PHARM 309
Pharmacokinetic Studies: Design Considerations

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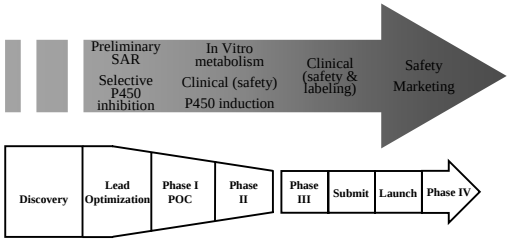
Pharmacokinetic/metabolism properties of a NDE/NME screened in all phases of the drug development continuum



Discovery Development Commercialization

Pharmacokinetic Analysis Conventional vs. Population Approach

	Conventional	Population
Subject	Healthy volunteers or patients	Target patient population, Special population (pediatrics, elderly)
Size	Small (~12)	Large (30-1000's)
Inclusion/Exclusion	Well controlled	~Clinical practice
PK Sampling	Dense	Sparse
Data Collection/Analysis	Simple	Complex
Inter-individual Variability	Minimal	Demographics, Disease states, etc.
PK/PD Relationships	Limited	Extensive

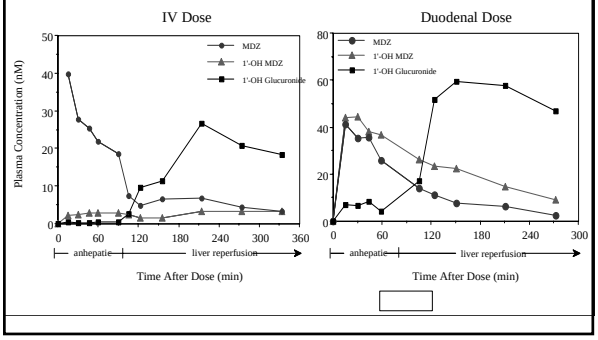
Descriptive Studies - General PK

- Small sample size (n = 4–12); generally not powered
- Characterize basic PK parameters (CL, V, F, $t_{1/2}$,f_u) for parent drug
- Oral and IV (not always feasible) dose
- Single and multiple dose
- Identify major metabolites in blood, urine, feces
- If ^{14}C-labeled drug, determine dose recovery and routes of excretion
- Dose escalation
  - dose proportionality of AUC
  - assess drug tolerability

In Vivo Intestinal MDZ Metabolism

- 1 mg IV or 2 mg PO during anhepatic phase of a liver transplant operation *(Paine et al., CPT, 1996)*

Arterial MDZ, 1-OH-MDZ, 1-OH-MDZ-Glucuronide Conc-Time Profile



Special Populations

Examples: liver and renal disease, elderly, pediatric, gender, genetic subgroups (e.g., poor metabolizers)

- Generally moderate sample size; powered to detect a minimum difference based on expected population variability
- Characterize basic PK parameters (CL, V, F, $t_{1/2}$,f_u) for parent drug
- Oral dose, unless IV indicated
- Measure active metabolites only
- Urine recovery of parent and known metabolites
- Assess drug tolerability at indicated doses

Population Pharmacokinetics (Pop-PK)

- Characterize PK and PD in target patient population using sparse sampling and pharmacostatistical methodologies:
- Large number of subjects (> 100, up to thousands)
- Oral dose: define time of dose and blood collection during Phase III or IV trials

- Fixed Effects: basic PK parameters (CL, V, $t_{1/2}$) for parent drug; obtain true population means and variance
- Random Effects: sources of between and within-subject variability (e.g., age, smoking, concomitant drug therapy)

- Apply different statistical methods to analyze data, depending on objectives (Mixed effect ANOVA, NONMEM)

Drug-Drug Interaction Studies

- Proof of Equivalency: Design study to prove there is no difference between test and control; i.e., drug X does not alter the PK of drug Y
  - Sample size based on within subject variability
  - Point estimate and confidence interval with specified range; e.g., AUC ratio (test/control) between 0.80 and 1.25

- Hypothesis Testing: Test for an expected difference between treatment and control
  - Sample size based on minimum expected difference and population variability; generally smaller than studies to prove no difference
  - T-test or ANOVA

- Oral dose: characterize basic PK (AUC) or PD parameters

Data Analysis: FDA Recommended

Method of Assessment
- PK and/or PD as a Surrogate

Acceptance Criteria
- **90% Confidence Intervals**
- **No Effect Boundaries**

Others
- Point Estimate
- Null Hypothesis (P values)
- Mean, SD
- **Clinical Relevance**

