Population Pharmacokinetic Analysis of Theophylline In Healthy Volunteers

2023-11-04

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For this document we will be working with the Theoph dataset in r.

- Task 1: Update the YAML Header
  - Update the title of the document
  - Add an author and date option with your name and today's date
  - Choose what type of output you would like to create (pdf or html recommend but not required)
  - Add a table of contents
  - Note: TOC in html will not appear in the Viewer window. You will need to open the .html file to see the TOC

See the Quarto site for help and information on available options

- pdf help https://quarto.org/docs/output-formats/pdf-basics.html
- html help https://quarto.org/docs/output-formats/html-basics.html
- Bonus:
  - Add more than one author
  - Look into some of the formatting features you can add such as cap-location or number-sections and add these to your header
  - For html documents see if you can change the location of the TOC
  - For pdf document see if you can add a list of tables and/or figures
- Task 2: Add Section Headers
  - Go through and add at least 2 section headers (for example for a report or analysis plan you might include an Introduction, Methods, etc.)
  - Choose one section and add at least one sub-header (for example in methods you may have a header for the data, modeling, simulations, etc)

For header help take a look at: https://quarto.org/docs/output-formats/html-basics

- Bonus:
  - Play around with the heading format. For example, ask for the headers to be numbered by adding "number-sections: true" to the YAML header.
  - You can specify that certain sections not be included in the TOC by adding {.unnumbered} after the header. You can also remove a section from the TOC by adding {.unnumbered .unlisted}. Try adding these features to your document.
  - A helpful piece of latex code is : `\cleardoublepage` which creates a page break for pdf documents. Add this after each section header so each section starts on a new page

- Task 3: Figures
  - Create a new r code chunk (keyboard shortcut is: option+commard+I)
  - Explore the Theoph data by plotting conc vs. time or another variable in the dataset.
  - Add a caption and label for your plot
  - Cross reference your plot in text
  - There is a picture of theophylline in your directory "theoph_structure.png" Insert this figure into your document

For help with adding figures take a look at: https://quarto.org/docs/authoring/figures.html

- Bonus:
  - Play around with the different echo options by hiding or showing the plot code
  - Duplicate your plot or create a second one and output the two figures side-by-side

- Task 4: Extras

  - Add some text to your document describing the plots you have made or google some background information on theophylline and add this
  - Add a url to your document by placing the link between <>
  - Next, add the urlcolor: option to your YAML header and choose what color you want the url to display as
  - You can add content to the margin of a document. Leave yourself a note in the margin about this document. The structure for this is for text and for figures or tables made in a code chunk and add the yaml option #| column: margin

add text

For help with adding items to the margin take a look at: https://quarto.org/docs/blog/posts/2022-02-17-advanced-layout/

*Extra Tasks:

- Tables:
  - Create a new r code chunk
  - Create a table summarizing the Theoph PK using gt or another package you are familiar with
  - Add a caption and label for your Table
  - Cross reference your Table in text.

For help with adding items to the margin take a look at: https://quarto.org/docs/authoring/tables.html

- Flow Charts
  - You can re-purpose flow charts to make model diagrams
  - You will need to a code chunk specifying mermaid instead of r as the type
  - For mermaid code chunks the same yaml options can be used but a different pipe is needed. Instead of #| you use %%|
  - Make a diagram for a one and two compartment model in your document

For help with adding items to the margin take a look at: https://quarto.org/docs/authoring/diagrams.html

- Callout Blocks
  - You can add attention grabbing notes to your document with callout blocks
  - There are five different types of blocks: note, warning, important, tip and caution.
  - You can add one of these blocks by: ::: {.callout-tip} some text :::

For help with adding items to the margin take a look at: https://quarto.org/docs/authoring/callouts.html

Synopsis

1 Introduction

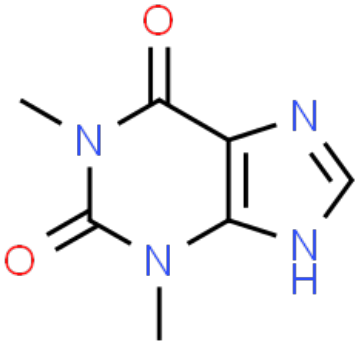
1.1 Background

Theophylline, and its derivatives play an important role in the current management of reversible airway obstruction. Knowledge of the relationship between plasma **theophylline** concentration and bronchodilator response [@Mitenko1973; @Jenne1972] has resulted in more effective use of these agents in the management of the acutely ill and the outpatient requiring regular therapy. The establishment of factors (including a number of diseases) which contribute to variation in **theophylline** kinetics has also improved our potential to provide safe, but effective treatment. The choice of dose and frequency of administration of any drug needs to be assessed with a view to producing effective 'steady state' plasma drug concentrations.

This information was taken from: [@Trembath1980] which can be found here: https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/j.1365-2125.1980.tb01063.x

The chemical structure of **theophylline** is show in below in Figure 1

Figure 1: Theophylline structure



2 Analysis Methods

2.1 Data Summary

The PK data are summarized below in Table 1.

