Population Pharmacokinetics of Theophylline in South Indian Patients

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Objectives for TDM

- To optimize dosage regimen for each individual patient in the least time.
- To optimize therapeutic serum concentration to achieve the expected clinical response without reaching the toxic levels.
- To check patient's compliance
- To check the drug's ADME in certain patients
- To monitor drug-drug interactions that may either increase or decrease the efficacy of the drug.

- To confirm the clinical symptoms as a consequence of disease or over dosage
- To measure the levels in certain physiological conditions such as age, sex, pregnancy etc.,
- To monitor the drug levels in certain pathological conditions involving liver, kidney and the CVS.
- To help follow-up in patients with long treatment periods to monitor and adjust the drug dosage.

Rationale for TDM of Theophylline

- Theophylline was used with out TDM for more than 40 years.
- Availability of hundreds of theophylline (a potent and potentially toxic agent) containing preparations is resulting in confusion and certain degree of causalities.

The need for TDM/TCI of theophylline is justified on the basis of following criteria:

- **Relationship between Clinical response and serum theophylline concentration:**
- Bronchodilation occurs over the serum theophylline concentration range of 5-20 ug/ml.
- Clinically important improvement requires peak serum concentrations >10ug/ml, but patients from mild disease may benefit from lower concentrations.
- At concentrations > 20ug/ml, both frequency and severity of ADR increase.
- In general, maintaining peak serum concentrations between 10 and 15 ug/ml will achieve most of the drug's potential therapeutic benefit with minimal risk of serious ADE.

Relationship between toxicity and serum theophylline concentrations:

- ADR associated with theophylline are generally mild when peak serum concentrations are <20ug/ml and mildly consist of transient caffeine like adverse effects such as nausea, vomiting, headache and insomnia.
- When the levels exceed 20ug/ml, it produces a wide range of ADR including persistent vomiting, cardiac arrhythmias and intractable seizures, which can be lethal.

Manifestations of patients reported with sign or symptom

	Acute over dosage		Chronic over dosage	
Sign/sym	**Study 1**	**Study2**	**Study 1**	**Study 2**
Asymptomatic	NR*	0	NR**	6
Gastrointestinal				
Vomiting	**73**	**93**	**30**	**61**
Abdominal pain	NR**	**21**	NR**	**12**
Diarrhea	NR**	0	NR**	14
Hematemesis	NR**	0	NR**	2

Metabolic/other				
Hypokalemia	**85**	**79**	**44**	**43**
Hyperglycemia	98	NR**	18	NR**
Acid/base dist	34	21	9	5
Rhabdomyolysis	NR**	7	NR**	0
Cardio vascular				
Sinus Tachycardia	**100**	**86**	**100**	**62**
Other supraven tachycardia	**2**	**21**	**12**	**14**
Ventricular premature beats	**3**	**21**	**10**	**19**
Atrial fibrillation/flutter	1	NR**	12	NR**
Multi focal atrial tachycardia	0	NR**	2	NR**
Ventricular arrhythmias with hemodynamic instability	7	14	40	0
Hypotension/shock	NR**	21	NR**	8

Neurologic				
Nervousness	NR**	**64**	NR**	**21**
Tremors	**38**	**29**	**16**	**14**
Disorientation	NR**	7	NR**	11
Seizures	**5**	**14**	**14**	**5**
Death	**3**	**21**	**10**	**4**

Johnson et al., J Pharmacokinet Biopharm. 1996; 24 (6): 245 - 172.

Jones et al., . Clin. Res Reg. Affairs. 1996; 13 (3&4): 133-165.

Factors associated with variation in theophylline elimination

Factors	Age Mean+/- SD	No of patients	Clearance; ml/kg/min (Mean+/- SD}	Half life; h Mean+/- SD
Premature neonates with apnea	7.5+/-4.4d 41+/-12d	6 8	0.29+/-0.1 0.64+/-0.3	30+/-6.5 20+/-5.3
Infants under 6m	12+/-4w 18+/-2w	8 3	Incomplete data 0.8+/-0.1	14+/-4 6.9+/-1
6 to 11m	34+/-10w 34+/-7w	4 5	2.0+/-0.5 Incomplete data	4.6+/-1.2 3.7+/-1
Young children 1-4y	2.5+/-0.9	10	1.7+/-0.6	3.4+/-1.1
Older children 4-12y 13-15y 6-17y	9.4+/-3 14+/-0.8 10.7+/-2.6	17 6 30	1.5+/-0.4 0.8+/-0.2 1.4+/-0.6	Not measured Not measured 3.7+/-1.1

Adults Otherwise healthy non smoking asthmatics Healthy Non smoking Vol (a) Healthy non smoking Vol(b)	31+/-10 22-35(a) 20-32(25.5)(b)	16 19 15	0.65+/-0.19 0.86+/-0.35 0.67+/-0.13	8.7+/-2.2 8.1+/-2.4 8.2+/-1.2
Non smokers with normal cardiac, liver and renal function	67+/-5.7	9	0.59+/-0.07	7.4+/-1.1
Abnormal Physiology Fever – associated with acute viral upper RTI	9-15(a)	6(during illness) 1 m later	Not measured Not measured	7.0+/-3.0 4.1+/-2.4
Cor pulmonale Acute pulmonary oedema Hepatic Cirrhosis	64 71+/-10 52+/-8.2 56+/-4	8 9 9 8	0.48+/-.2 0.33(0.0672.35)(d) 0.43(0.13-3.3)(d) 0.21(0.1-0.6)(d)	Not measured 19(3.1-82) d 14.1(7.1-59.1) d 32(10.4-56) d

Dosage titration required for children and adults

Titration Step	Children <45 kg	Children >45 kg and adults
Starting Dose	12-14 mg/kg per day Maximum 300 mg/day divided Q 4-6 hr	300 mg/day divided Q 6-8 hr
After 3 days, if tolerated, increase dose to	16 mg/day maximum 400 mg/day divided Q 4-6 hr	400 mg/day divided Q 6-8 hr
After 3 more days	20 mg/kg per day maximum 600 mg/day divided Q 4-6 hr	600 mg/day divided Q 6-8 hr

