

# Design, Need, and Timing of Food Effect Studies: an Industry Experience

ASCPT Annual Meeting  
Food for Thought: Need, Timing and  
Labelling Implications for Clinical Food  
Effect Studies

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# The small print

I am an employee and share holder of Pfizer Inc.  
The comments presented are my own and not  
meant to represent those of my company.

# Outline

- Current conditions
  - Need
  - Design
  - Timing
- Potential knowledge gaps and remedies

# Current conditions



# Need – huge!

- People eat a wide variety of foods
  - Continuously, frequently (babies, little kids)
  - Very little (fasting)
  - Variable content (vegetarian, paleo, high carbohydrate)
- People take a wide variety of medications
  - Some require fasting
  - Some require food
  - Some it doesn't matter
  - Some foods interfere with optimal response

# Need – Performance of Dosage Forms

- Concern about dose dumping of extended release formulations in the presence of food or ethanol
  - Hendeles L, et al. Food-induced dose dumping of once-a-day theophylline. *Lancet*. 22: 1471 (1984).
  - Jedinger N, et al The design of controlled-release formulations resistant to alcohol-induced dose dumping – A review. *Eu J Clin Pharm* 87:217 (2014).

# Study Design (Now)

## Subjects

- At least 12 (bioavailability); more (BE comparison)
- Healthy volunteers or patients (if safety a concern)

## Treatment

- Drug – (highest) dose (perhaps as part of SAD study)
- Meal – large (800 – 1000 kcal), high fat (50% kcal) consumed over 30 minutes
- Fasting – total of 14 hours with 2 hours npo around test drug administration

## Observations

- Serial blood sample collection to fully characterize PK

# Who Participates Now?

Search of ClinicalTrials.gov using key words:

- 'food effect' (n=3982 trials)
- ... and 'healthy volunteers' (n=2029 trials)
- ... and 'pharmacokinetics' (n=740 trials)
- ... and 'cancer' (n=734 trials)
- ... and 'Japanese' (n=34 trials)
- ... and 'children'/'pediatric' (n=1 (NCT 2046841))
- ... and 'hepatic impairment' (n=0)
- ... and 'renal impairment' (n=0)



# Looking more closely...

- ~ 30% 'food effect' **are cohorts within SAD**
- ~ 20% enrolled men only
- Age range: **18** (19,20) – (40, 45) **50** (55, 60, 65, 70, 80, 90, no limit)
- Upper age range higher if patient population of interest (post menopausal women, cancer patients, hepatitis)
- Meal – standard high fat breakfast
- Ethanol – 240 mL 40% EtOH in 4 shots

# Are there information gaps?

child

Patient  
Nauseated

Healthy volunteer  
High fat meal  
PK assessment

CKD patient  
Limited diet

Patient  
Compliant?

# Gaps in Knowledge – Take **with** Food

- If a food effect needed/desirable to achieve therapeutic effect – how much food (what kind of food) is needed?
- Potential responses
  - Key pharmacodynamic assessment
  - Pivotal trial study data

