# PHA 4120

## Problem Set "One Compartment Model with i.v. Injection Only Urinary Elimination

A 70 kg patient was given a bolus i.v. injection of 1000 mg of a drug. The drug is not bound to plasma proteins and is excreted unchanged solely into the urine. When the plasma concentration ($C_p$) and the cumulative amounts excreted into the urine ($U_t$) were assayed, the following data was obtained.

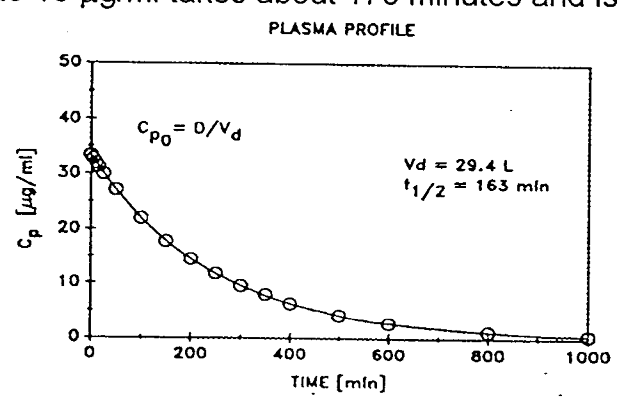
| time t[min] | Cp[μg/ml] | $U_t$[mg] |
|---|---|---|
| 5 | 32.7 | 20.5 |
| 10 | 32.0 | 40.9 |
| 15 | 31.3 | 60.7 |
| 25 | 30.0 | 98.8 |
| 50 | 27.1 | 188.2 |
| 100 | 22.0 | 340.9 |
| 150 | 17.8 | 464.8 |
| 200 | 14.5 | 565.3 |
| 250 | 11.8 | 647.2 |
| 300 | 9.55 | 713.5 |
| 350 | 7.95 | 767.5 |
| 400 | 6.30 | 811.0 |
| 500 | 4.15 | 877.0 |
| 600 | 2.74 | 917.8 |
| 800 | 1.19 | 964.3 |
| 1000 | 0.52 | 984.4 |

1. Plot the plasma data on linear coordinate paper and estimate $t_{1/2}$ and $V_d$.

**Answer:**

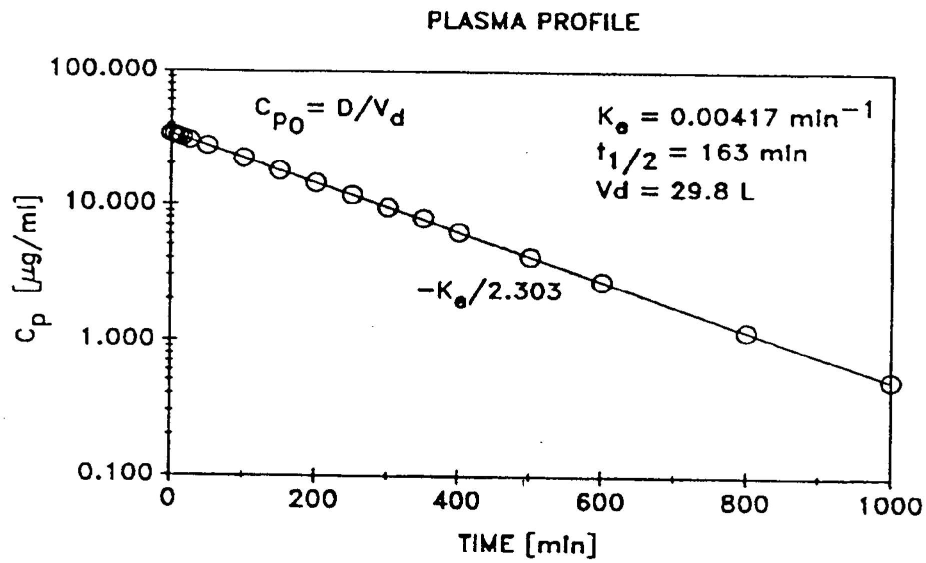
It is difficult to get a correct estimate of the intercept $C_p$ from this plot. The best guess would be $C_p$ = 34.0 mg/ml. the volume of distribution $V_d$ calculated with this value is 29.4 liters.

It is also difficult to estimate the half-life $t_{1/2}$. The decrease of plasma level from 20 μg/ml to 10 μg/ml takes about 170 minutes and is equivalent to one half-life.



