Highly Variable Drugs: Experience with Propafenone

Yu Chung Tsang, Ph.D, Radu Pop, Ph.D and Michael Spino, Pharm. D

Apotex Inc., 150 Signet Dr., Weston, Ontario, Canada, M9L 1T9

Highly Variable Drugs

- Drugs that exhibit variable disposition kinetics in the body
- Intra-subject cv >30% in bioavailability parameters
- Challenge - have long been a problematic group of drugs for bioequivalence assessment

What Is Bioequivalence?

- Bioequivalence is a means of comparing two formulations or products
  - It determines if they deliver the same amount of drug into the body at the same rate
  - Brand vs itself or generic vs brand

Criteria For Bioequivalence

- The test should be within 80 to 125% of the reference
- Employ confidence interval testing (eg. 90%) of the ratios for greater assurance
- Works well with most drugs
  - Difficult to meet for highly variable drugs
  - eg. PROPAFENONE

Propafenone

- Is an antiarrhythmic agent - used for ventricular arrhythmias
- Is nearly completely absorbed following oral administration
- Undergoes extensive first-pass hepatic metabolism
- Has a wide range of $t_{1/2}$
  - eg. 2 - 32 hrs

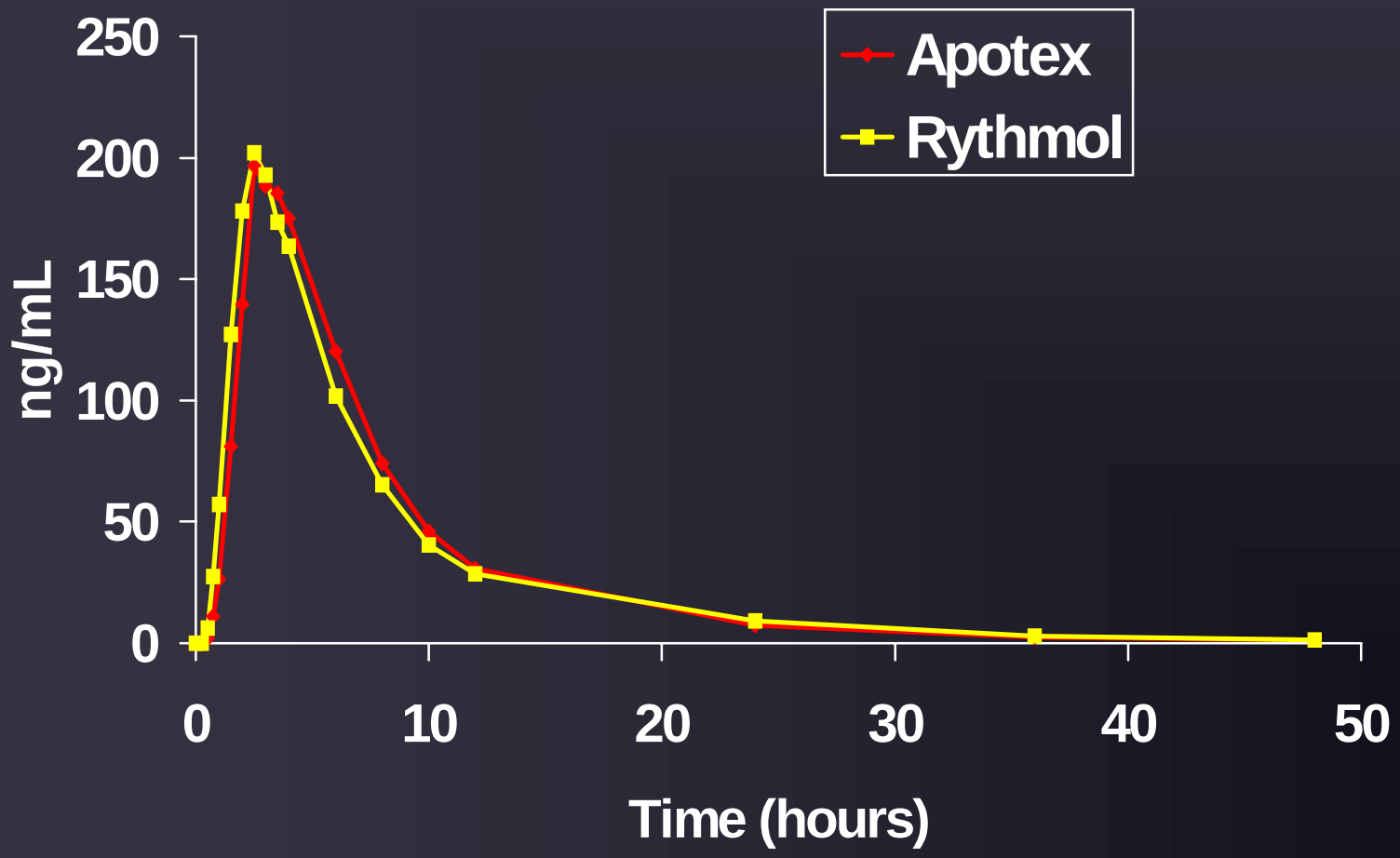
Bioequivalence Of Propafenone Tablets

- Comparative bioavailability study
  - Apotex vs Rythmol
- Study design
  - Standard randomized 2-way crossover
  - Single dose: 1 x 300 mg tablet given after a 10-hour fast
  - 18 healthy male volunteers
  - Washout period: 1 week

Cont'd

- Serial blood samples were collected for 48 hours
- Plasma propafenone levels measured by a validated HPLC/UV method
  - Limit of quantitation = 5.0 ng/mL
  - Precision: 2.5 - 9.5 % cv