# Case study –

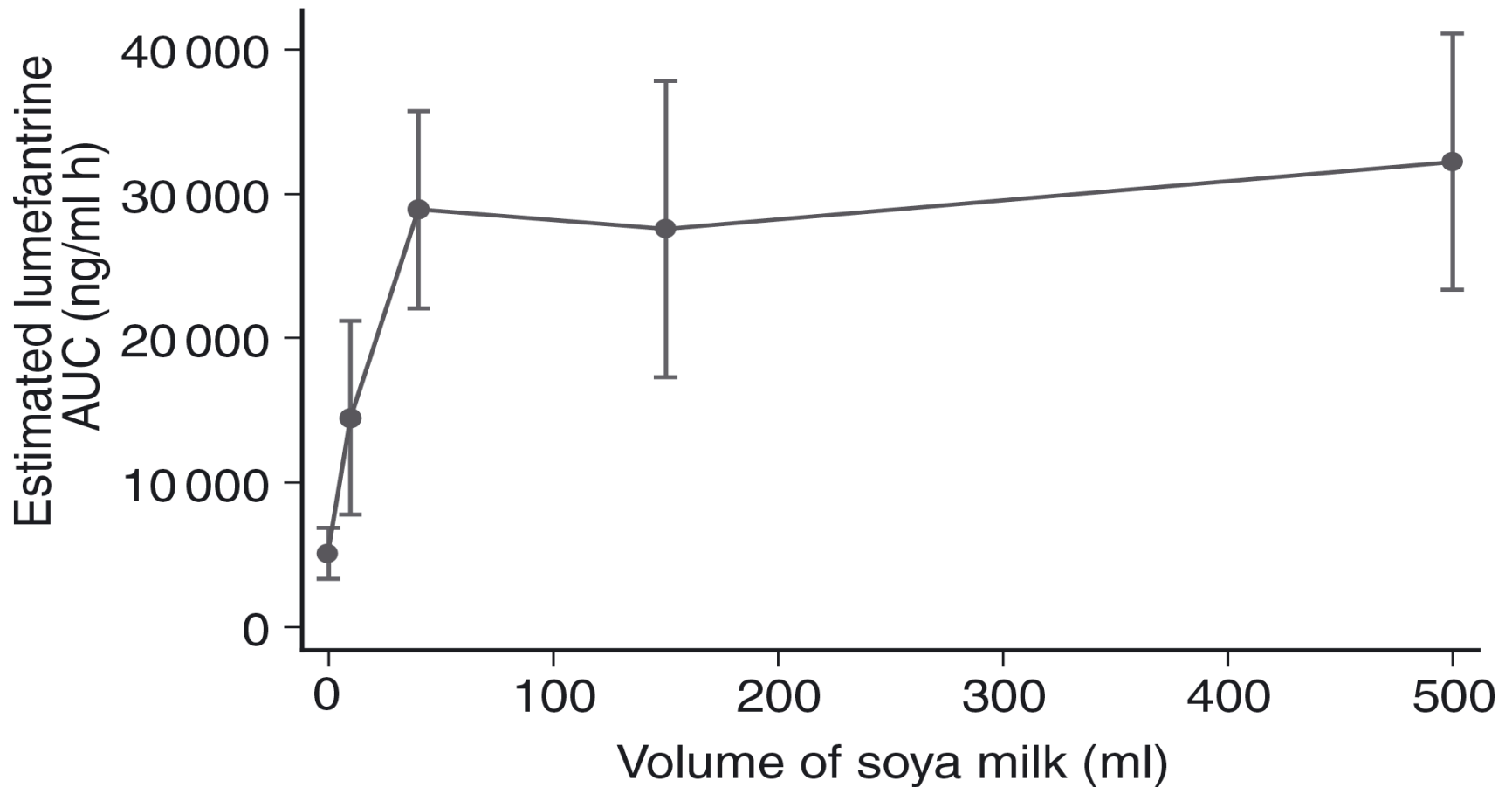
## Coartem in treatment of malaria

### 2.1 Administration Instructions

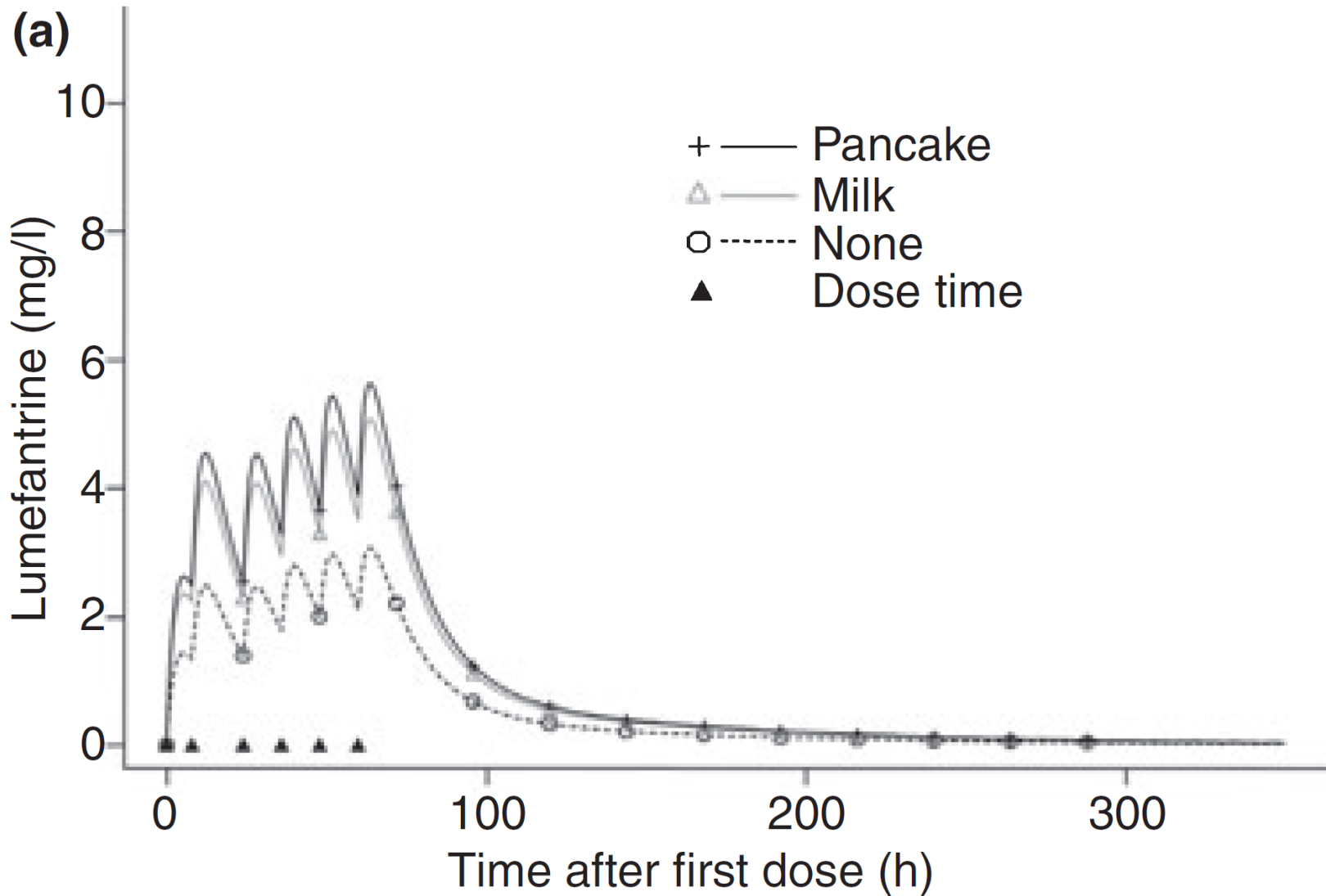
Coartem Tablets should be taken with food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of artemether and lumefantrine.

For patients who are unable to swallow the tablets such as infants and children, Coartem Tablets may be crushed and mixed with a small amount of water (one to two teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.



**Figure 1** Relationship between estimated AUC and volume of milk taken; dots represent mean and bars represent 95% CI around mean.



# Gap in Knowledge – Take on an Empty Stomach

- If a food effect must be avoided to achieve therapeutic effect – how much separation is needed?
- Potential responses
  - Alternative study design
  - Key pharmacodynamic assessment
  - Pivotal trial study data