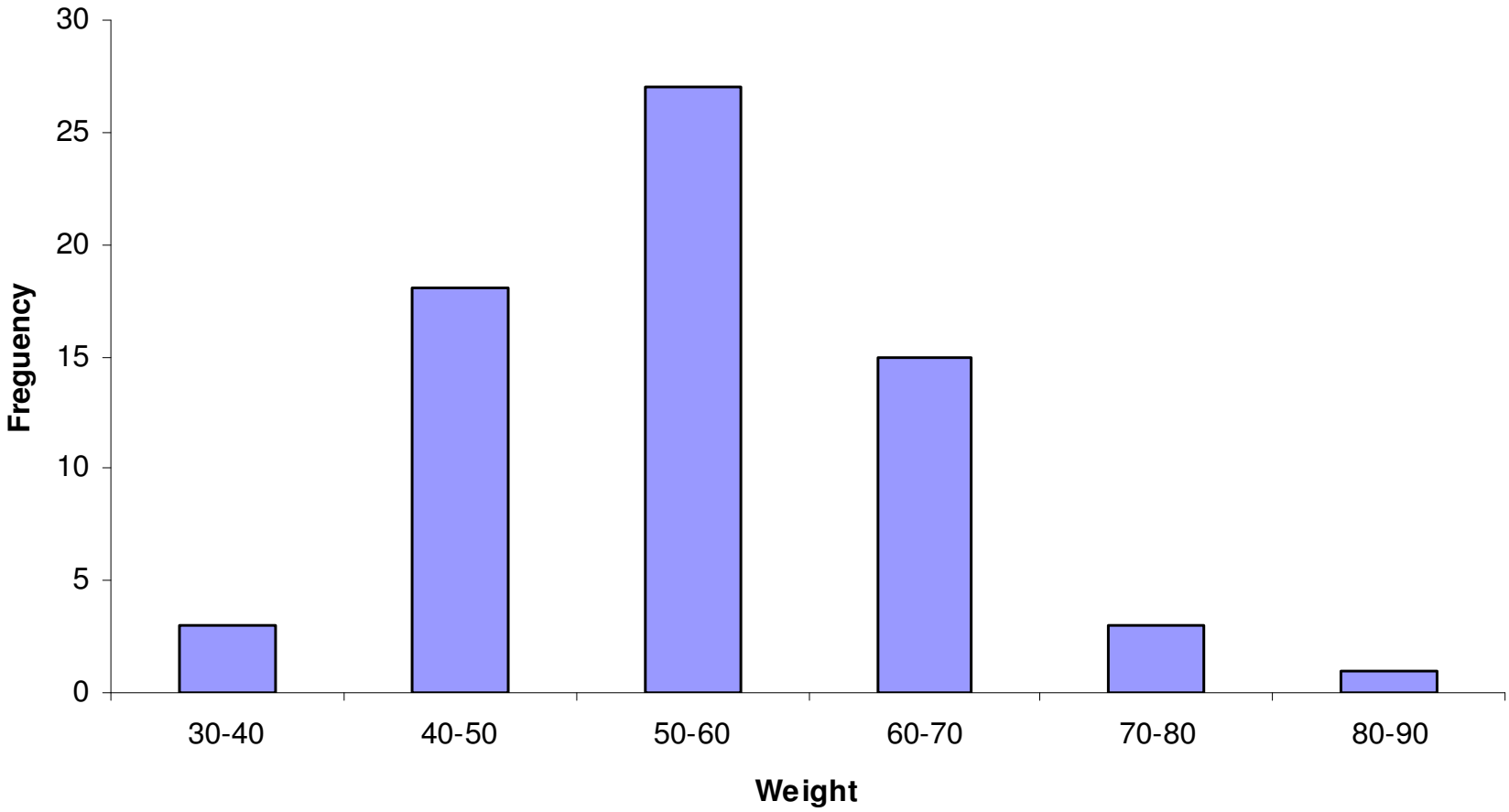
PURPOSE OF WORK

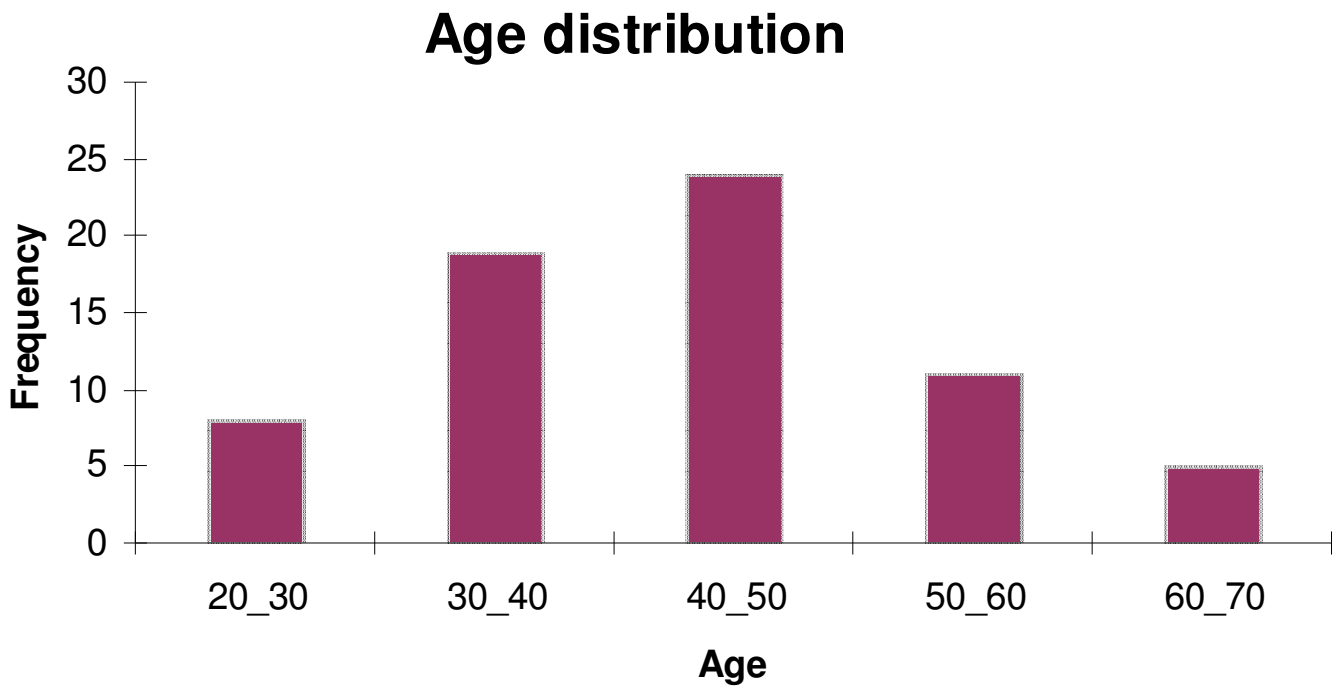
- Theophylline pharmacokinetics information is available in some populations such as Caucasians, Chinese, Japanese, Thai & Africans.
- But no data is available in Indian population and the drug levels are monitored in patients to optimize the therapy.

