TEACHER VERSION
PARACETAMOL ABSORPTION

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Abstract: We offer drug absorption data on paracetamol, an analgesic pain reliever, for two different sets of patients, vegetarian and non-vegetarian. Students build a two compartment model for plasma and non-plasma (tissue) compartments of human patients and determine parameters in a complete model analysis.

Keywords/Tags: Paracetamol, analgesic, vegetarian, non-vegetarian, modeling, data analysis, parameter estimation, system, linear, differential equation.

STATEMENT

Paracetamol is an analgesic (pain reliever) and this study[1] seeks to determine the effects of diet on the absorption (meaning the amount of the drug which gets into the plasma portion of the body from the non-plasma portion of the body through which it is ingested) of paracetamol from the non-plasma part of the body after it is ingested into the non-plasma part of the body through swallowing a solution of 'Coca Cola' in which the paracetamol was dissolved in the liquid. Two kinds of subjects were involved (a) vegetarian and (b) non-vegetarian.[1]

We will use data from experiments on 10 patients reported in [1] and attempt to model the amount of paracetamol in the non-plasma portion of the body, principally in the tissue are where the analgesic effect takes place.

We use a two compartment model in Figure 1 which is built from understanding the flow or kinetics of paracetamol absorption in the human body. $Q_A(t)$ is the concentration (mg/L) of paracetamol in the patient's non-plasma (or tissue) and $Q_B(t)$ is the concentration (mg/L) of paracetamol in the plasma (or bloodstream). A is the non-plasma compartment, B is the plasma compartment, V_A and V_B are the respective volumes of the compartments (in liters or L), Q_A and Q_B are the respective concentrations of the compartments (mg/L), and the k's are the flow rates in units L/time, where

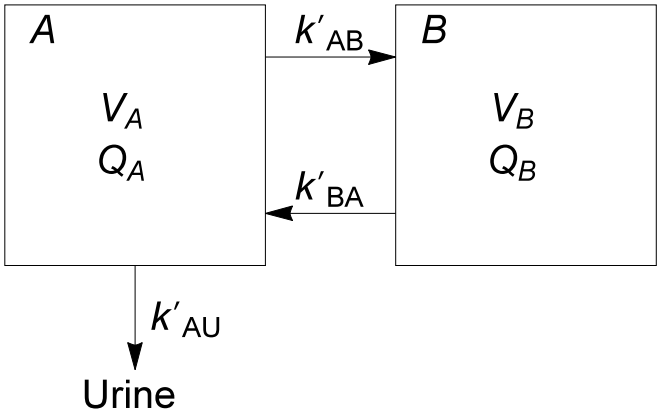

Figure 1. Two compartment model for exchange of paracetamol between the plasma and non-plasma compartments of a human with urinary excretion.

time is in hours. In our work we shall assume the ratio of non-plasma volume to plasma volume (V_A/V_B) is 7.4. Although, one could just leave $R = V_A/V_B$ as a parameter for the model as well or assume other values of R, say in the range 7 to 20 and compare models.

Patients and Data Collection

The purpose of the experiments in [1] was to study the effect of diet on the time for absorption of the parcetamol, for this is the time it will take for the drug to have its analgesic (pain killing) effect. Two different diets or regimens were studied, vegetarian and non-vegetarian. There were 10 patients in each diet group. Thus two sets of patient data were collected with the following protocol:

> Following an overnight fast, 20 mg/kg of paracetamol ... was taken, dissolved in 400 ml of 'Coca Cola'. Fluid was withheld for the next 2 h, during which time the volunteers remained seated, and no food was allowed for 4 h after dosing. Venous blood was taken from an indwelling cannula at 0, 15, 30, 45, 60 and 90 min, and at 2, 3, 4, 5, 6, 7, 8, and 24 h, and urine was collected at 0, 4, 8, 12 and 24 h. Plasma and urine were stored frozen at -20° C until analyzed.[1, p. 238]

Patient Data

Time (h)	0.0	0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0
Paracetamol (mg/L)	0.0	4.5	8.0	9.0	10.5	11.0	11.0	9.0	7.5	5.0	4.0	3.0	2.5

Table 1. Time concentration of paracetamol in vegetarian diet patients, averaged over the 10 patients.

Time (h)	0.0	0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0
Paracetamol (mg/L)	0.0	11.25	13.5	15.25	13.75	13.0	12.0	8.75	7.75	5.75	4.25	3.25	2.0

Table 2. Time concentration of paracetamol in non-vegetarian diet patients, averaged over the 10 patients..

Model Building Activities

Each patient in the study [1] was given an initial dose of paracetamol, $Q_A(0) = 20$ mg/kg of body mass, which "is ingested into the non-plasma part of the body through swallowing a solution of 'Coca Cola' in which the paracetamol was dissolved in the liquid."[1, p. 238].

1. Plot the data of paracetamol concentrations for vegetarian and non-vegetarian patients. Explain what you see.
2. Build a model for the change in the concentration of paracetamol in both the non-plasma and plasma volumes, $Q_A(t)$ and $Q_B(t)$, respectively of the body using the information offered in Figure 1 for each situation, vegetarian and non-vegetarian diets. Use $Q_A(0) = 20$ mg/L and $Q_B(0) = 0$ mg/L.
3. Solve your model for $Q_B(t)$, the concentration of paracetamol in the plasma or blood.
4. Use the assumption that the ratio of non-plasma volume to plasma volume (V_A/V_B) is 7.4 to eliminate variables.
5. Using the data from both the vegetarian diet patients (Table 1) and then the non-vegetarian diet patients (Table 2) estimate all the parameters in the model you built.
6. Plot the concentrations in plasma ($Q_B(t)$) of paracetamol in both the vegetarian and non-vegetarian patients cases and compare your models with the respective data sets.
7. Use the results from your modeling with your determined parameters to compute and plot the total amount of paracetamol in the non-plasma (tissue) for each set of patients.
8. From your analysis can you say there is any effect of diet (vegetarian or non-vegetarian) on absorption of paracetamol into the non-plasma (tissue) portion of the human body? If so what is that effect?
9. Write out a two paragraph description of what your modeling activity tells you with caveats and concerns you have about the implications.

COMMENTS

We enclose several analyses in a Mathematica notebook, 5-20-ParacetamolAbsorption-TeacherVersion.nb (and accompanying pdf file for those who do not use Mathematica) in which complete analysis of a reasonable two compartment flow model for both data sets, vegetarian and non-vegetarian. We believe the results we obtained say that the absorption rate for paracetamol, an analgesic pain reliever, is slower for those with a vegetarian diet than those with a non-vegetarian diet. The paper [1]

gives a great deal of background and physiological narrative and should interest students interested in this area of applications of differential equations.

We had difficulty in finding the ratio R of the volume of non-plasma mass to plasma mass for humans, but our estimates suggested in the literature and common lore suggest that $R = V_A/V_B$ is about 7-12 range depending on the individual. Indeed, in our analysis we estimated, not only the parameter flow rates, but also the value of R in an analysis for vegetarian and non-vegetarian patients and here we found R to be 7.4 for vegetarians and 11.8 for non-vegetarians. This is somewhat disturbing, but in fact, we do not know anything about these two pools. Indeed, the non-vegetarians could have been "chunkier!"

Perhaps students in further research might ascertain a more reasonable range for R and produce a slightly different, but same conclusion, model.

REFERENCES

[1] Prescott, K. Yoovathaworn, K. Makrananda, R. Saivises, and K. Sriwatanakul. 1993. Impaired absorption of paracetamol in vegetarians. *British Journal of Clinical Pharmacology*. 36: 237-240.