General Considerations for Pharmacokinetic DDI Study

- Will NDE alter exposure to other drugs?
  - Inhibition of DME or transporter
  - Induction of DME or transporter

- Will other drugs alter exposure to NDE?
  - Enzymes responsible for NME metabolism
  - Contribution of metabolism to elimination

Reynolds, FDA 2001

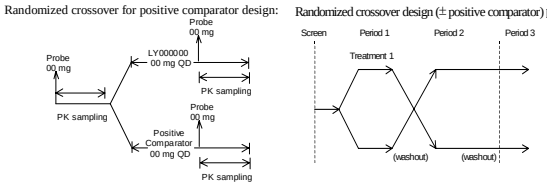
Types of DDI Study Designs

Clinical Pharmacology (Conventional):
- Probes (e.g. midazolam, desipramine) ± positive comparator
- Inhibitor/inducer (e.g., ketoconazole, quinidine)

Phase 3 Trials (Population):
- Confirming
- Screening

Clinical Practice:
- Combination therapy (e.g. oncology)

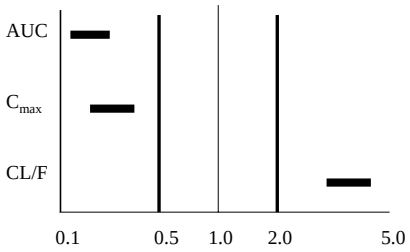
Conventional DDI Study Designs



Parallel design?

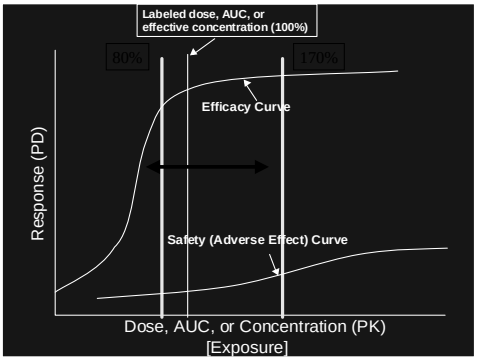
Data Analysis: Confidence Interval Approach

Example: 90% CI with clinical acceptance range b/w 0.5 to 2.0 or 0.8 to 1.25



Yuen GJ et al., Clin Pharmacol Ther 61 (2): 147, 1997 (ASCPT 3/97, San Diego, CA)

Dose Adjustment Based on PK/PD



Huang SM, Lesko, LJ, Williams RL, J Clin Pharmacol, 39 :1006-1014, 1999

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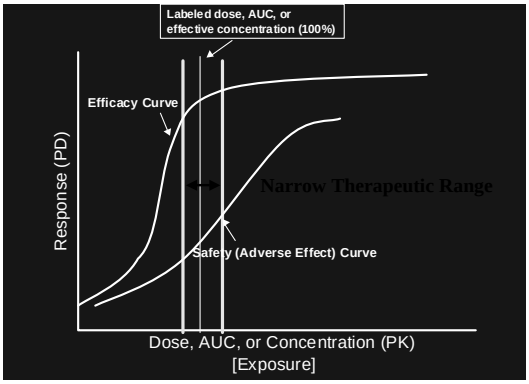

Sample Size Calculation for a 3A Study

- Given Mean CV C_{max} = 30%, AUC = 22% and a balanced two-period crossover design sample size may be calculated for the probability of correctly concluding no interaction
- Study size based on ratio of test and the requirement that a 90% confidence interval is contained within a range of 0.8 and 1.25

If $\beta = 0.2$, power = 0.8, $\alpha = 0.05$

C_{max} μ_T/μ_R :	0.85	0.9	0.95	1.0	1.05	1.10	1.15
Sample Size:	292	80	40	32	38	68	156
AUC μ_T/μ_R =	0.85	0.9	0.95	1.0	1.05	1.10	1.15
Sample Size =	168	46	24	20	24	40	90

Aprepitant -Midazolam (CYP3A) Interaction Study

- Healthy young males
- Open-label, randomized, single-period design, parallel dose arms
- Two aprepitant doses: 125/80-mg and 40/25-mg regimen, qd x 5days
- N = 8 subjects/dose group

- Single dose oral midazolam: pre-study, days 1 and 5
- Determine PK: AUC, C_{1h} and $t_{1/2}$