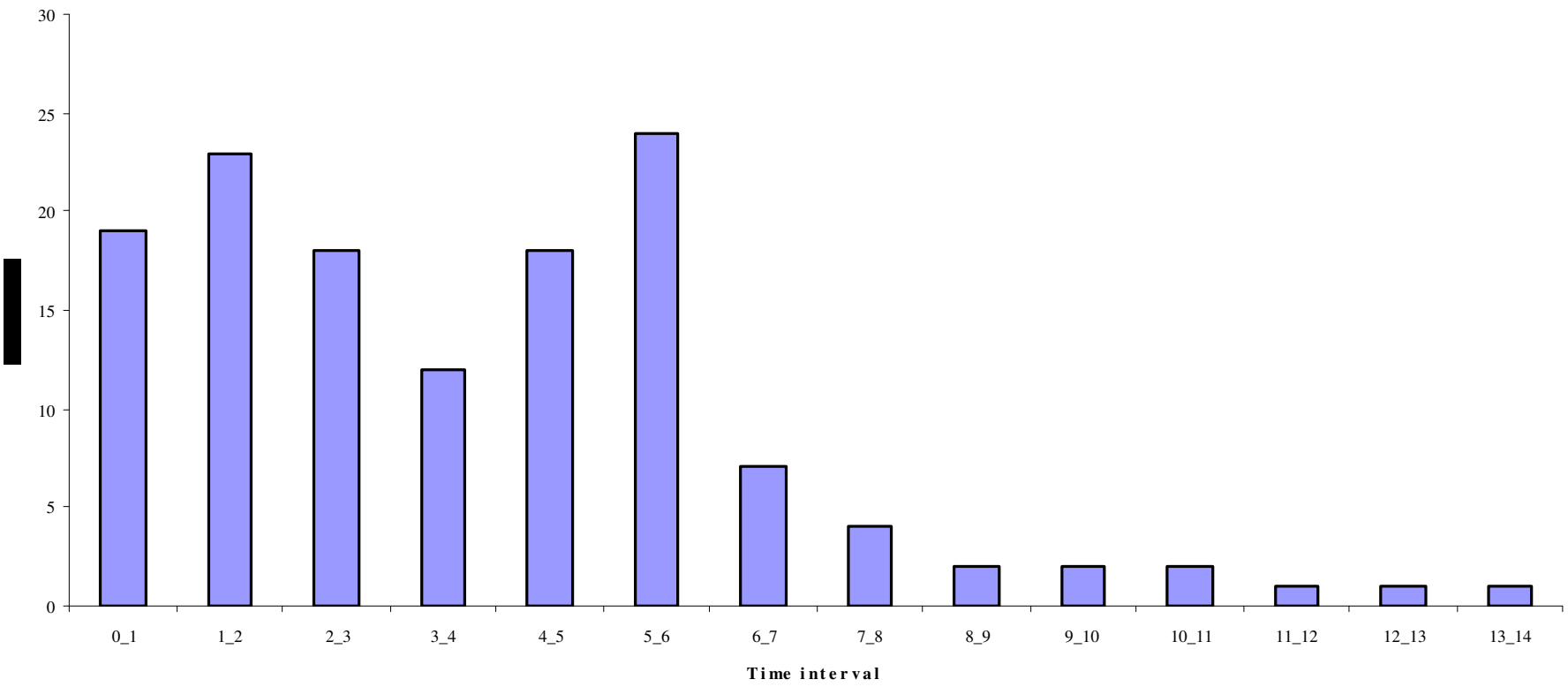
Range and Mean (+/- SD) Values for Patients (n=67; M:23 & F:44) Under Study

Smokers: 4; No CHF & Hepatic Disease

Parameter	Range	Mean (+/-SD)
Age (years)	23-70	43.89(+/-10.50)
Body Weight (Kg)	37-90	56.7(+/-9.76)
Height (cm)	140-179	155(+/-7.98)
Dose (mg)	200-400	258.28(+/-54.80)
Serum level (ug/ml)	1.77-12.50	8.04(+/-2.10)
Sampling Time (hrs)	0.33-13.5	2.76(+/-2.90)


Weight Distribution of Patients
Freguency
30
25
20
15
10
5
0
30-40
40-50
50-60
60-70
70-80
80-90
Weight


Age distribution
Frequency
30
25
20
15
10
5
0
20_30
30_40
40_50
50_60
60_70
Age


Time points of sample collection
30
25
20
15
10
5
0
0_1
1_2
2_3
3_4
4_5
5_6
6_7
7_8
8_9
9_10
10_11
11_12
12_13
13_14
Time interval

Method of Drug Analysis

- Theophylline in the serum samples was estimated by reverse phase High Pressure Liquid Chromatography (HPLC) method developed by (Diane T .Holland et al. 1998).

- HPLC system consisted of LC-8A solvent delivery module and SPD-10A*VP* UV-Visible spectrophotometric detector (Shimadzu,Kyoto, Japan).
- Column: Wakosil II 5C-18RS-100A, 5µm, 4.6X 250mm SS column (SGE, Japan)
- Data Processor :Class CR-10
- Injection Port :Rheodyne (with 20 uL capacity),Cotati,CA,U.S.A.
- Mobile Phase: Potassium dihydrogen phosphate pH(4.9) and Methanol mixture (60:40)
- Flow rate : 1ml/min
- Pressure : 150 kg.f/cm2
- Column temperature : Room temperature
- UV-detection at : 274nm
- Detector sensitivity : 0.001 a.u.f.s

Analysis Method

- Patient serum theophylline samples were stored at –80^{0}C prior to analysis. Caffeine as used as IS.
- Samples were deproteinated by mixing 250ul of serum with 250ul of 0.8 M Perchloric acid.
- After vortex mixing, the proteins were removed by centrifugation at 13000g (RT) for 4-5 min.
- An aliquot of the supernatant (350ul) was taken out and mixed with approximately 27ul of 4M Sodium hydroxide, to bring the sample pH ~ 5.0.
- This was done in a vial ready for direct injection onto HPLC column. 20ul were injected.

Pharmacostatistical Analysis

- The population pharmacokinetic analysis was performed using WFN - NONMEM (Version V) in conjunction with FORTRAN g77 compiler.
- Data files were constructed using Excel. All the demographic data (patient id, age, sex, weight, height, dose etc.,), time.

- An analysis was then performed by a forward, stepwise technique where each covariate, which individually caused a decrease in objective function value, was added cumulatively to the model.
- This process was continued until no further reduction in the objective function value resulted. Finally, a backward elimination step was performed by setting the coefficient of each covariate, in turn, to zero and noting the change in the objective function value.