Mean Plasma Concentrations

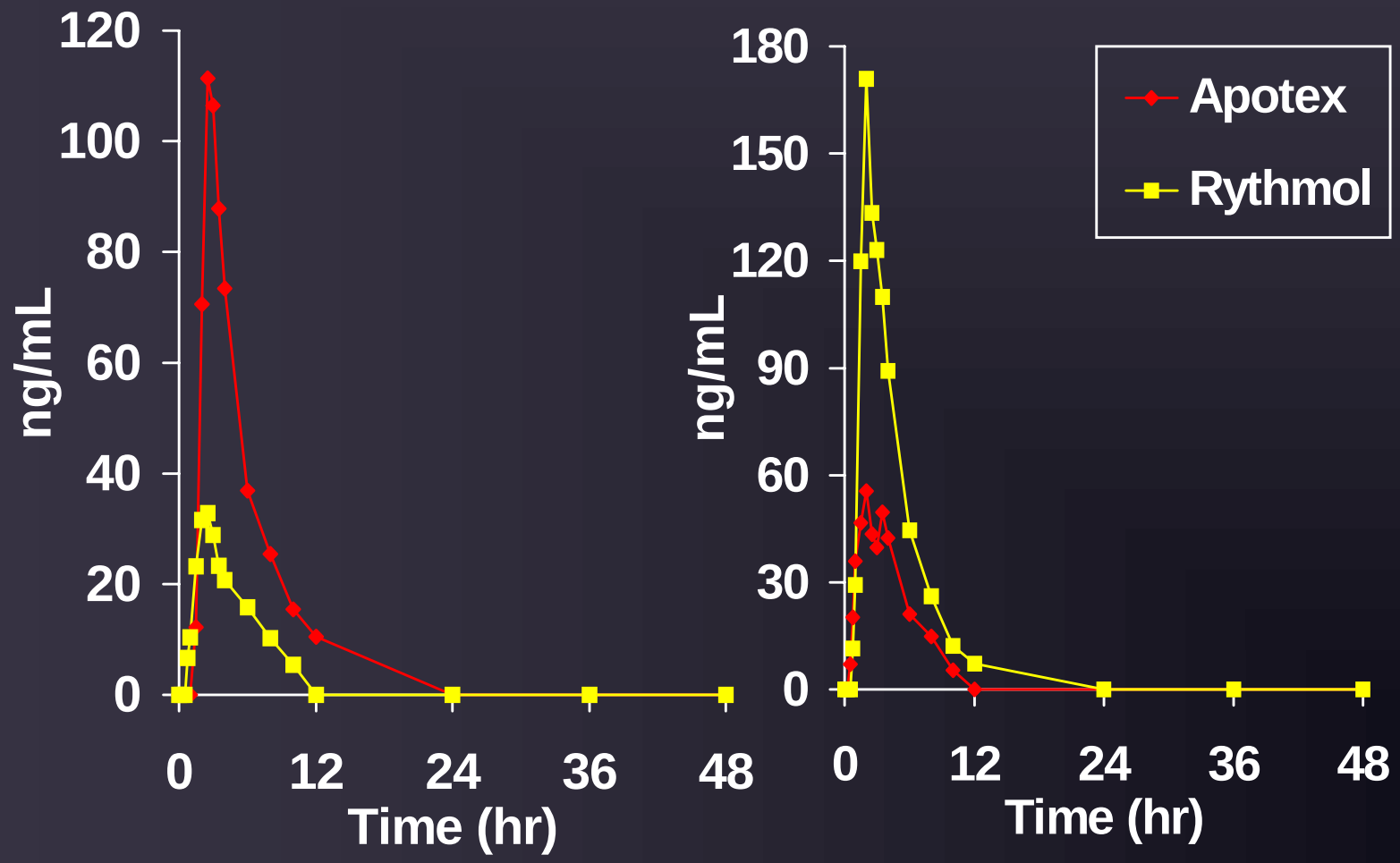


Results

Parameter	Mean (cv)		ANOVA
	Apotex	Rythmol	
AUC_T (ng*hr/mL)	1377 (139)	1398 (144)	p=0.32
C_{max} (ng/mL)	223 (84)	219 (92)	p=0.45
T_{max} (hr)	2.94 (34)	3.08 (31)	p=0.66
$t_{1/2}$ (hr)	2.92 (63)	3.31 (68)	p=0.58

