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Comparison of Parametric (NONMEM®) and Non-Parametric (NPEM®) Methods for Population Pharmacokinetic (PK) Modeling of Bi-Modal Populations

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ABSTRACT

Purpose. Debate exists whether the most appropriate population analysis method is parametric (NONMEM®) or non-parametric (NPEM®), especially for data from a bi-modal population (i.e., poor/extensive metabolizers (PM and EM)). This simulation study compared the capability of NONMEM® and NPEM® to estimate PK parameters for a bi-modal population. **Methods.** Concentration data were simulated using a one compartment PK model with first-order absorption and elimination. The PK model was fit to the simulated datasets using NONMEM® (first-order: FO and first-order conditional: FOCE) and NPEM®. The bias (PE%) and precision (|PE|%) of the individual predicted estimates of clearance (CL) and volume of distribution (Vc) were calculated. The log-transformed individual estimates of CL and Vc were tested for a statistical difference between the PM and EM subjects. A sign test was conducted to test for statistical differences in bias and precision of estimates for NONMEM® versus NPEM®. **Results.** The model minimized successfully for all datasets and methods except for two datasets using NONMEM® FOCE. The predicted CL was statistically different for the PM and EM subjects. Estimates of Vc did not achieve statistical difference for all datasets and methods. All methods were able to predict CL with minimal bias (< ± 6%) and a high degree of precision (< 10%). On average the median PE% for Vc was -0.9%, -12%, and 5.5% for NONMEM® FO, FOCE, and NPEM®, respectively. The 75th percentile |PE|% of Vc on average was 28%, 38%, and 52% for NONMEM® FO, FOCE, and NPEM®, respectively. The estimates of CL for NONMEM® FOCE were statistically less biased than NPEM® and the estimates of CL and Vc for NONMEM® were statistically more precise than NPEM®. **Conclusion.** NONMEM® and NPEM® adequately estimated the PK parameters for a bi-modal population. NONMEM® PK estimates were generally more precise than NPEM®.

INTRODUCTION

- Interethnic differences are important sources of individual variation in drug disposition and response.
- Genetics can account for 20-95% of variability in drug disposition and effects (1). Therefore, PK/PD comparisons across different ethnic groups have become an important topic in the global acceptability of foreign clinical data (2,3).
- Population PK/PD analysis can provide valuable information regarding the influence of ethnic differences on the PK/PD of a compound.
- Debate exists whether a parametric approach or a non-parametric approach is appropriate for this type of evaluation.
  - Parametric (NONMEM®)
    - Assumes a specific distribution for interindividual variability of parameters.
    - Assumes unimodal distributions unless subpopulations are defined.
  - Non-parametric (NPEM®)
    - Does not assume a specific distribution for interindividual variability of parameters.
    - Does utilize a specified range for parameters.

OBJECTIVE

- Using simulated data, assess the ability of NONMEM® and NPEM® to accurately and precisely predict the PK parameters of individual subjects when ethnic differences are present.

METHODS

Data Simulation

Pharmacokinetic Model

- PK parameters for nifedipine, clomipramine, and reboxetine were selected because these compounds exhibit poor and extensive metabolizer subgroups (4,5,6)
- One compartment model with first-order absorption and elimination
- Interindividual variability of CL (20 %CV), V (20 %CV), and Ka (30 %CV) for each metabolism subgroup – exponential error model
  - $X_j = \bar{X} \cdot \exp(\eta_j)$ (η - normal distribution)

METHODS, continued

- Residual variability – 15 %CV – proportional error model
  - $C_{ij} = \bar{C}_{ij} \cdot (1 + eps1_{ij} + eps2_{ij})$
  - Eps1: 4 %CV and Eps2: 11 %CV (eps - normal distribution)
- Concentrations simulated at approximate steady-state conditions
  - Nifedipine: 10 doses of 5 mg tid
  - Clomipramine: 31 doses of 100 mg qd
  - Reboxetine: 15 doses of 4 mg bid

Simulation Dataset Characteristics

- 24 Simulation Datasets
  - Three medications
  - Two population sizes (n=50 or n=200)
  - Two distributions of subpopulations (10%/90% and 40%/60%)
    - 40/60 not expected for poor metabolism but could reflect differences for a different type of subpopulation (e.g., gender)
  - Two Sampling Schemes
    - Dense: 10-14 samples during a dosing interval
    - Sparse: Four samples during a dosing interval (random)
      - Each interval divided into 4 time windows / one sample per window
- All data simulated using SAS®, version 8.2

