Bioequivalence of Modified Release Formulations

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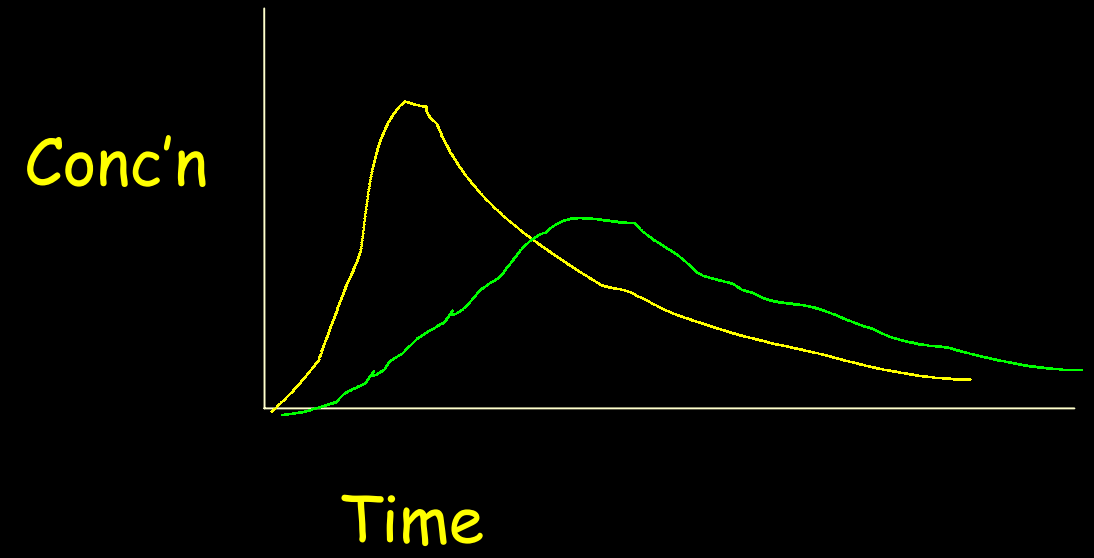
Conflict of Interest Statement:

F. Jamali has received remuneration in forms of research grants, contracts and/or consulting fees from the following pharmaceutical houses:

Apotex (Canada)
Bayer (Germany)
Boots (UK)
Cayman (USA)
Dey Labs (USA)
Dupont (Canada)
Great Valley (USA)
Hoechst-Roussel (Canada)
Janssen (USA)
KaliChemie (Germany)
Knoll (USA)
Merck-Frosst (Canada)
Miles (USA)
Novapharm (Canada)
Prographarm (France)
Rhone Poulenc (Canada)
Roche (USA)
Sandoz (USA)
Searle (Canada, USA)
Sepracor (USA)
Squibb (Canada)
Sterling-Winthrop (Canada, USA)
Upjohn (Canada)
WhiteHall-Robins (USA)
Wyeth-Ayerst (Canada, USA)

Modified Release Formulations:

- FDA, HPB Guidelines
- Similar AUC and Cmax
  80-125%, 90% CI
- ~~Tmax~~



- Monitoring Cmax = time course,

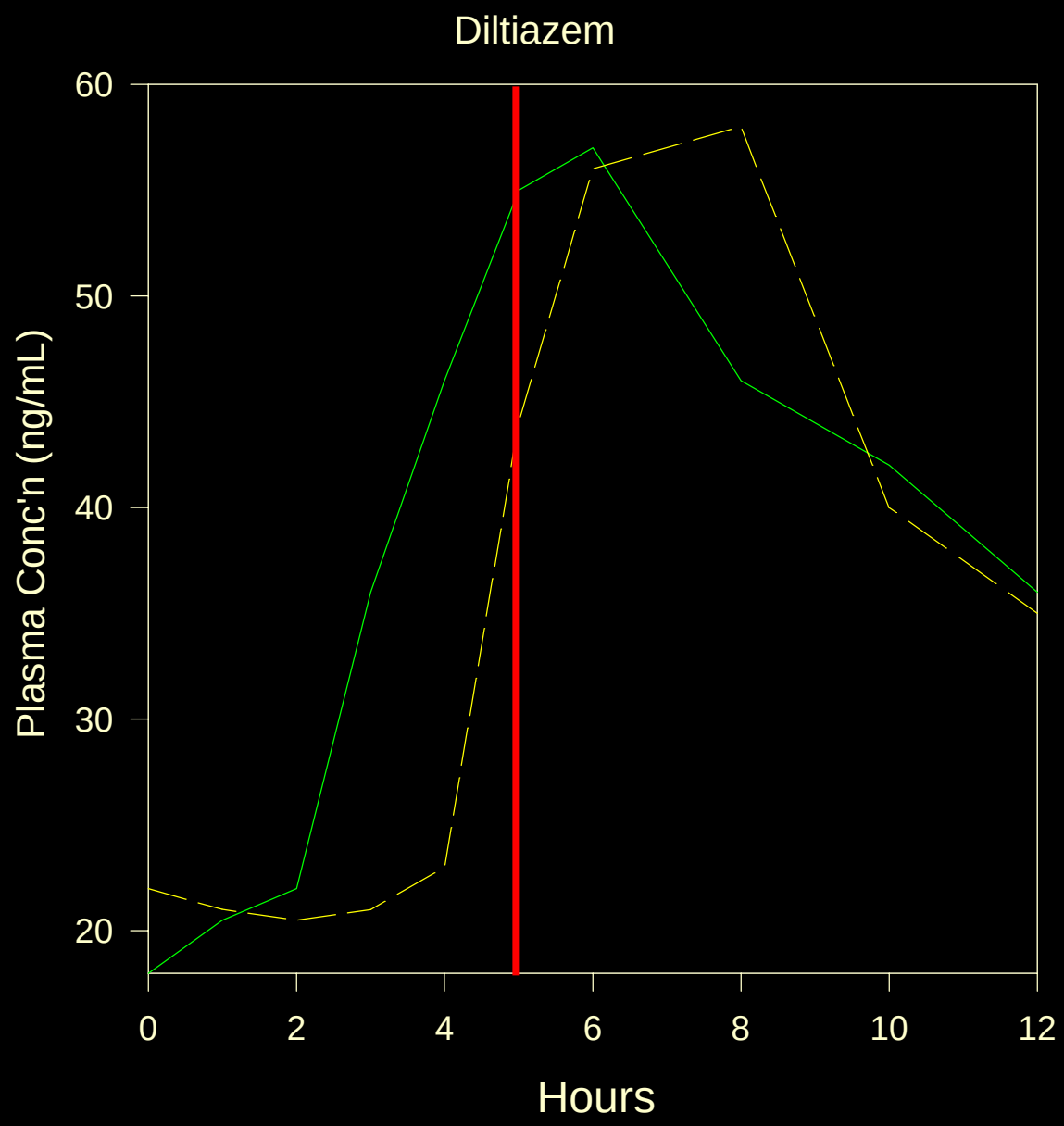
and/or