Note: Log-transformation for AUC_T and C_{max}

Plasma Profiles From Two Subjects



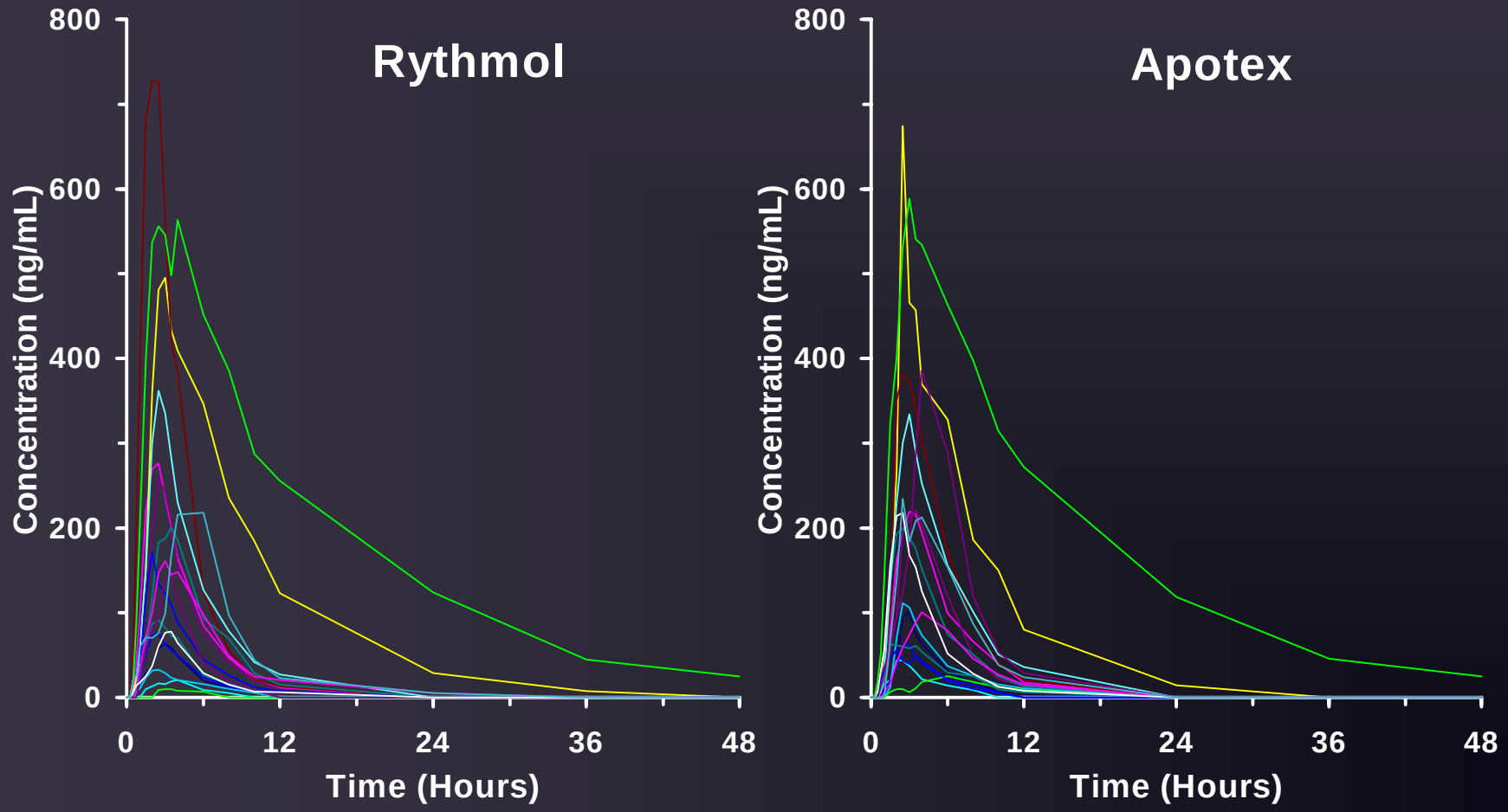
Results - Cont'd

Parameter	Test/Ref (%)	90% CI	CI Within 80-125%
AUC_T (ng*hr/mL)	117	84-162	No
C_{max} (ng/mL)	113	81-156	No

Reasons For Failure

- In-vitro dissolution profiles were similar
  - >95% dissolved by 30 min in 0.1 N HCl
  - Bioavailability is absorption-rate limited
- Believe that the formulation is OK!
- Inter-subject cv: >100% for AUC_T
- Intra-subject cv (sqrt(MSE)) = 46%
  - A highly variable drug
  - Apparent lack of BE was probably due to highly variable disposition

Inter-subject Variability



Sources Of Variability

- Metabolism (hydroxylation) of propafenone is genetically determined
  - Fast ($t_{1/2}$: 2-10 hr) vs slow ($t_{1/2}$: 10-32 hr) metabolizers
    - 5x higher drug levels in slow metabolizers
  - Ultra-fast metabolizer?
    - High first-pass metabolism
    - Lower levels, closer to LOQ of the assay, less precise

Sources Of Variability - Cont'd

- Hydroxylation of propafenone is saturable
  - Nonlinear increase in BA as dose increases in fast metabolizers
  - Kinetics is linear in slow metabolizers
- Higher variability with fast metabolizers
- Problem is magnified after log-transformation
  - For a given difference, the smaller the values, the larger the difference between the logs

Re-analysis Of BE Data

- Analyze the "slow" metabolizers only
  - No criteria found in the literature
  - Use the median across subjects as cut-off