Midazolam Concentration - Time Profiles

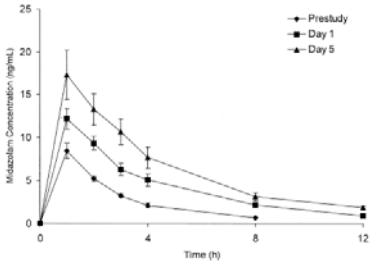

Fig 1. Plasma concentration–time profiles of midazolam before (prestudy) and during (on days 1 and 5) administration of 125 mg aprepitant on day 1 and then 80 mg on days 2 to 5. Midazolam was administered as a single oral 2-mg dose on each of the periods assessed (prestudy, day 1, and day 5). Data represent mean values in 8 healthy male subjects. The 12-hour measurement at the prestudy visit was below the limit of quantitation. *Error bars* represent standard error.

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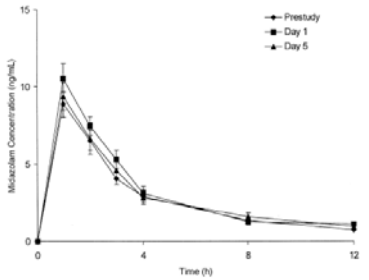

Fig 2. Plasma concentration–time profiles of midazolam before (prestudy) and during (on days 1 and 5) administration of 40 mg aprepitant on day 1 and then 25 mg on days 2 to 5. Midazolam was administered as a single oral 2-mg dose on each of the periods assessed (prestudy, day 1, and day 5). Data represent mean values in 8 healthy male subjects. *Error bars* represent standard error.

Table 1. Summary of midazolam pharmacokinetics (2-mg oral dose) with aprepitant (days 1 and 5) and without aprepitant (prestudy)

Parameter	*Prestudy*	*Day 1*	*Day 5*	*GMR: Day 1/ prestudy*	*P value*	*GMR: Day 5/ prestudy*	*P value*
125/80 mg aprepitant							
$AUC_{0-\infty}$ (ng · h/mL) (mean* and 95% CI)	23.0 (17.7-29.7)	52.1 (40.2-67.6)	75.7 (58.4-98.1)	2.27 (1.64-3.14)	<.01	3.30 (2.39-4.56)	<.01
C_{1h} (ng/mL) (mean* and 95% CI)	8.1 (6.0-10.8)	11.8 (8.8-15.7)	15.7 (11.7-20.9)	1.46 (1.01-2.09)	.043	1.94 (1.35-2.78)	<.01
$t_{1/2}$ (h) (mean† and range)	1.69 (1.0-2.5)	3.27 (2.7-4.5)	3.32 (2.2-4.5)	–	–	–	–
40/25 mg aprepitant							
$AUC_{0-\infty}$ (ng · h/mL) (mean* and 95% CI)	30.8 (22.0-43.1)	37.7 (26.9-52.7)	31.4 (22.5-43.9)	1.22 (0.93-1.61)	NS	1.02 (0.77-1.35)	NS
C_{1h} (ng/mL) (mean* and 95% CI)	8.6 (7.0-10.5)	10.4 (8.4-12.7)	9.0 (7.4-11.1)	1.21 (0.91-1.61)	NS	1.05 (0.79-1.40)	NS
$t_{1/2}$ (h) (mean† and range)	2.26 (1.2-3.7)	2.59 (1.2-5.2)	2.00 (1.0-4.6)	–	–	–	–

GMR, Geometric mean ratio, 125/80 mg aprepitant, 125 mg on day 1 and then 80 mg/d on days 2 to 5, $AUC_{0-\infty}$, area under plasma concentration–time curve from time 0 to infinity, C_{1h}, maximum observed concentration, $t_{1/2}$, half-life, 40/25 mg aprepitant, 40 mg on day 1 and then 25 mg/d on days 2 to 5, CI, confidence interval, NS, not statistically significant ($P > .05$).
*Geometric mean.
†Harmonic mean.

Aprepitant -Midazolam (CYP3A) Interaction Study: Conclusions

- Investigators chose a null hypothesis approach; was ratio different from 1.0?
- No evidence of a power calculation to determine sample size
- Concluded that the 125/80 dose schedule inhibited CYP3A activity: classed as a moderate inhibitor (2-5 fold effect)
- Claimed that 40/25-mg dose had no effect, but statistically a weak claim (did not adhere to 0.80-1.25 bioequivalency standard)
- Labeling reflects 125/80-mg results, since that is the recommended dose to prevent nausea during chemotherapy