A blood brain pharmacokinetic model

Pharmacokinetics, an emerging field in BioPhysics and chemistry is the study of the time variation of drug and metabolite levels in various tissues and fluids of the body. Compartment models are used to interpret data. In our problem, we consider a simple blood-brain compartment model as shown in the figure below:

k21

Input d(t) k12

K

where, Compartment 1 = Blood

Compartment 2 = Brain

This model is made such that it can aid to help estimate dosage strengths of an orally administered antidepressant drug. The rate of movement of drug from compartment i to compartment ‘ j’ is denoted by the rate constant kji and the rate at which the drug is removed from the blood is represented by the rate constant K. A pharmaceutical company must deal with many factors like dosage strengths that will aid a physician in determining a patient’s dosage in order to maintain the right concentration levels and also minimizing irritation and other side effects (Brannan 208).

If we assume that the drug is rapidly absorbed into the blood stream after it is introduced into the stomach, a mathematical representation of the dosage will be of a periodic square wave given as follows:

Based on our model and the equations we can solve the problems:

1. If we let xj(t) be the amount of drug in milligrams in compartment ‘ j’, j = 1, 2. The mass balance law states:

(i)

Using the mass balance law and the figure, we find:

System in Blood compartment:

System in Brain compartment:

From (i) and the above equations, we can find the following:

(ii)

The systems above are the rates of drug over time in the compartments.

2. If we let ci(t) denote the concentration of the drug and Vi denote the apparent volume of distribution in compartment i, we can use the relation ci = xi/Vi in the equations of system (ii) to obtain:

(iii)

Dividing the above systems by V1 and V2 respectively, we get :

3. Assuming x1(0) = 0 and x2(0) = 0, and the various parameters listed below:

k21

k12

K

V1

V2

Tb

0. 29/h

0. 31/h

0. 16/h

6L

0. 25L

1h

and with the numerical simulation program Maple , we can perform simulations of the system with given parameters to recommend two different encapsulated dosage strengths A= RTb.

=> Guidelines to use for recommendation of drug dosage:

1) Target concentration level in the brain should be kept as close as possible between levels 10 mg/L and 30 mg/L and concentration fluctuation should not exceed 25% of the average of the steady-state response.

2) Lower frequency of administration (once every 24 hours or once every 12 hours is best). Once every 9. 5 hours is unacceptable and multiple doses are acceptable (i. e. taking two capsules every 4 hours)

Analysis: Drug usage of more than 4 times per day is unacceptable which makes maximum allowable dose to be 3, making 3 doses at 8 hours interval per day the best choice. We can then simulate from Tp = 8 to Tp = 12, 16 and 24.

From the numerical simulations obtained from Maple, we obtain the following data:

Tp(h)

R (mg/h)

Steady-state variance

Comments

8

4

9. 04 mg/L to 12. 5 mg/L

Below effective therapeutic concentration

8

5

11. 7 mg/L to 15. 5 mg/L

8

6

14. 4 mg/L to 19. 2 mg/L

8

8

19. 2 mg/L to 25. 3 mg/L

8

9

21. 1 mg/L to 27. 9 mg/L

8

10

23. 2 mg/L to 31. 2 mg/L

Above maximum therapeutic concentration

12

5

10. 9 mg/L to 6. 5 mg/L

Below minimum therapeutic concentration

12

6

8. 6 mg/L to 14. 1 mg/L

Below minimum therapeutic concentration

12

7

8. 32 mg/L to 15. 1 mg/L

Below minimum therapeutic concentration

12

8

10. 6 mg/L to 18. 3 mg/L

12

10

13. 2 mg/L to 22. 8 mg/L

12

13

17. 9 mg/L to 30 mg/L

16

10

9. 11 mg/L to 19. 5 mg/L

Sharp fluctuations; Below minimum therapeutic concentration

16

12

10. 7 mg/L to 23. 5 mg/L

Sharp fluctuations.

16

13

11. 5 mg/L to 25. 4 mg/L

Sharp fluctuations.

16

14

12. 5 mg/L to 27. 3 mg/L

Sharp fluctuations.

16

16

14. 3mg/L — 31. 4mg/L

Sharp fluctuations; Above maximum therapeutic concentration

24

15

6. 19mg/L — 24mg/L

Sharp fluctuations; Below minimum therapeutic concentration

24

20

8. 52mg/L — 32mg/L

Sharp fluctuations; Above maximum therapeutic concentration

Obtained corresponding Graphs from Maple and their respective Tp and R values are listed below:

Tp = 8, R = 4 Tp = 8, R = 5

Tp = 8, R = 6 Tp = 8, R = 8

Tp = 8, R = 9 Tp = 8, R = 10

Tp = 12, R = 6 Tp = 12, R = 8

Tp = 12, R = 10 Tp = 12, R = 12

Tp = 12, R = 13

Tp= 16, R= 10 Tp= 16, R= 12

Tp= 16, R= 13 Tp= 16, R= 14

Tp= 16, R= 16

Tp= 24, R= 15 Tp= 24, R= 20

Some Comments:

When Tp= 8 and R = 4, the recommended dosage is below minimum therapeutic concentration range.

When Tp= 8 and R = 10 , the recommended dosage is above maximum therapeutic concentration range.