Pharmacokinetic Analysis

NONMEM® (Parametric)

- PK model described above fit to each dataset using four estimation methods
  1. FO
  2. FOCE/Interaction
  - Added estimation of two subpopulations for CL and Vc (paired): $MIX
  3. FO
  4. FOCE/Interaction

NPEM® (Non-parametric)

- PK model described above fit to each dataset parameterized by Ka, CL, and V (where: kel=CL/V)
- Specified parameter ranges encompassed the full range of the parameter in the dataset
- Standard deviation of assay was estimated as a linear function with a residual variability of 4 %CV
- Remaining sources of residual variability modeled using a constant CV error model (estimated gamma)

Comparison of Methods

- Parameters: CL, Vc, Cmax, and C_c
- Calculated summary statistics of percent prediction error (bias) and absolute prediction error (precision) for each parameter
  - PE %=100•(Parameter - True Parameter) / (True Parameter)
  - |PE|%=Absolute value of PE%
- Statistical differences between each NONMEM® estimation method and NPEM® were assessed by performing a sign test using:
  - Difference of the median PE% for the two methods (bias)
  - Difference of the 75th percentile |PE|% for the two methods (precision)
  - Alpha value of 0.05
  - A positive difference for the sign test was assumed for datasets/methods with an unsuccessful minimization

RESULTS

Data: Nifedipine / Clomipramine / Reboxetine

- **Dataset Number (DSN): Population Size / % Poor Metabolism / Sampling Scheme**
  - DSN=1: n=50 / 10% / Full
  - DSN=2: n=50 / 10% / Sparse
  - DSN=3: n=200 / 10% / Full
  - DSN=4: n=200 / 10% / Sparse
  - DSN=5: n=50 / 40% / Full
  - DSN=6: n=50 / 40% / Sparse
  - DSN=7: n=200 / 40% / Full
  - DSN=8: n=200 / 40% / Sparse

RESULTS, continued

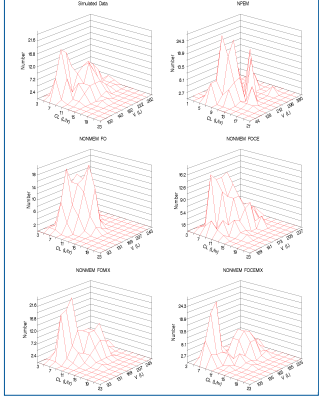
Table 1: Mean of Dataset Mean Pharmacokinetic Parameter Values and Mean %CV

Drug Name	Metabolism Population	Number of Datasets	Ka (1/hr) (%CV)	CL (L/hr) (%CV)	V (L) (%CV)
NIF	Extensive	8	7.1 (30%)	63.27 (19.6%)	222.48 (19.7%)
NIF	Poor	8	7.2 (25.8%)	37.03 (18.4%)	175.98 (17.9%)
CLM	Extensive	8	1.16 (31.7%)	63.43 (19.2%)	4016.84 (19.6%)
CLM	Poor	8	1.13 (24.9%)	12.78 (19.1%)	1180.55 (18.6%)
RBX	Extensive	8	0.8 (29.0%)	9.44 (20.5%)	186.42 (19.9%)
RBX	Poor	8	0.76 (24.9%)	6.13 (20.9%)	128.22 (20.0%)

Pharmacokinetic Analysis

- While methodologically, NONMEM® assumes a unimodal distribution of all PK parameters, the empirical joint-density plots indicated that this assumption does not prevent NONMEM® from estimating multi-modal distributions of individual parameter values (**Figure 1**)

Figure 1: Empirical Joint Probability Density Plot of (CL,V): Reboxetine Dataset #7



RESULTS, continued

Pharmacokinetic Analysis, continued

- All methods exhibited a small degree of bias in the estimation of CL (±6%), Cmax (±12%), and Cc (±8%) based upon the median PE% for each dataset
- A larger degree of bias was noted for the estimation of V
  - NONMEM® methods: median PE% -75% to 16%
  - NPEM® : median PE % -63% to 6%
- All methods exhibited a high degree of precision in the estimation of CL (20%), Cmax (25%), and Cc (27%) based upon the 75th percentile |PE|% for each dataset
- The precision for the estimation of V was weaker
  - NONMEM® methods: 75th percentile |PE|% 8% to 110%
  - NPEM® : 75th percentile |PE|% 12% to 254%