- Additive error model was utilized to describe the inter-individual variability. Both FO and FOCE methods were attempted and the results compared.
- The strength of relationships between various covariates like body weight (WT), age (AGE), height (HT) sex (SX), smoker status (SM), alcohol status (AL) was shown by hypothesis testing of full-reduced models during covariate screening.

Final Model

- A backward elimination process employed to eliminate covariates from the full model resulted in the final model.
- An increase in the objective function of 3.8 or greater ($p<0.05$) on removal of a covariate from the full model signified that the variable had influence, and that covariate was retained in the final model.

Pharmacokinetic Model

- The base model for analysis was prepared using a One compartment linear model with first order absorption with the subroutine ADVAN2 in PREDPP module.
- The primary pharmacokinetic parameters clearance (CL), volume of distribution (V), from depot (oral) compartment were modeled . K, the first order, terminal elimination constant, was calculated from CL/V at the completion of modeling

Base Model

- $SUBROUTINE ADVAN2
- $PK
- ;THEOPHYLLINE PROGRAM BASE MODEL
- KA=THETA(1)
- CL=THETA(2)+ETA(1)
- V=THETA(3)+ETA(2)
- K=CL/V
- S2=V
- $ERROR
- Y=F+ERR(1)

Final Model

- $SUBROUTINE ADVAN2
- $PK
- ;THEOPHYLLINE PROGRAM FINAL MODEL
- KA=THETA(1)
- CL=THETA(2)*(WT/56.7)**0.75+ETA(1)
- V=THETA(3) *(WT/56.7)+ETA(2)
- K=CL/V
- S2=V
- $ERROR
- Y=F+ERR(1)

- Individual CL & V equations including covariate & error terms
- CL= $\theta(2)*(WT/56.7)**0.75+(\eta 1)$
- $V=\theta(3)*(WT/56.7)+(\eta 2)$

- ΔOBJ: 7.4 ($p<0.01$)

Parameter Estimates (FO)

Parameter	Meaning	Estimation	95% CI
θ1	Coefficient (Ka)	2.02	1.17 – 2.87
θ2	Coefficient (CL)	2.26	1.81-2.71
θ3	Coefficient (V)	15.9	12.88-18.92
ω1	Inter patient Variability (CL)	0.0152	0.0088-0.022
ω2	Inter patient Variability (V)	0.256	0.159-0.353
ε1	Residual Error	14.8% (9)	

Parameter Estimates FOCE

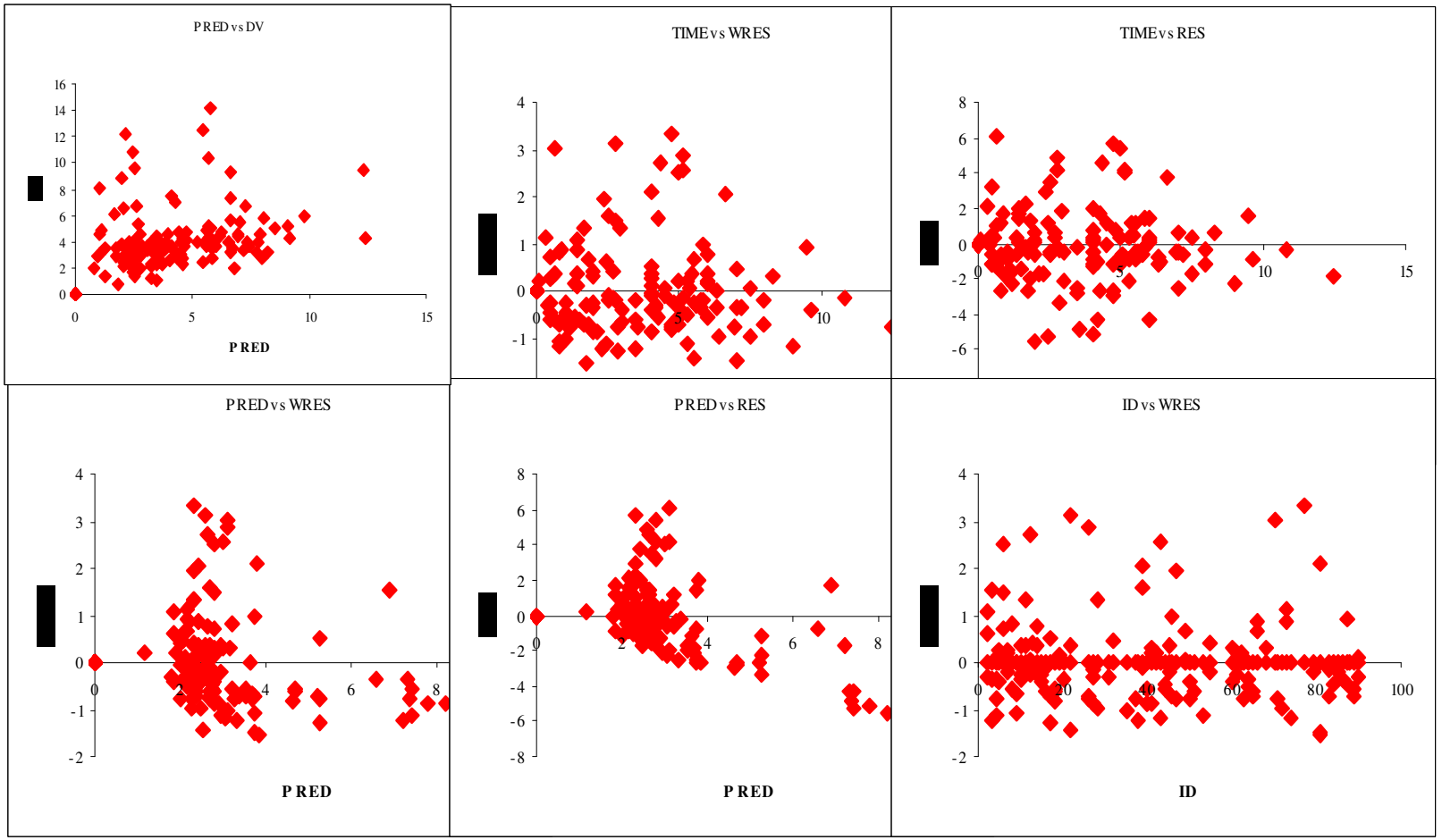
Parameter	Meaning	Estimation	95% CI
θ**1**	Coefficient (Ka)	1.75	1.35-2.15
θ**2**	Coefficient (CL)	2.39	1.96-2.82
θ**3**	Coefficient (V)	15.3	11.2-19.4
ω**1**	Inter-patient Variability (CL)	0.096	0.069-0.123
ω**2**	Inter-patient Variability (V)	0.277	0.186-0.368
ε**1**	Residual Error	13.2% (7)	