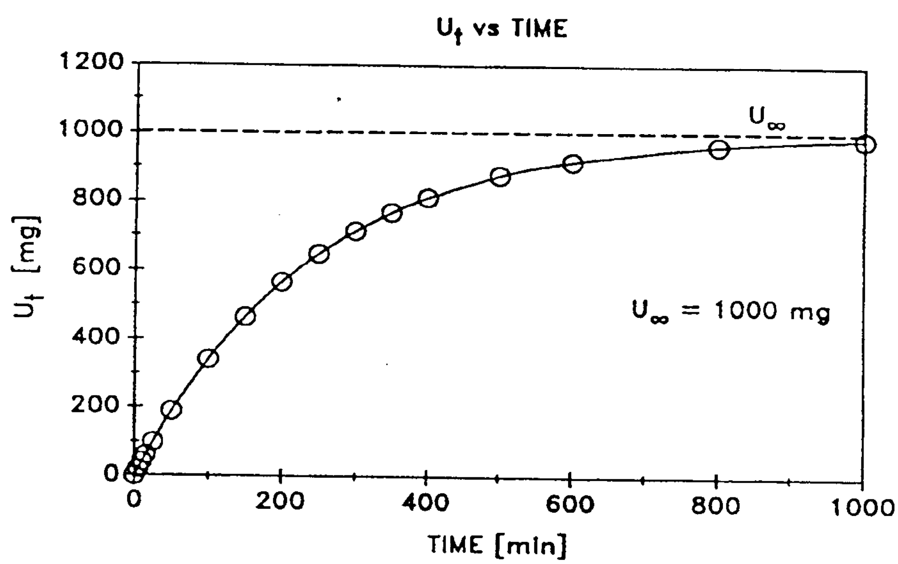
| | |
|---|---|
| 2. | Plot the plasma data on semilogarithmic paper and determine $k_e$, $t_{1/2}$ and $V_d$. |

**Answer:**




| | |
|---|---|
| 3. | Plot $U_t$ vs t on linear coordinate paper. Estimate $U_\infty$ |

**Answer:**



| 4. | Determine $k_e$ using only urinary excretion data. Use two different methods. |
|---|---|

**Answer:**

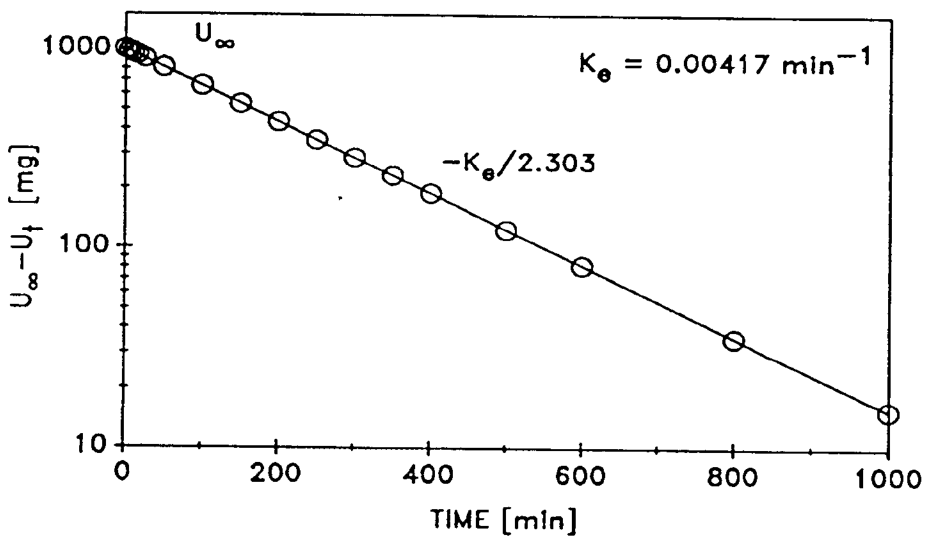
a) $\Sigma$- plot

$$\log (U_\infty - U) = \log U_\infty - \frac{k_e}{2.303} \cdot t$$

$U_\infty$ = 1000 mg

| t[min] | $U_\infty$ - U[mg] | t[min] | $U_\infty$ - U [mg] |
|---|---|---|---|
| 5 | 979.5 | 250 | 352.8 |
| 10 | 959.1 | 300 | 286.5 |
| 15 | 939.3 | 350 | 232.5 |
| 25 | 901.2 | 400 | 189.0 |
| 50 | 811.8 | 500 | 123.0 |
| 100 | 659.1 | 600 | 82.2 |
| 150 | 535.2 | 800 | 35.7 |
| 200 | 434.7 | 1000 | 15.6 |

