Note to the last HW: please do not ask me to look over/debug your code or how to enter the dataset☺ Please discuss with your study partner or/and work together to figure out this practice exercise. You may also come to my office hour. However I would not be able to provide you with any additional support beyond what has been provided below via email.

1. Eight healthy male subjects participated in a food interaction study to evaluate the magnitude of the food interaction of a new hypertensive therapy, Drug P, and its metabolite, Drug M. Four subjects (numbers 1, 2, 5, 7) were randomized to take Drug P with food(Fed) in the first treatment period but without food (Fasted) in the second treatment period. The other four subjects (numbers 3, 4, 6, 8) took Drug P without food in the first treatment period but with food in the second treatment period.

Drug concentration values were assayed from plasma samples taken at 0, 10, 20, 30, 40, and 50 minutes, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, and 36 hours after dosing. AUC (areas under the concentration curve) was estimated from zero hours to 36 hours using the PK(Pharmacokinetic) sample data above. The data can be found in the file foodeffect.txt and is listed below.

subj, seq, AUC.Fed, AUC.Fasted

1, +/-, 809.44, 967.82

2, +/-, 428, 746.45

3, -/+, 757.71, 901.11

4, -/+, 906.83, 1146.96

5, +/-, 712.24, 678.16

6, -/+, 561.77, 745.51

7, +/-, 511.84, 568.98

8, -/+, 756.6, 852.86

(a) Plot the mean AUC by period for each sequence. Identify the study design.

Ans:



This is a two period crossover design.

|  |  |  |
| --- | --- | --- |
| **Sequence** | **Period 1** | **Period 2** |
| 1 | Food | Fast |
| 2 | Fast | Food |

(b) Write the ANOVA model for this study. Include all appropriate main effects and interactions. Explain what each symbol in the model means. Designate each effect as either fixed or random. Indicate the ranges of subscripts. State the assumptions for this model.

Ans: Yijkl = μ + δk + αi + βj + πl(k) + εijkl

Where

δk: Fixed effect due to Sequence k, k=1,2.

αi: Fixed effect due to Treatment i, i=1,2

βj: Fixed effect due to Period j, j=1,2

πl(k): random effect, lth subject in kth sequence l. l=1,2, …, n

εijkl : Error term - i.i.d. N(0, σ²)

(c) Perform the analysis of variance in accordance with your model in part (b). Write down the results below.

Factor Type Levels Values

Seq fixed 2 1, 2

Period fixed 2 1, 2

treatment fixed 2 fast, food

subject(Seq) random 8 1, 2, 5, 7, 3, 4, 6, 8

Analysis of Variance for AUC, using Adjusted SS for Tests

Source DF Seq SS Adj SS Adj MS F P

Seq 1 90966 90966 90966 1.92 0.215

Period 1 1674 1674 1674 0.25 0.633

treatment 1 84597 84597 84597 12.75 0.012

subject(Seq) 6 284668 284668 47445 7.15 0.015

Error 6 39816 39816 6636

(d) Does food appear to have an effect on the AUC of the new hypertensive therapy at the 0.05 level of significance? Justify your answer.

Ans: yes. The treatment (food vs. fast) was significant. P-value =0.012<0.05. AUC is much higher under fasted.

(e) Is there evidence of a period effect? Justify your answer.

Ans: No, there doesn’t appear to be a period effect. P-value=0.633>0.05

SAS Code:

\* draw profile plot;

**proc** **glm** data=drug;

class period seq;

model AUC=period seq;

**run**;**quit**;

/\* draw profile plot in another way;

proc sort data=drug;

by seq period;

run;

proc means data=drug mean noprint;

var AUC;

by seq period;

output out=drug\_out mean=mAUC;

run;

symbol1 interpol=join value=dot ;

proc gplot data=drug\_out;

plot mAUC\*period=seq;

run;quit;

\*/

**proc** **glm** data=drug;

class period seq subj treatment;

model AUC=seq subj(seq) period treatment;

random subj(seq)/test;

**run**;**quit**;