Population Mean Values corresponding to patients weighing 56.7 kg (mean TBW)

Parameter	FO Method	FOCE Method
Ka (h-1)	**2.02**	**1.75**
CL (L/h)	**2.26**	**2.39**
V (L)	**15.9**	**15.3**

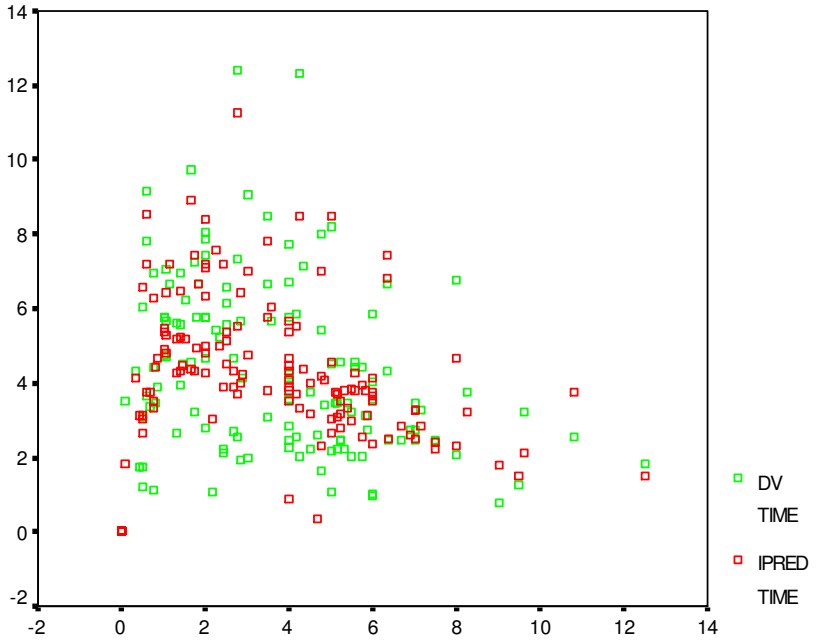
Final Model – FO Method

(NM Graphics – Mark Sale)