# Abiraterone

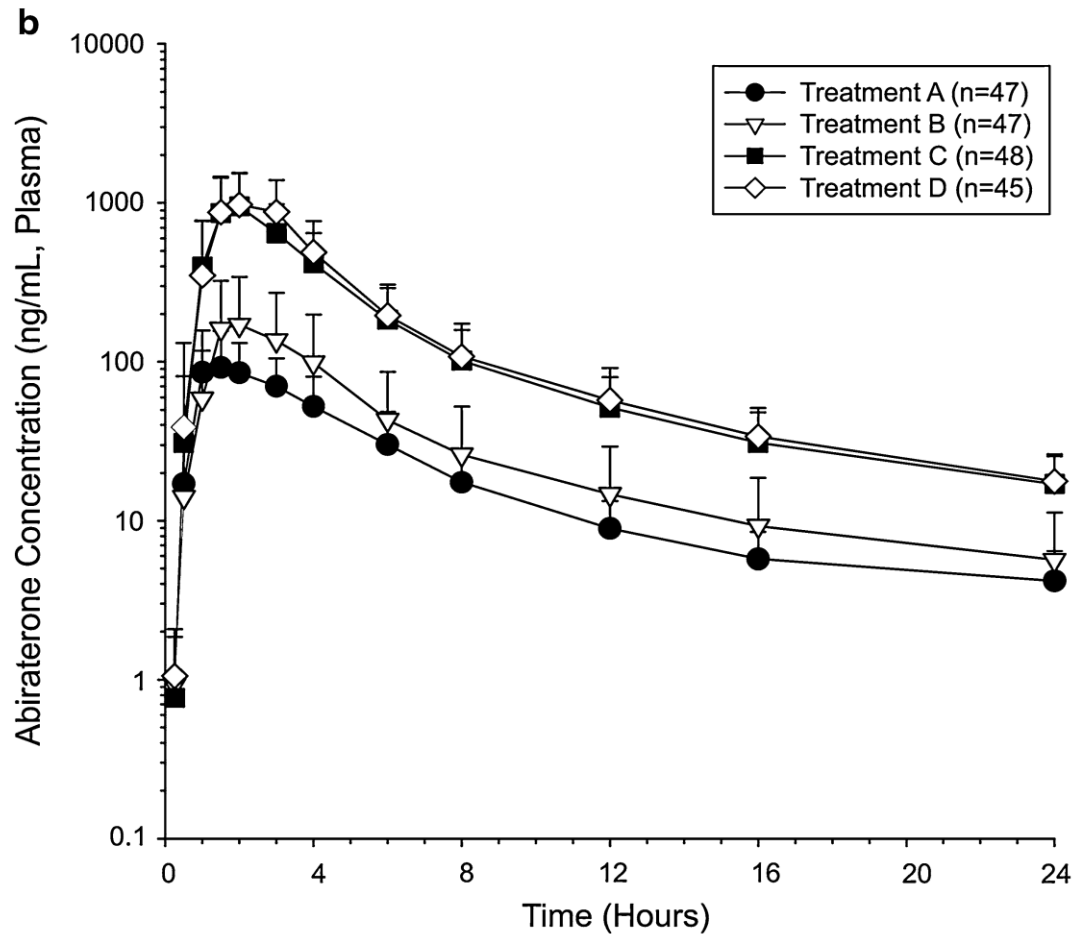
## -----DOSAGE AND ADMINISTRATION-----

Recommended dose: ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water. Do not crush or chew tablets. (2.1)

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone  $C_{\max}$  and  $AUC_{0-\infty}$  were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water [see *Dosage and*



# Timing of Dosing & Meals



# Gap in Knowledge – May be taken with or without food

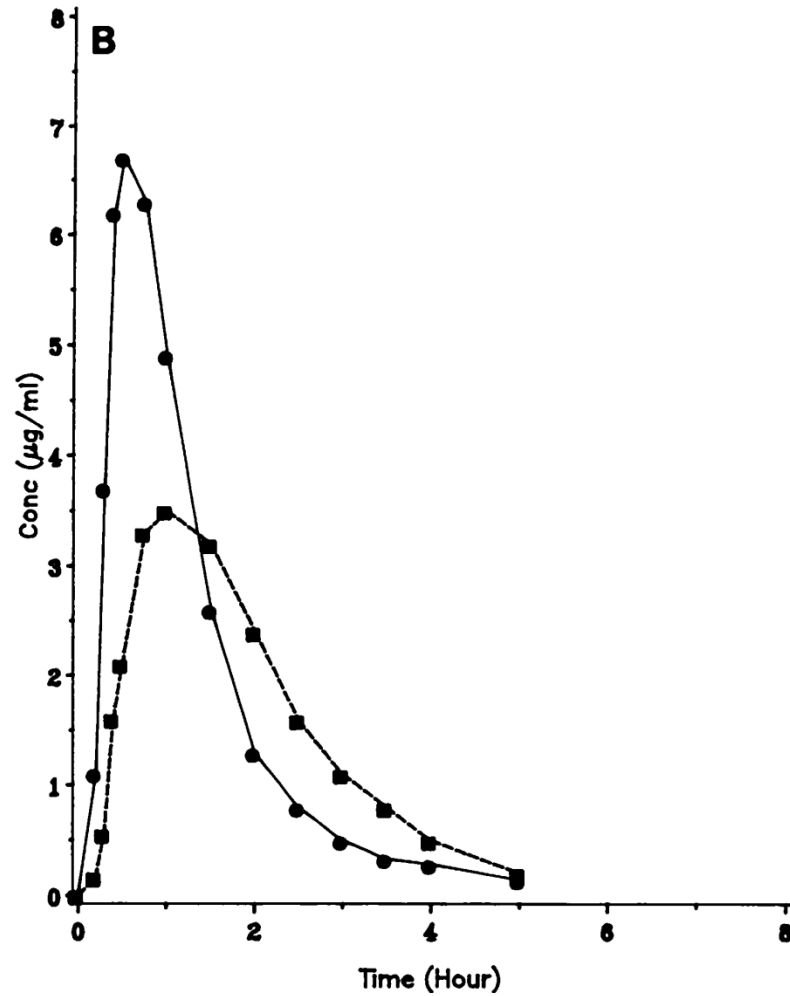
- If AUC remains the same, but  $C_{max}$  is diminished and  $t_{max}$  delayed, is that OK?
- Potential responses
  - Pharmacodynamic response
  - Pivotal trial study data