SIGMA MINUS PLOT



| b) urinary excretion rate |
|---|

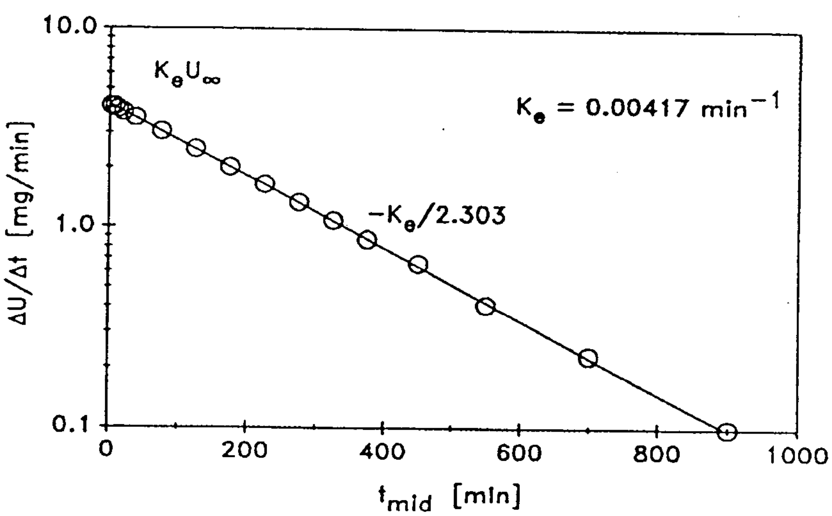
$$\log\frac{dU}{dt} = \log k_e \cdot U_\infty - \frac{k_e}{2.303}\cdot t$$

or

$$\log\frac{\Delta U}{\Delta t} = \log k_e \cdot U_\infty \frac{k_e}{2.303}\cdot t_{mid}$$

| Time interval [min] | $\Delta t$ [min] | $\Delta U$ [mg] | $\frac{\Delta U}{\Delta t}$ / [mg/min] | $t_{mid}$ [min] |
|---|---|---|---|---|
| 0-5 | 5 | 20.5 | 4.10 | 2.5 |
| 5-10 | 5 | 20.4 | 4.08 | 7.5 |
| 10-15 | 5 | 19.8 | 3.96 | 12.5 |
| 15-20 | 10 | 38.1 | 3.81 | 20.0 |
| 25-50 | 25 | 89.4 | 3.58 | 37.5 |
| 50-100 | 50 | 152.7 | 3.05 | 75.0 |
| 100-150 | 50 | 123.9 | 2.48 | 125.0 |
| 150-200 | 50 | 100.5 | 2.01 | 175.0 |
| 200-250 | 50 | 81.9 | 1.64 | 225.0 |
| 250-300 | 50 | 66.3 | 1.33 | 275.0 |
| 300-350 | 50 | 54.0 | 1.08 | 325.0 |
| 350-400 | 50 | 43.5 | 0.87 | 375.0 |
| 400-500 | 100 | 66.0 | 0.66 | 450.0 |
| 500-600 | 100 | 40.8 | 0.41 | 550.0 |
| 600-800 | 200 | 46.5 | 0.23 | 700.0 |
| 800-1000 | 200 | 20.1 | 0.10 | 900.0 |

URINARY EXCRETION RATE PLOT



5. Plot the rate of urinary excretion against the plasma concentration. Estimate the renal clearance.

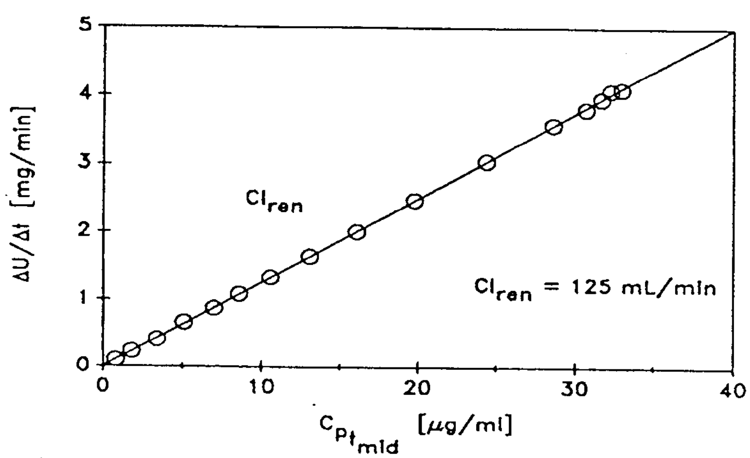
$$\frac{dU}{dt} = k_e \cdot V_d \cdot C_p = Cl_{ren} \cdot C_p$$