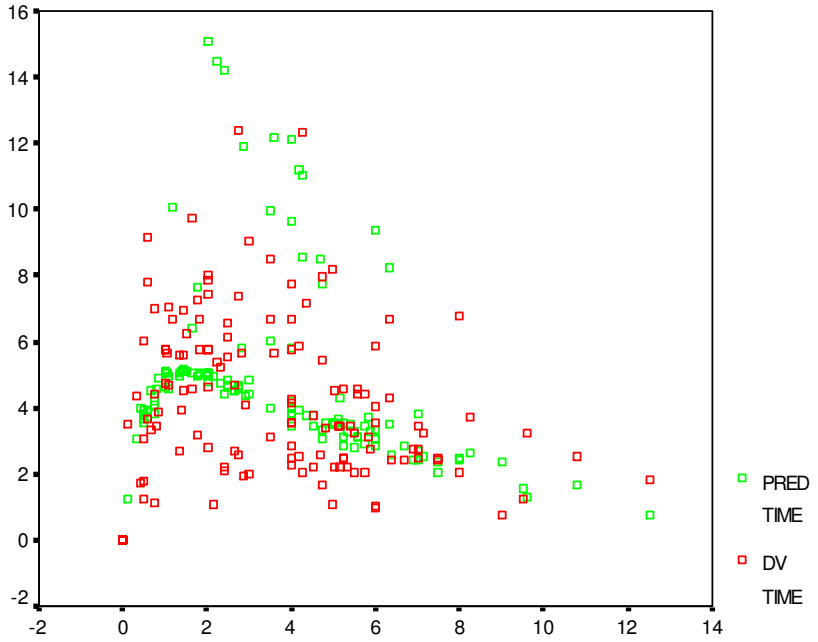


Final Model

Time vs DV & IPRED

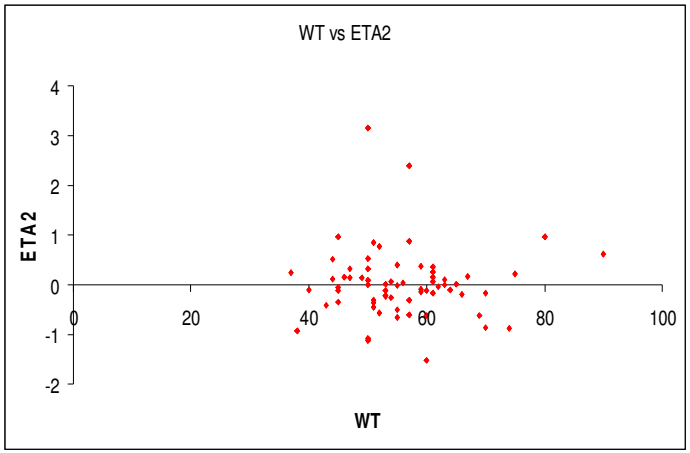


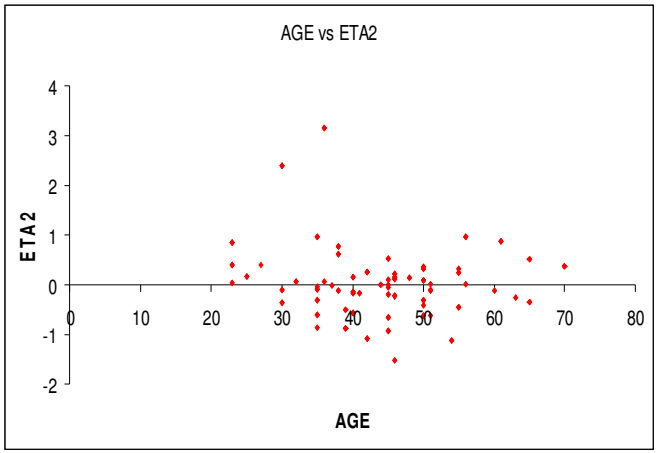
Time vs DV & PRED

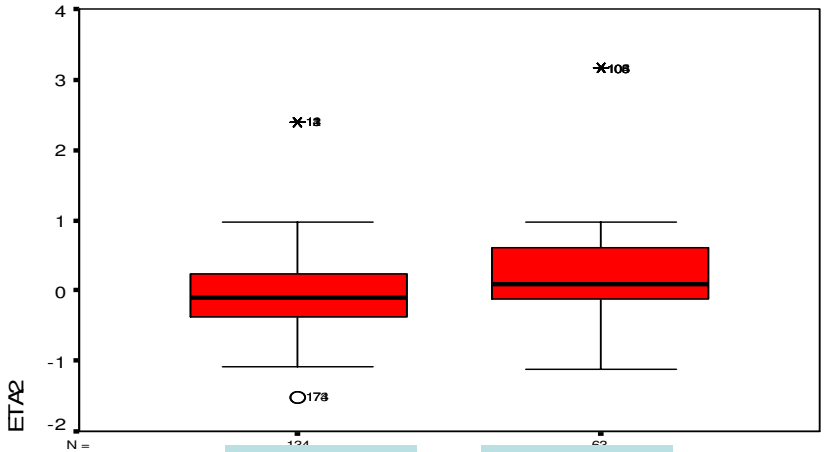


Empirical Bayes Estimates of ETA

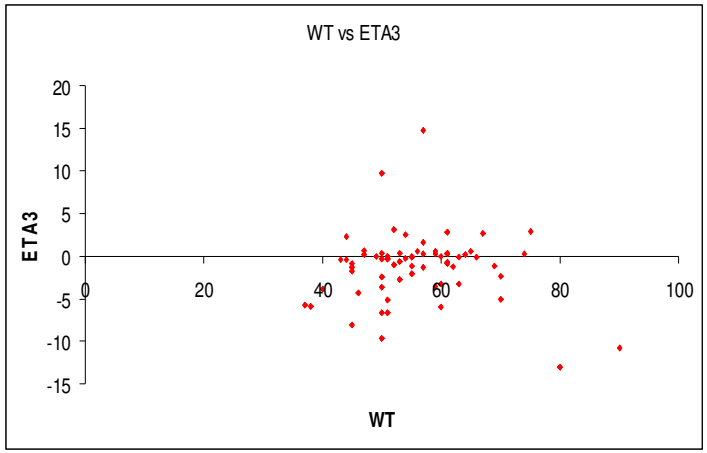
BSV_{CL} versus WT, AGE &SEX