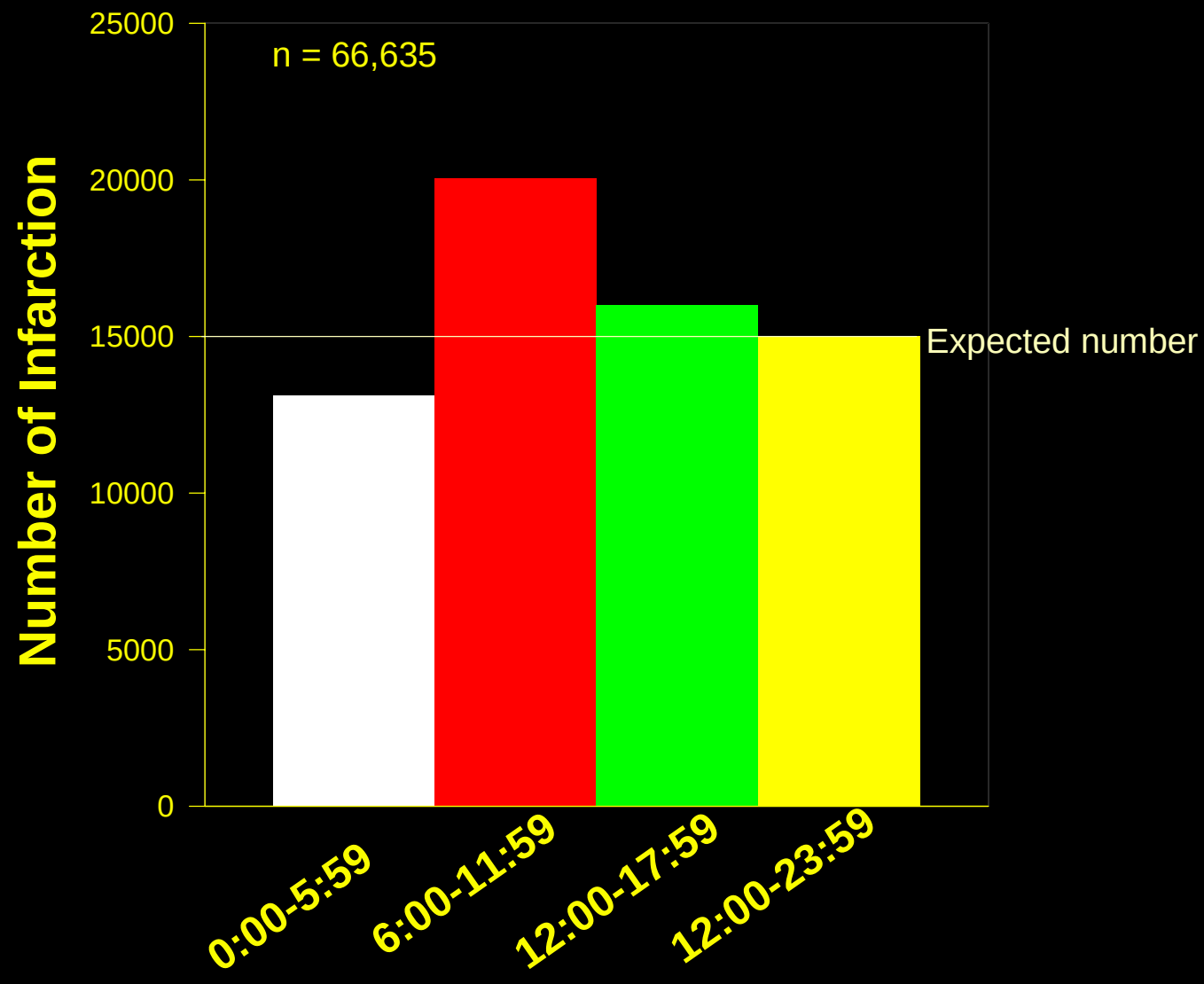
- Since Modified-release formulations are intended for chronic use, the PK time-course of the drug is unimportant.