or

$$\frac{\Delta U}{\Delta t} = Cl_{ren} \cdot C_{p_{mid}}$$

| $\frac{\Delta U}{\Delta t}$ [mg/ml] | $t_{mid}$[min] | $C_{p_{mid}}$ from plot # 2 [μg/ml] |
|---|---|---|
| 4.10 | 2.5 | 33.0 |
| 4.08 | 7.5 | 32.3 |
| 3.96 | 12.5 | 31.7 |
| 3.81 | 20.0 | 30.7 |
| 3.58 | 37.5 | 28.6 |
| 3.05 | 75.0 | 24.4 |
| 2.48 | 125.0 | 19.8 |
| 2.01 | 175.0 | 16.1 |
| 1.64 | 225.0 | 13.1 |
| 1.33 | 275.0 | 10.6 |
| 1.08 | 325.0 | 8.6 |
| 0.87 | 375.0 | 7.0 |
| 0.66 | 450,0 | 5.1 |
| 0.41 | 550.0 | 3.4 |
| 0.23 | 700.0 | 1.8 |
| 0.10 | 900.0 | 0.8 |

URINARY EXCRETION RATE vs PLASMA CONCENTRATION



| 6. | Plot $U_t$ vs $AUC_t$. Determine the renal clearance. |
|---|---|

**Answer:**

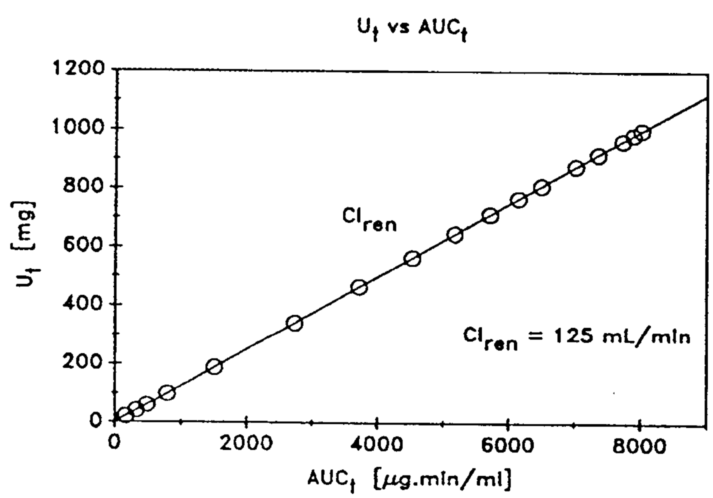
$$U_t = Cl_{ren} \cdot AUC_t$$

$AUC_t$ can be determined by the trapezoidal rule or calculated:

$$AUC_t = \frac{C_{p_0}}{k_e}\left(1 - e^{-k_e \cdot t}\right)$$

$C_{p0}$ = 33.4 $k_e$ = 0.004165

| t[min] | $U_t$[mg] | $AUC_t \frac{\mu g / \min}{[ml]}$ |
|---|---|---|
| 5 | 20.5 | 165.2 |
| 10 | 40.9 | 326.9 |
| 15 | 60.7 | 485.3 |
| 25 | 98.8 | 792.4 |
| 50 | 188.2 | 1506.6 |
| 100 | 340.9 | 2729.8 |
| 150 | 464.8 | 3723.1 |
| 200 | 565.3 | 4529.6 |
| 250 | 647.2 | 5184.6 |
| 300 | 713.5 | 5716.4 |
| 350 | 767.5 | 6148.2 |
| 400 | 811.0 | 6498.9 |
| 500 | 877.0 | 7014.8 |
| 600 | 917.8 | 7355.0 |
| 800 | 964.3 | 7727.2 |
| 1000 | 1000.0 | 8013.4 |



7. Compare the renal clearance with the total body clearance that you can calculate from dose and $AUC_{\infty}$.

**Answer:**

Total body clearance

$$Cl_{tot} = \frac{D}{AUC_{\infty}} = \frac{1000}{8013.4} = 0.125\frac{mg \cdot ml}{\mu g \cdot ml} = 125\ ml/min$$

Total body clearance and renal clearance are equal, indicating that renal excretion of the unchanged drug is the only way of drug elimination.

8. What could you conclude as to the major process for elimination of this drug.

**Answer:**

Glomerular filtration only

or

glomerular filtration, tubular secretion and tubular reabsorption with the same magnitude of tubular secretion and reabsorption.