  - 8 subjects were selected
    - had AUC_T >median for both products

	Intra-subject cv	90% CI
AUC_T	11%	82-101
C_{max}	20%	75-112

Proof Of High Variability

- Part of a large study
- Rythmol was given to the same subject on two occasions separated by 1 week
- n = 16
- Inter-period ratio: 0.37-2.09 for AUC_T and 0.39-2.25 for C_{max}
- Intra-subject cv = 29% for both parameters

What is n for demonstrating BE With CV = 29%?

- Assuming no difference (brand vs brand) and 90% probability of acceptance, n=40 subjects
- With a 5% difference due to chance (generic vs brand), n=52 subjects
- In Canada, propafenone is classified as a drug with a narrow therapeutic range
  - 95% CI
  - A fasting and a food challenge study
- Even higher n!

Bioequivalence Standards: Do We Have The Right Balance?

- For most drugs, current "Report A" and "B" standards of TPD are appropriate
- For HVD, they are inappropriately austere
  - The tighter standards for propafenone are clearly unjustified
  - The current goalposts are too narrow when biological variability is so high
  - It is unethical and costly to require a large number of subjects

What Is The Right Balance?

- Standards should be reasonable
  - When the brand has trouble passing against itself, it indicates the criteria are unrealistically austere
  - In such cases new criteria should be established and such criteria should not be more onerous than the current one
- Regulatory authority should be responsive in accepting new criteria

Acknowledgement

- David Dawod