Chronobiology

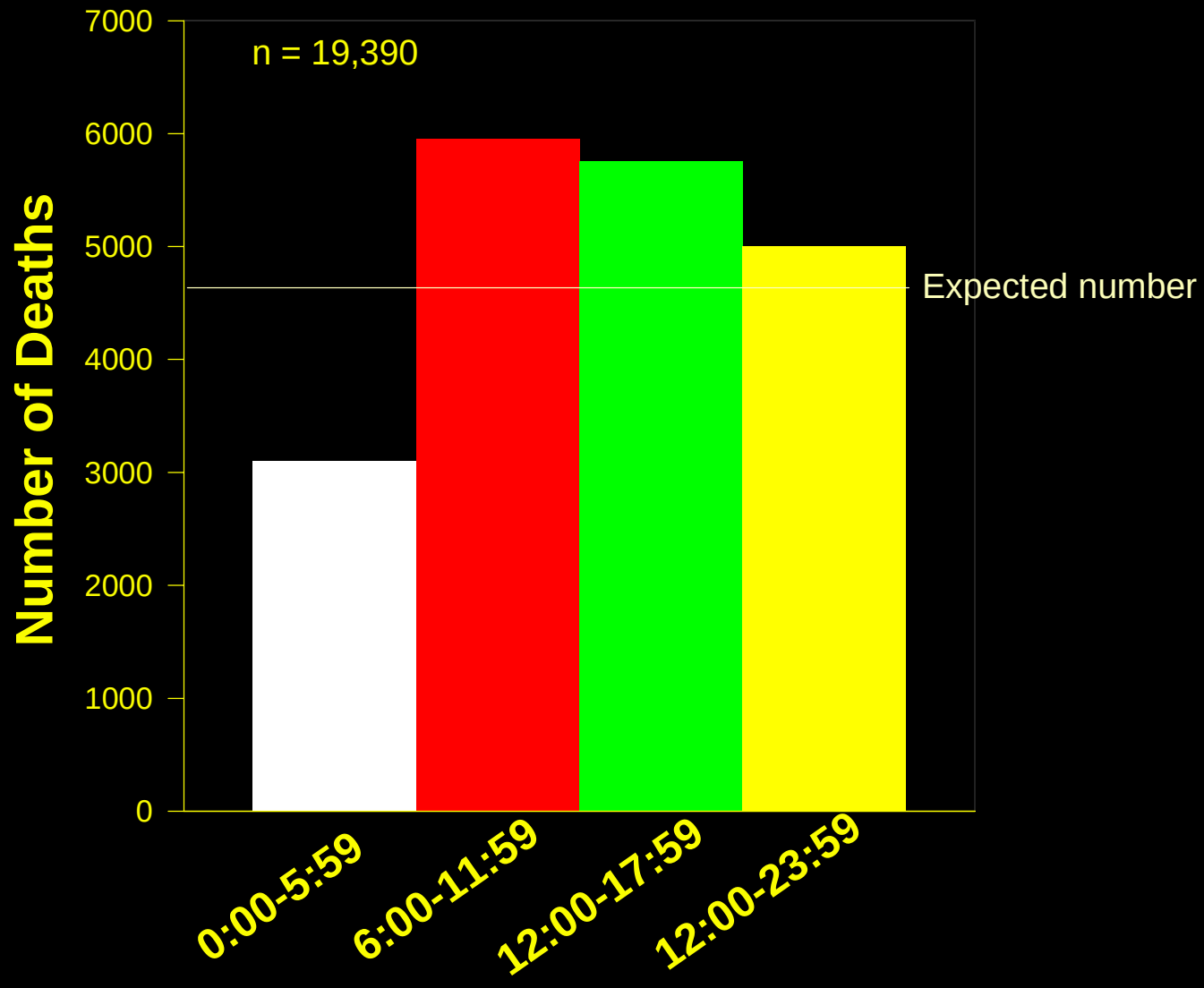
Examples:

- Cardiovascular events
- Asthma attacks
- Allergic reactions
- Morning stiffness
- ……