When Tp= 8 and R = 5 to 7, the recommended dosage is below effective therapeutic concentration range.

When Tp= 8 and R = 4, the recommended dosage is below therapeutic concentration range.

When Tp= 12 and R = 5 to 7, the recommended dosage is below minimum therapeutic concentration range.

When Tp= 16 and R = 12 to 14, sharp fluctuation is seen.

When Tp= 24 and R = 20, sharp fluctuation is seen and the recommended dosage is below therapeutic concentration range.

=> Calculation and Analysis of dosage strength ‘ A’

Now we can calculate the dosage frequency for the remaining dosage frequency intervals of 8 hours and 12 hours:

(8 hour interval) (R being from 5 mg/h to 9 mg/h)

A = RTb = 5 mg/h x 1h= 5 mg

A = RTb = 9 mg/h x 1h= 9 mg

(12 hour interval) (R being from 8 mg/h to 13 mg/h)

A = RTb = 8 mg/h x 1h = 8 mg

A = RTb = 13 mg/h x 1h= 13 mg

4. From the simulation, we can know that it is best to skip the dose than to try to catch up and double the dose and ultimately overdose from the figures illustrated. If we assume the patient is at a 12 hour interval dose frequency, and R being 10mg/h, the following scenarios can be simulated:

Scenario: missed a dosage and skipped Scenario: missing a dosage & catching up

Analysis: From the scenarios simulations above, we can have a clear picture of what will go through the patient’s drug level.

In the 1st scenario, where the patient missed a dosage and skipped, the concentration level in the brain of the patient stays within the recommended level.

In the 2nd scenario, where the patient tries to catch up, the drug level will cross the recommended level and that also by a lot. Thus, skipping the dose is better than to catch up overdosing the drug level resulting in fatality.

5. Supposing the drug can be packaged in a timed-release form so that Tb = 8 hours and R also adjusted likewise, we get the following data from the Maple:

Tp(h)

R(mg/h)

Steady-state variance

Reasons

12

0. 75

10. 4mg/L — 13mg/L

12

1

13. 9mg/L — 17mg/L

12

1. 5

21mg/L — 25. 5mg/L

12

1. 75

24. 5mg/L — 29. 8mg/L

12

2

28. 1mg/L — 34mg/L

Above maximum therapeutic concentration

16

1

9mg/L — 14. 3mg/L

Below minimum therapeutic concentration

16

1. 25

11. 2mg/L — 17. 7mg/L

16

1. 5

13. 6mg/L — 21. 3mg/L

16

2

18. 3mg/L — 28. 4mg/L

16

2. 25

20. 5mg/L — 31. 8mg/L

Above maximum therapeutic concentration

16

2. 5

22. 8mg/L — 35. 4mg/L

Above maximum therapeutic concentration

24

2

8. 7mg/L — 23. 3mg/L

Sharp fluctuation

24

2. 25

9. 86mg/L — 25. 9mg/L

Sharp fluctuation

24

2. 5

10. 9mg/L — 29mg/L

Sharp fluctuation

T= 12, R= 0. 75

T= 12, R= 1

T= 12, R= 1. 5

T= 12, R= 1. 75

T= 12, R= 2

T= 16, R= 1 T= 16, R= 1. 25

T= 16, R= 1. 5 T= 16, R= 2

T= 16, R= 2. 25 T= 16, R= 2. 5

T= 24, R= 2 T= 24, R= 2. 5

Analysis: If the drug can be packaged in a timed release form so that Tb = 8 and R is also adjusted likewise, we perform the simulations for the dosage of interval of a 12 hour frequency. We observe zero sharp fluctuations. Every graph seems to produce the concentration level within the recommended range of 10mg/L to 30mg/L when R is between 0. 75 mg/h and 1. 75 mg/h.

=> Calculation and Analysis of new dosage strength ‘ A’

We can calculate the new strength level of the drugs as:

(12 hour frequency interval): A= RTb = 0. 75 mg/h * 8h = 6mg

A= RTb = 1. 75 mg/h * 8h = 14mg

Same analysis can be performed for 16 hour frequency interval. We observe zero sharp fluctuations and every graph produce the concentration level within the recommended range of 10mg/L to 30mg/L; R being in between 1. 25mg/h and 2mg/h.

=> Calculation and Analysis of new dosage strength ‘ A’

We can calculate the new strength level of the drugs as:

(16 hour frequency interval): A = RTb= 1. 25 mg/h * 8h = 10mg

A = RTb= 2. 00 mg/h * 8h = 16mg

Thus, this changes our recommendation.

Simulation Program Maple: We used the following code and simulated varying R and P values.

g := t—> piecewise(0 <= t and t <= 1, R, 1 < t and t < P, 0, P < t and t < P+1, R, P+1 < t and t < 2*P, 0)

DEplot({diff(x(t), t) = (1/6)*g(t)+(1/6)*(. 31*. 25)*y(t)-x(t)*(. 29+. 16), diff(y(t), t) = (. 29*6)*x(t)/(. 25)-. 31*y(t)}, [x(t), y(t)], t = 0 .. 40, x = 0 .. . 50, y = 0 .. 80, scene = [t, y], [[x(0) = 0, y(0) = 0]], stepsize = . 1, color = blue)