# Case Study - Cefaclor

## **CLINICAL PHARMACOLOGY**

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is the same whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed when the drug is administered to fasting subjects and generally appears from three fourths to 1 hour later. Following administration of 250 mg, 500 mg, and 1 g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 mcg/mL respectively were obtained within 30 to 60 minutes. Approximately

# Case Study - Cefaclor



Barbhaiya et al. AAC 1990; 34(6):1210-13.

# Cefaclor

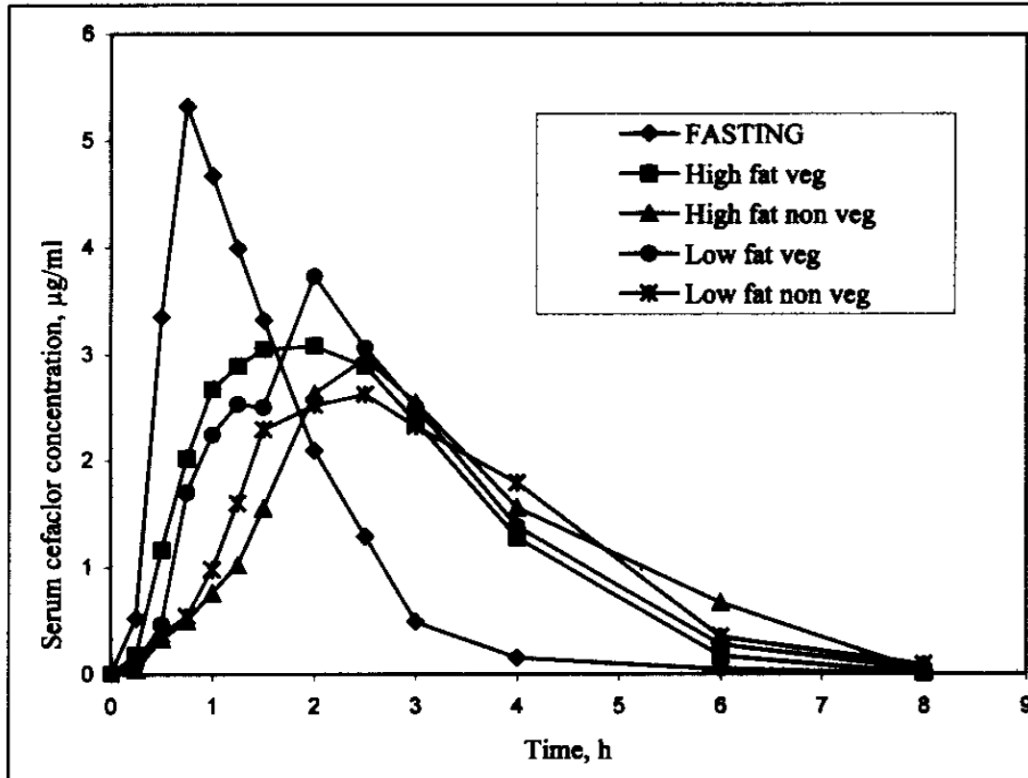


Fig. 1 : Plot of mean serum cefaclor concentrations Vs time for all five treatments

# Cefaclor - pharmacodynamics

*Table III: Mean (SD) of time above and time to reach MIC<sub>50</sub> (2 µg/ml) for fasting and all other treatments (n=18)*

<b>Treatments</b>	<b>Time above MIC<sub>50</sub> (2 µg/ml) in min.</b>	<b>Time to reach MIC<sub>50</sub> (h)</b>
Fasting (A)	128.64 (30.08)	0.48
High-fat vegetarian (B)	133.42 (25.02)	1.02
High-fat non-vegetarian (C)	111.82 (40.53)	1.56
Low-fat vegetarian (D)	145.87 (34.11)	1.18
Low-fat non-vegetarian (E)	124.99 (28.89)	1.00

# Summary

- Knowledge of the effect of food on PK is key to safe and effective use of medications
- Food effect studies are part of almost every development plan
- Preliminary assessment conducted early in clinical plan
- Most common design – high fat breakfast in healthy volunteers
- Additional data collected (modeled, simulated) to fill gaps