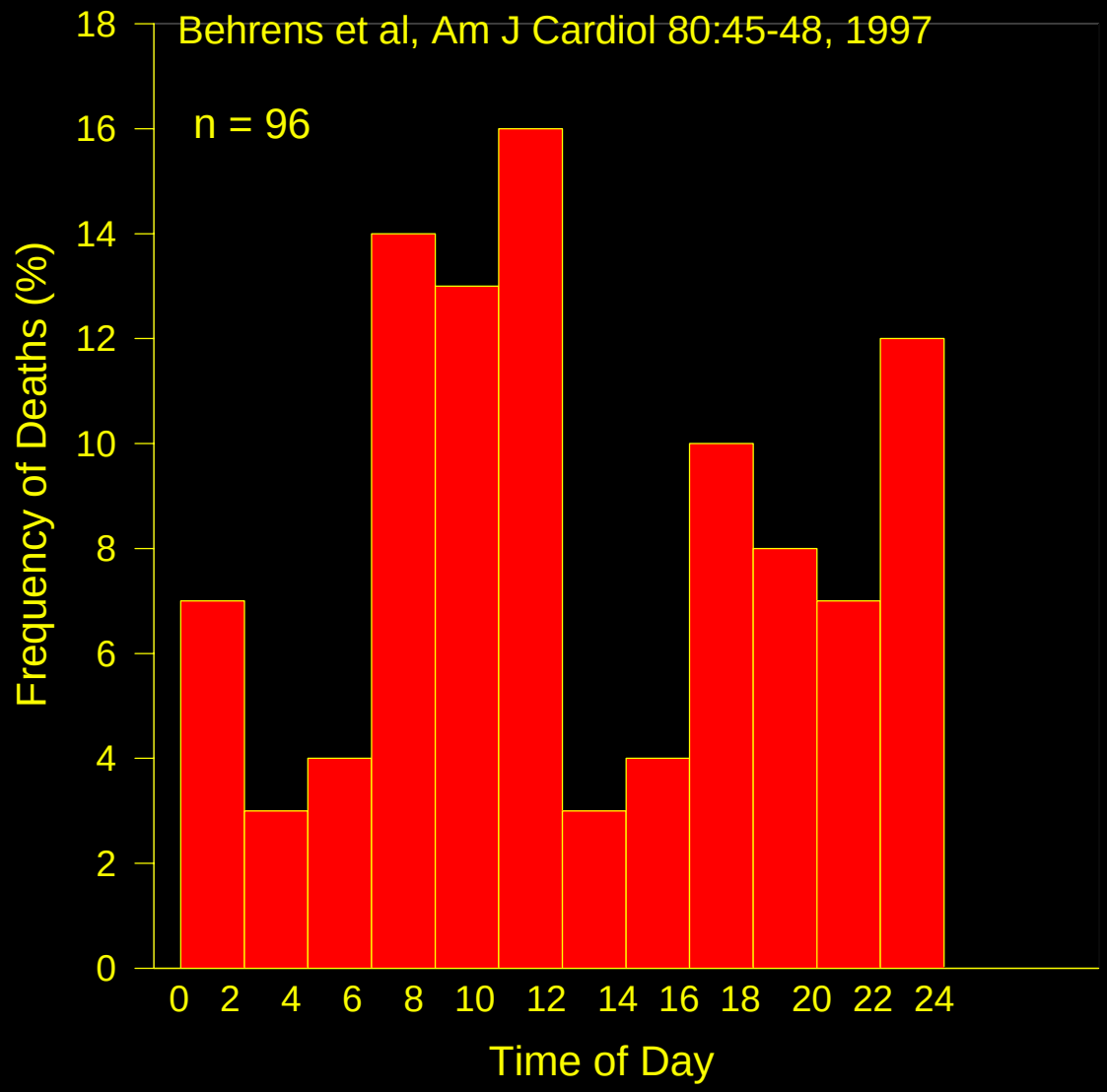

Diltiazem
Plasma Conc'n (ng/mL)
60
50
40
30
20
0
2
4
6
8
10