This comment is in the margin

Table 1: Summary Table of Theophylline Concentrations

Subject	Wt	Dose	Time	conc
1	79.6	4.02	0.00	0.74
1	79.6	4.02	0.25	2.84
1	79.6	4.02	0.57	6.57
1	79.6	4.02	1.12	10.50
1	79.6	4.02	2.02	9.66
1	79.6	4.02	3.82	8.58

2.2 Model Development

Various structural models were tested during model development as showed in Figure 2 and Figure 3 below.

Figure 2: Theophylline 1 Compartmental Model

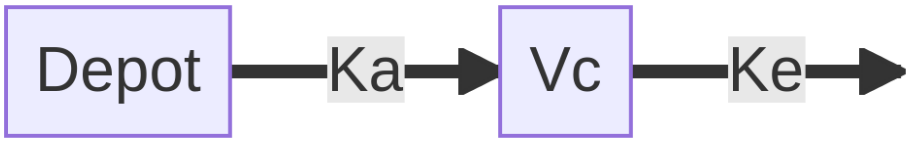
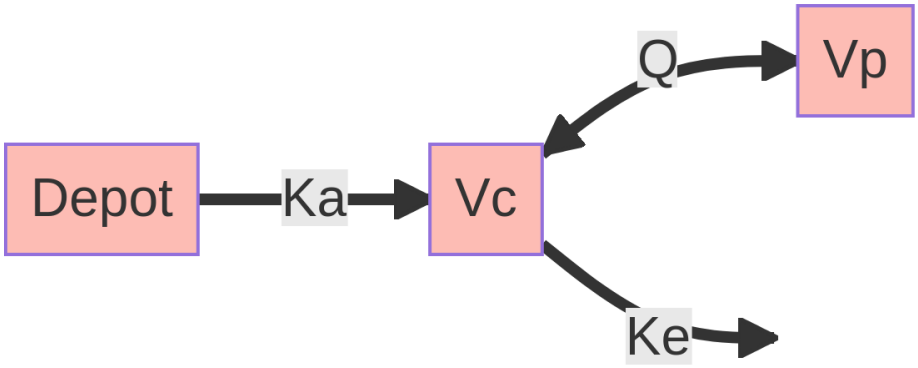


Figure 3: Theophylline 2 Compartmental Model



3 Results

As described in Section 2 there were a total of 10 participants in the current study. The PK profiles are summarized in Figure 4, Figure 5a and Figure 5b below.

Figure 4: Theophylline Concentration versus Time by Subject

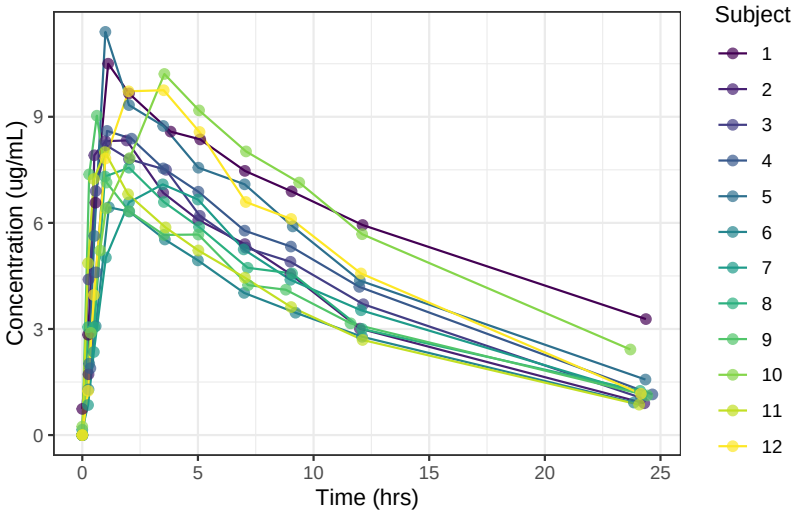
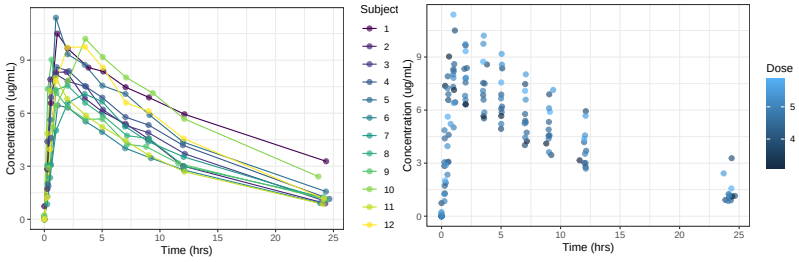


Figure 5: Theophylline Concentration versus Time Colored by Subject and Dose

(a) Theophylline Concentration versus Time by Subject

(b) Theophylline Concentration versus Time by Dose



> **Note**
>
> This document has not been QCed

Figure 6: Theophylline Concentration versus Time by Subject