Table 2: Summary Statistics of the PE% and the |PE|% of each Dataset

Method	N*	Mean (SD) (Min, Max) CL	V	Cmax	C_C
Median PE%					
FO	24	-1.91 (1.84) (-5.99, 0.18)	-12.12 (23.18) (-75.35, 16.42)	3.06 (3.89) (-1.46, 12.15)	0.11 (3.21) (-6.59, 5.54)
FOCE	22	-0.17 (1.69) (-4.77, 1.88)	-0.89 (7.72) (-16.44, 13.66)	-0.72 (1.33) (-2.69, 1.78)	-0.46 (2.03) (-4.00, 4.16)
Mix-FO	24	-1.05 (1.19) (-4.29, 0.57)	-3.32 (6.68) (-16.20, 8.85)	1.06 (1.70) (-2.16, 5.84)	0.72 (1.92) (-4.29, 5.29)
Mix-FOCE	21	0.44 (1.07) (-1.71, 2.23)	-2.55 (6.91) (-18.79, 11.37)	-0.45 (1.31) (-2.92, 1.86)	-0.94 (1.32) (-3.78, 1.91)
NPEM	24	2.16 (2.49) (-3.74, 5.02)	-5.51 (13.93) (-62.87, 5.80)	-1.73 (2.88) (-6.03, 4.89)	-3.47 (1.96) (-7.57, 0.45)
75th Percentile |PE|%					
FO	24	8.03 (2.83) (4.59, 13.83)	37.96 (28.89) (9.21, 110.24)	11.02 (6.04) (5.14, 25.29)	11.97 (2.58) (6.75, 17.12)
FOCE	22	7.63 (3.21) (4.41, 18.56)	28.20 (17.28) (8.32, 69.26)	8.23 (2.54) (5.02, 13.19)	10.56 (1.93) (5.75, 13.58)
Mix-FO	24	7.23 (2.04) (4.49, 10.43)	23.99 (10.25) (9.22, 47.38)	8.87 (4.24) (4.66, 22.38)	10.61 (2.41) (6.00, 14.44)
Mix-FOCE	21	7.14 (2.21) (4.21, 10.22)	22.96 (8.72) (7.88, 41.09)	8.58 (3.20) (4.72, 16.08)	10.31 (1.91) (6.93, 13.00)
NPEM	24	9.95 (2.34) (7.14, 16.38)	52.33 (49.71) (11.75, 254.15)	12.33 (3.73) (7.75, 19.59)	14.96 (3.63) (10.93, 27.25)

*Nc Number of datasets with a successful minimization

Comparison of Methods

- **Table 3** shows the percentage of datasets for which the indicated NONMEM® method had a larger median PE% or a larger 75th percentile |PE|% than the NPEM® method
- A percentage less than 50% indicates that the NONMEM® method was less biased or more precise than NPEM®
- Red values indicate that the percentage of datasets was statistically significantly less than or greater than 50% (p<0.05)

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RESULTS, continued

Table 3: Percent of Datasets where the NONMEM® Method Exhibited More Bias (Less Precision) than the NPEM® Method - All Subjects

	No. Datasets	NONMEM® FO	FOCE	Mix-FO	Mix-FOCE
Clearance					
All Datasets	24	33 (25)	21 (17)	21 (0)	21 (13)
10% Poor Metabolism	12	25 (8)	8 (0)	17 (0)	8 (0)
40% Poor Metabolism	12	42 (42)	33 (33)	25 (0)	33 (25)
Volume					
All Datasets	24	50 (21)	33 (17)	42 (0)	42 (13)
10% Poor Metabolism	12	58 (8)	33 (0)	50 (0)	42 (0)
40% Poor Metabolism	12	42 (33)	33 (33)	33 (0)	42 (25)

CONCLUSIONS

- Parametric and non-parametric methods are adequate for fitting pharmacokinetic models to data with two well-defined subpopulations of CL and V.
- The bias of CL and V estimates was generally not statistically different between the two methods.
- The precision of CL and V estimates was generally statistically higher for the parametric methods than the non-parametric methods.

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