12
Hours



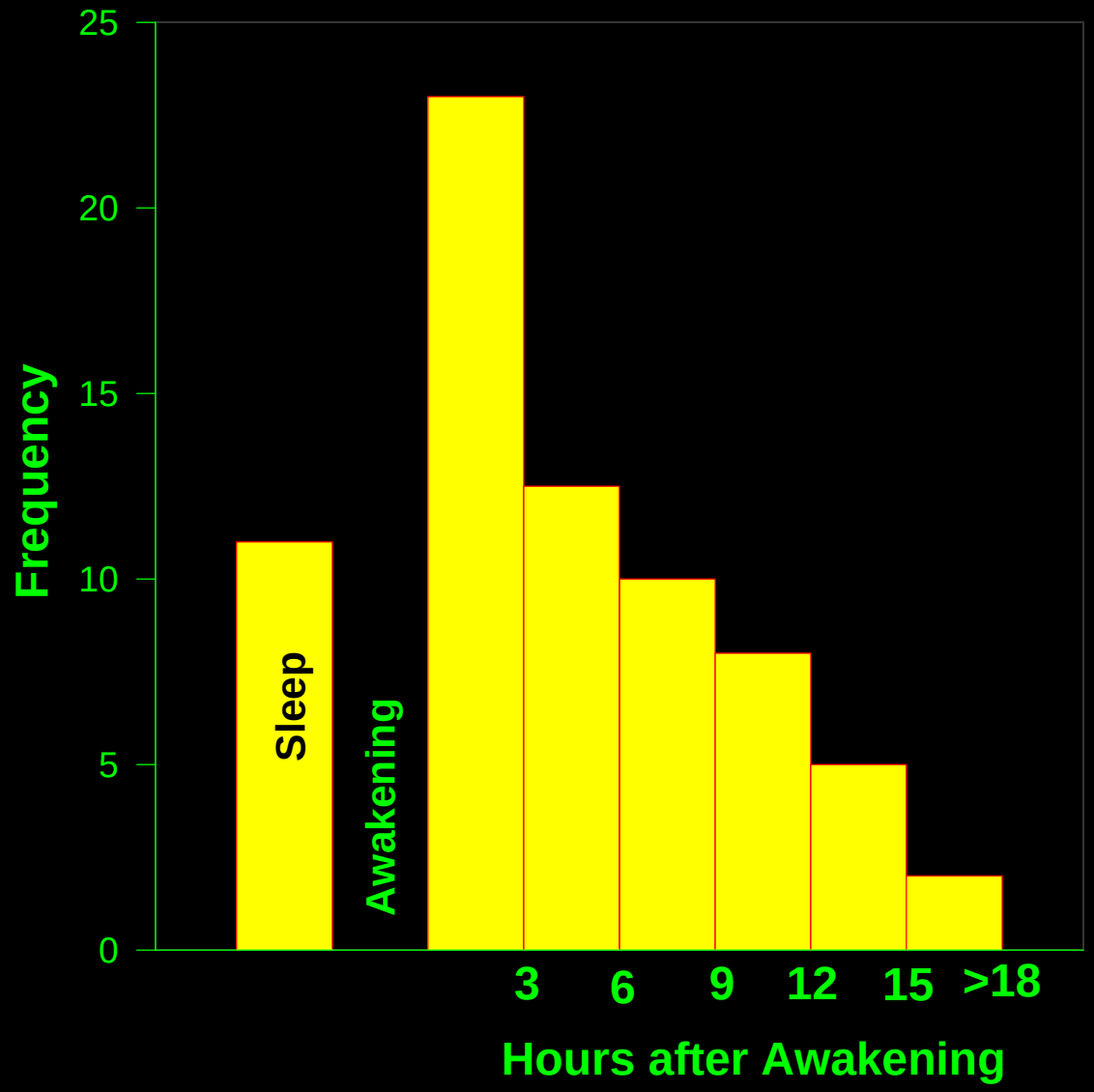
Cohen *et al* Am J Cardiol 79:1512-1516, 1977