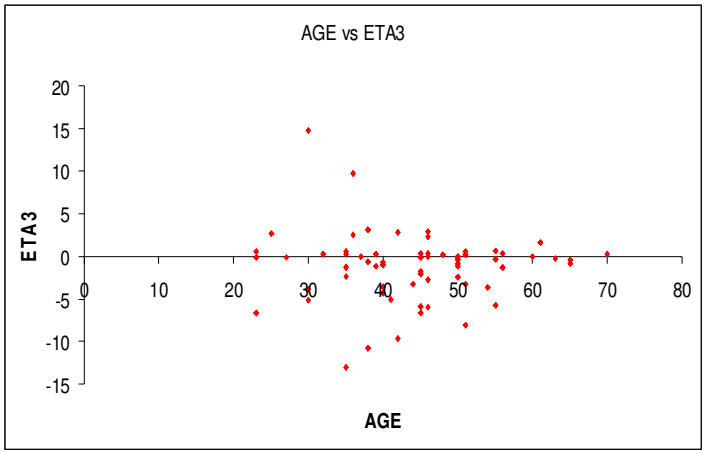


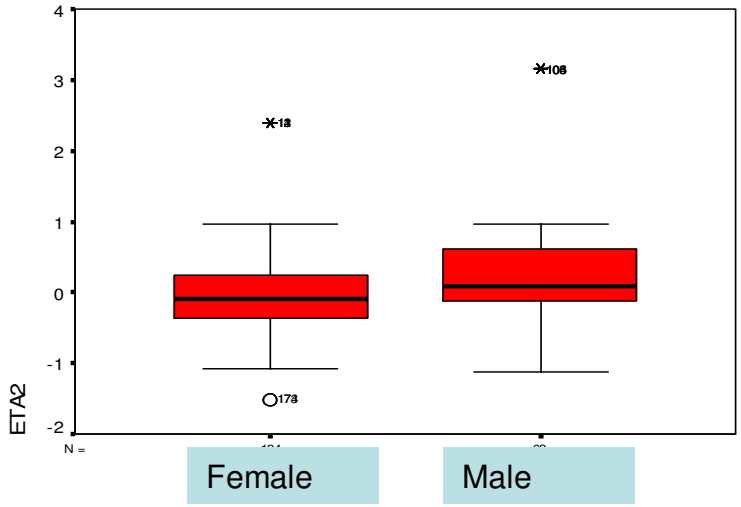




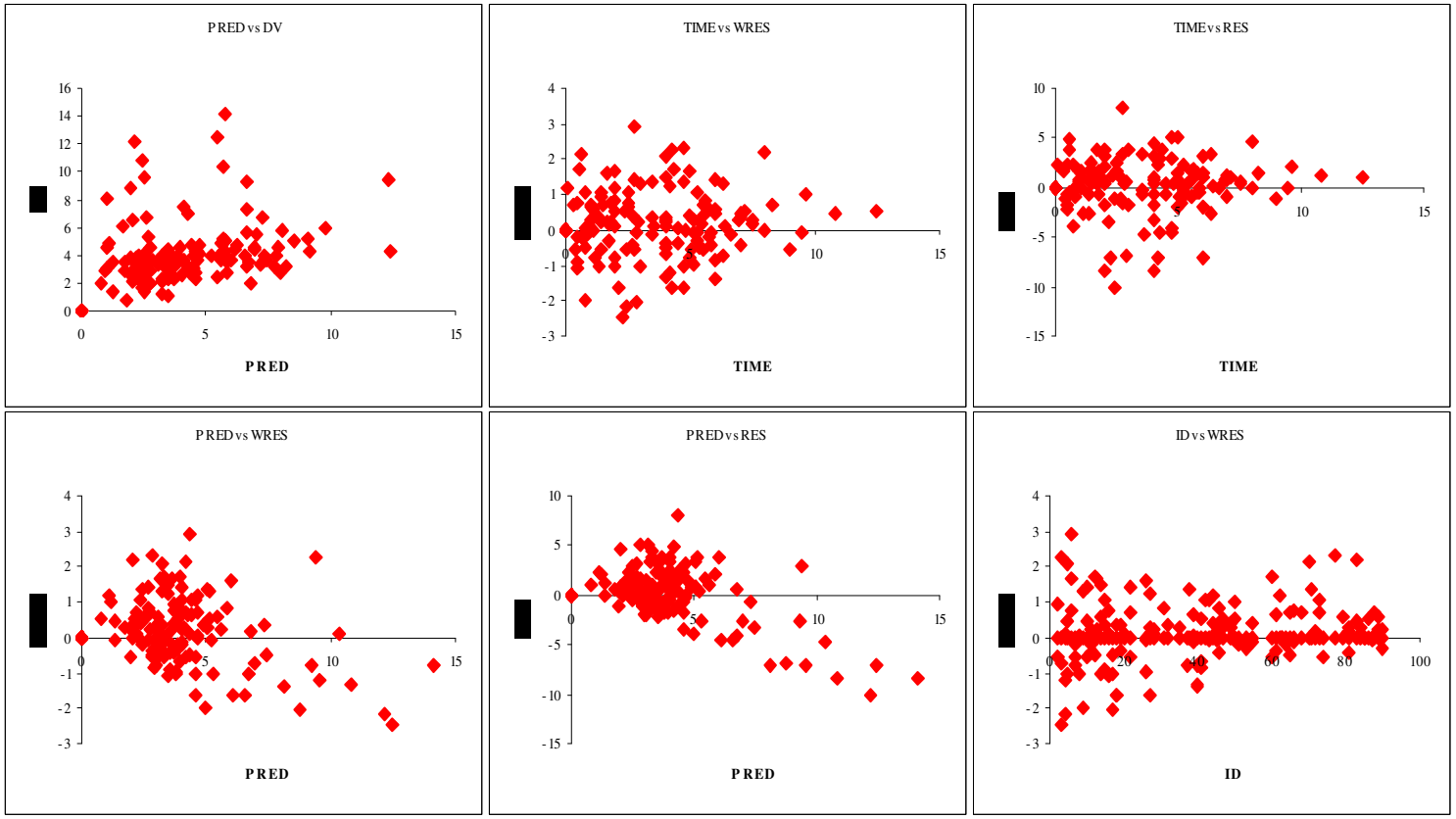
BSV_{VD} versus WT, AGE &SEX



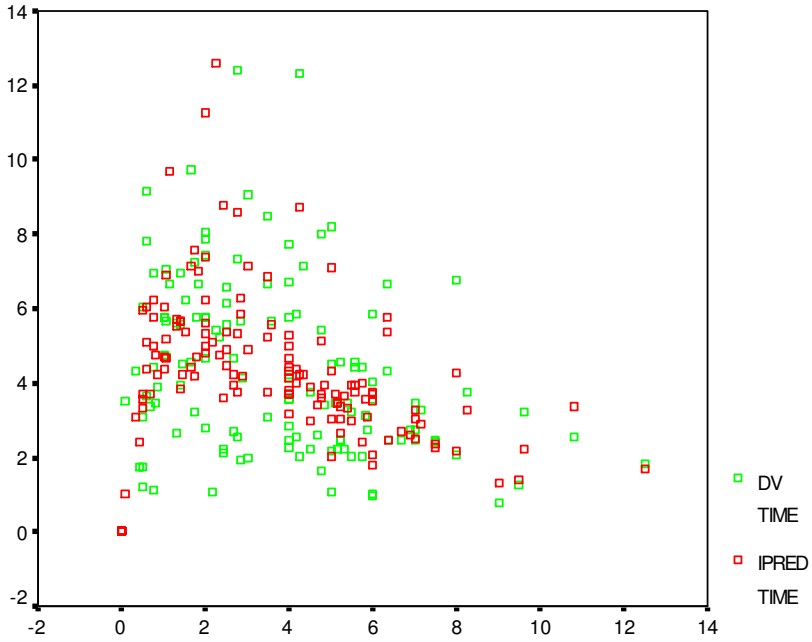




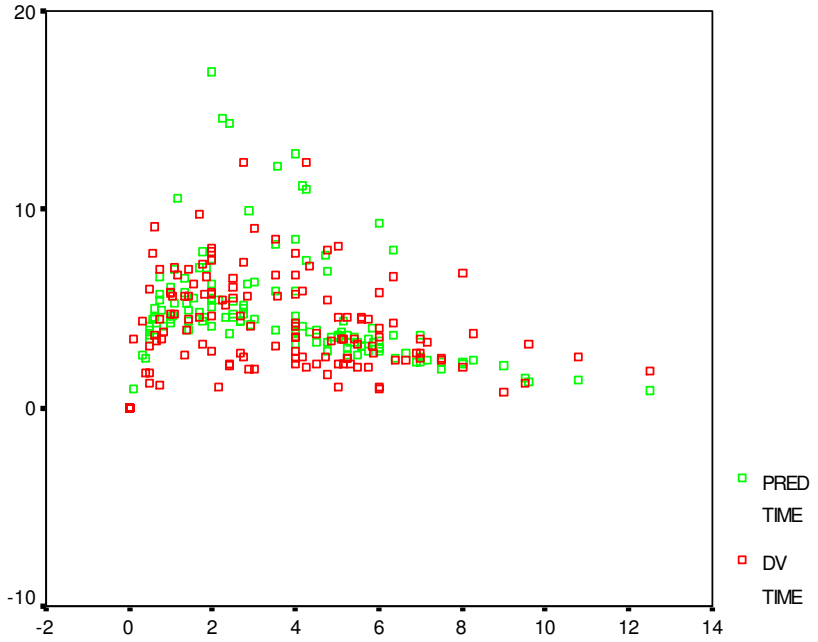
Final Model FOCE



Time vs DV & IPRED

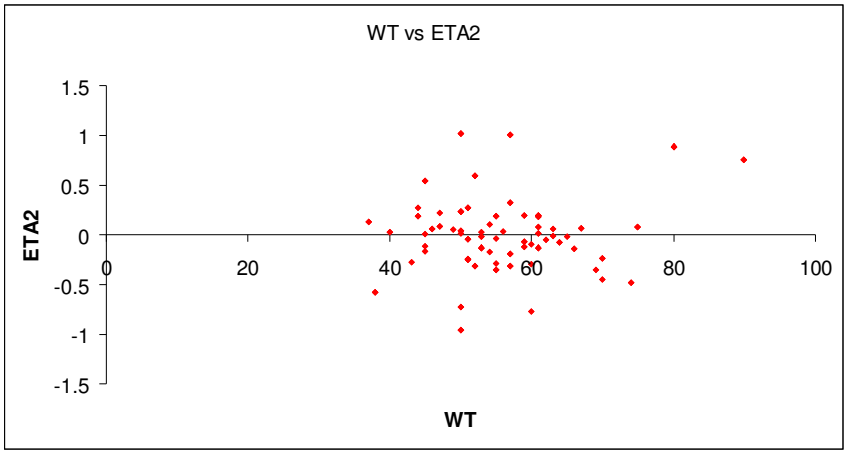


