}\left[e^{-Kat}\right]$$

Example: Sigma minus

Ka=1.99/h
Kr=.15/h

$$X_u^\infty ?$$

$$X_u^\infty = \frac{Kr \, F \, X_0}{K}$$
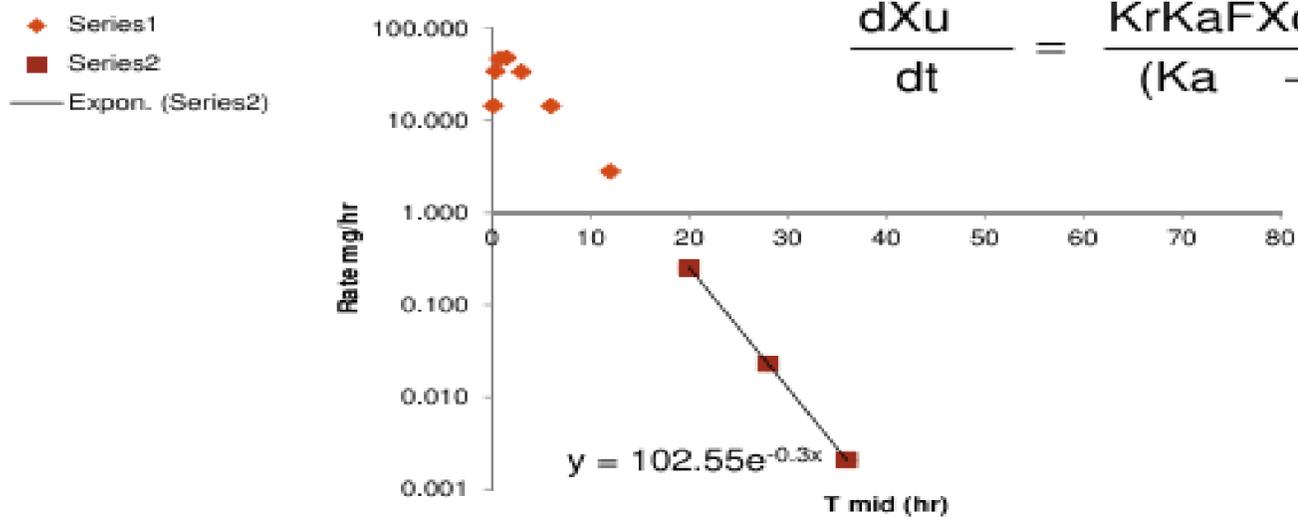
or

intercept is

y = 40.765e$^{-1.999x}$

Example: Rate method

- A single oral dose of an antibiotic was given to a 60-kg man at a dose level of 500mg (F=0.924). Urine samples were removed periodically and assayed for parent drug. The following data were obtained, calculate K,Kr, Ka utilizing the rate method

A	B	C	D	E	F	G
Interval	Amount recovered in the urine	dt	T mid	Rate	Extrapolated	Residual
0-0.25	3.597	0.25	0.125	14.388	98.776	84.387
0.25-0.5	8.489	0.25	0.375	33.957	91.638	57.681
0.5-1	23.102	0.5	0.75	46.204	81.888	35.683
1-2	47.410	1	1.5	47.410		
2-4	66.561	2	3	33.280		
4-8	57.186	4	6	14.297		
8-16	22.417	8	12	2.802		
16-24	2.034	8	20	0.254		
24-32	0.184	8	28	0.023		
32-40	0.017	8	36	0.002		
40-48	0.002	8	44			
48-56	0.000	8	52			
56-64	0.000	8	60			

Example: Rate method

- 1- Calculate the rate (dx/dt) (Column B/ Column C)
- 2-Calculate T mid
- 3- Plot the rate against T mid
- 4- The equation of the terminal line is

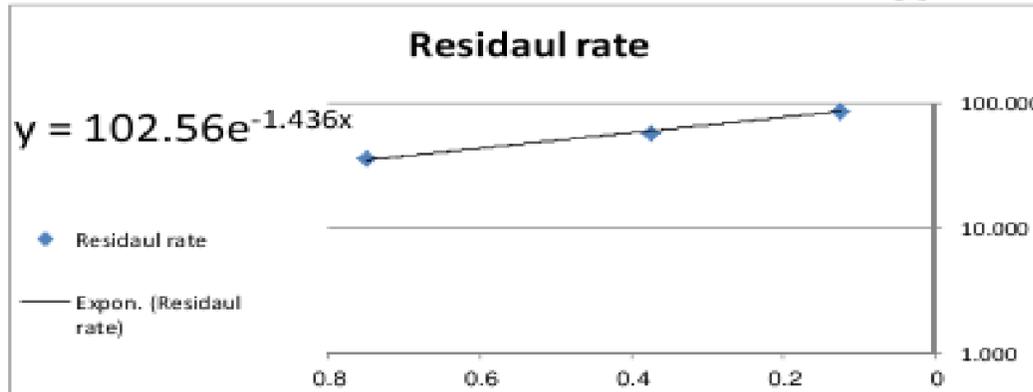$$\frac{dXu}{dt} = \frac{KrKaFXo}{(Ka - K)}\left[e^{-Kt} \right]$$

$$K=0.3/hr$$

Series1
Series2
Expon. (Series2)

Rate mg/hr

100.000
10.000
1.000
0.100
0.010
0.001

0 10 20 30 40 50 60 70 80

$y = 102.55e^{-0.3x}$

T mid (hr)

Example: Rate method

5- Find the early concentrations on the extrapolated line using the equation $y = 102.55e^{-0.3x}$ for example at t=0.25 Y=98.776 mg/h

6- To find the residual line Column F –Column E

7- plot residual C Vs. T-mid

$$\frac{dXu}{dt} = \frac{KrKaFXo}{(Ka - K)}\left[e^{-Kat} \right]$$

Residaul rate

$y = 102.56e^{-1.436x}$

◆ Residaul rate

—— Expon. (Residaul rate)

0.8   0.6   0.4   0.2   0

100.000

10.000

1.000

$$98.723 = \frac{KrKaFXo}{(Ka - K)}$$

$Kr = 0.166 / h$

$Ka = 1.4 / h$