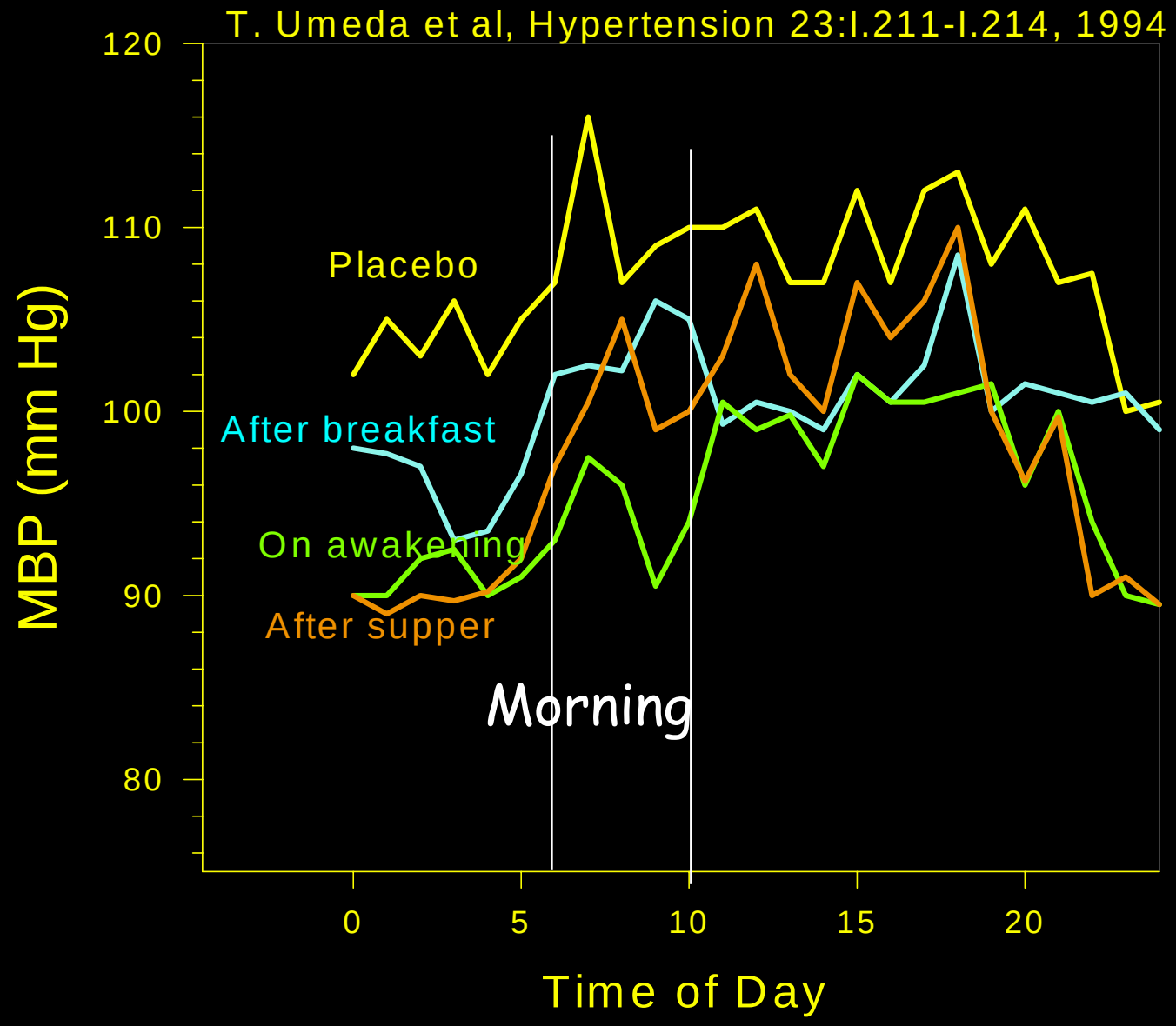


Cohen *et al* Am J Cardiol 79:1512-1516, 1977

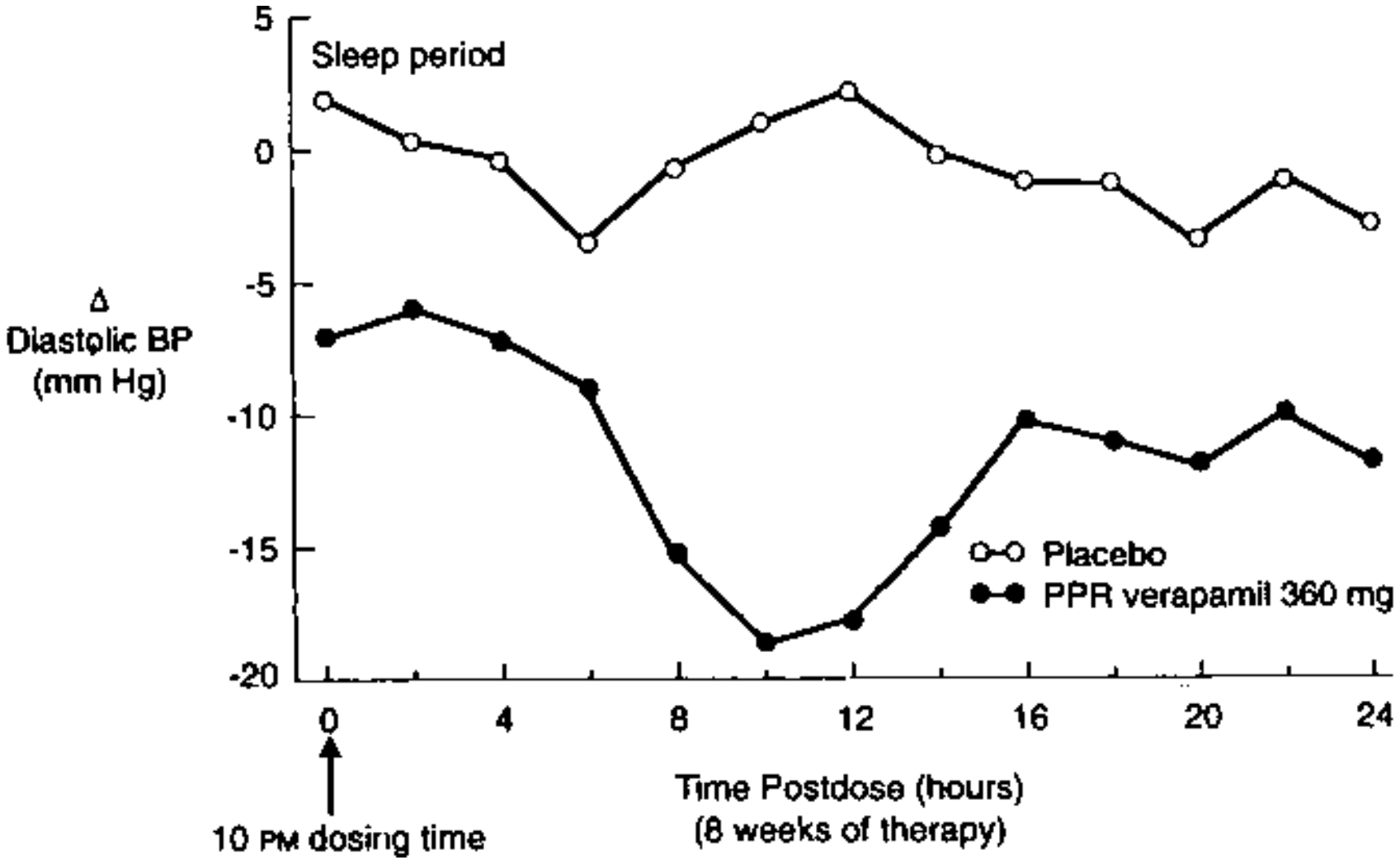

Behrens et al, Am J Cardiol 80:45-48, 1997
n = 96
Frequency of Deaths (%)
0
2
4
6
8
10
12
14
16
18
0 2 4 6 8 10 12 14 16 18 20 22 24
Time of Day

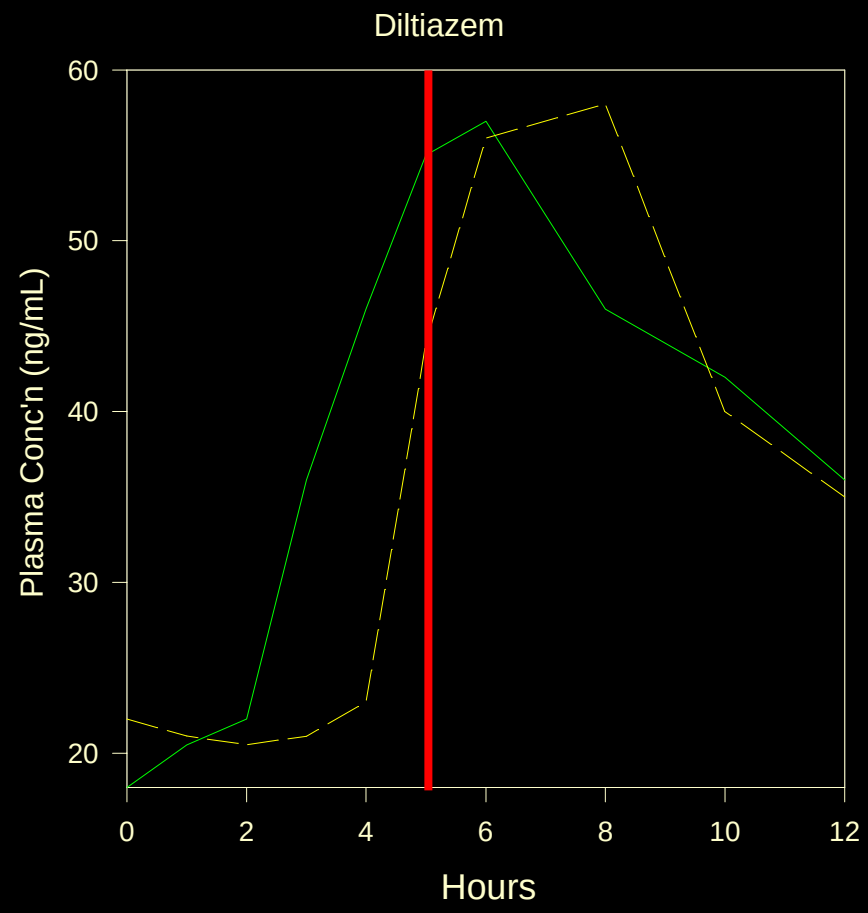
Willich *et al* Am J Cardiol 70: 65-68, 1992




T. Umeda et al, Hypertension 23:I.211-I.214, 1994
120
110
100
90
80
MBP (mm Hg)
Placebo
After breakfast
On awakening
After supper
Morning
0
5
10
15
20
Time of Day

W.B. White Am J Hypertens 9:29S-33S, 1996.





Is the PK time course, therapeutically important?

Conclusion:

In assessing bioequivalence of modified release formulations, in addition to AUC and Cmax, the **time-course of absorption** should be considered.