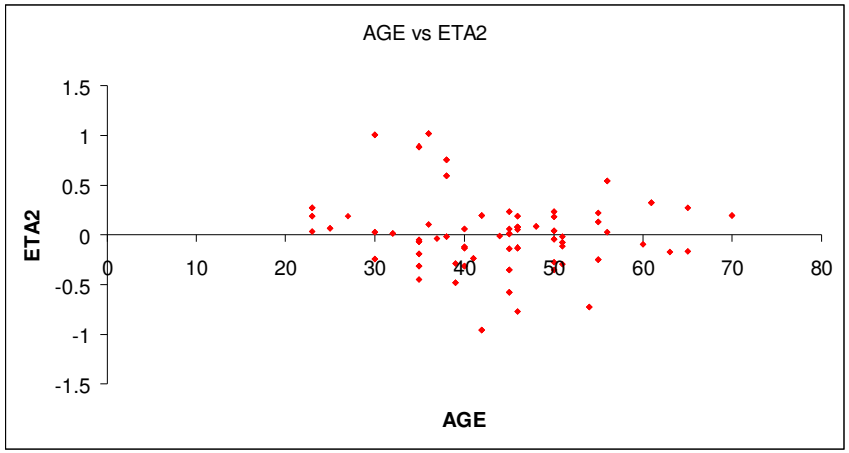
Time vs DV & PRED

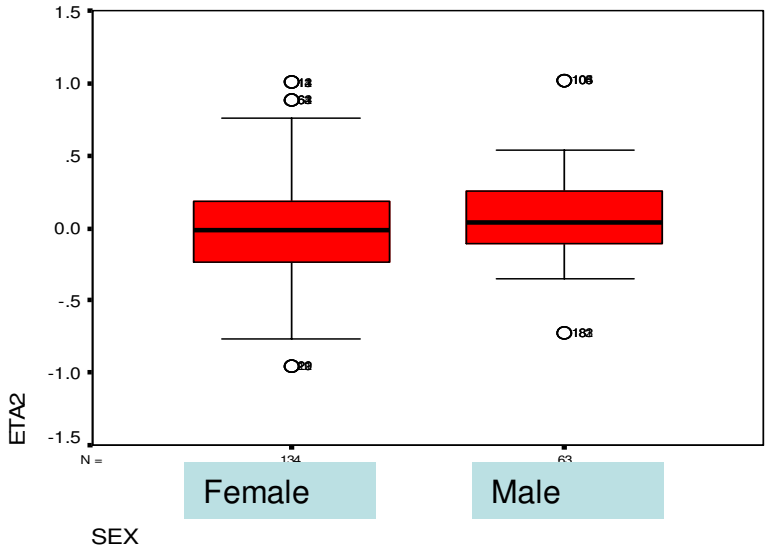


Empirical Bayes Estimates of ETA

BSV_{CL} versus WT, AGE &SEX



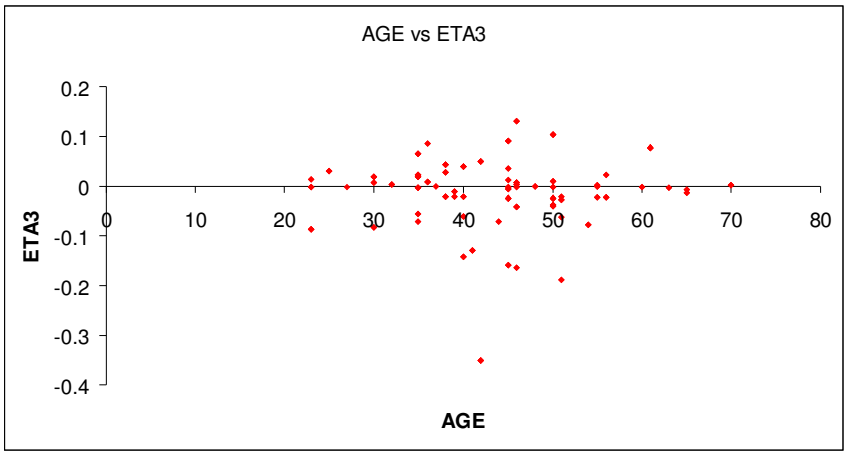


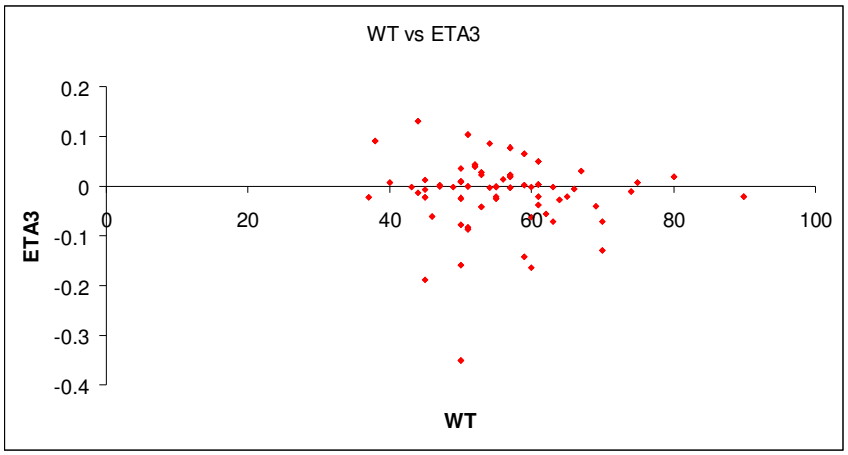


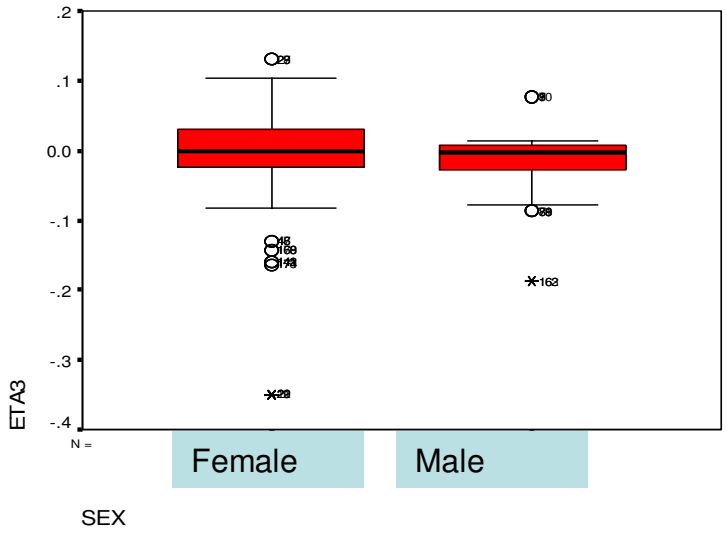
Female

Male

BSV_{VD} versus WT, AGE &SEX







Population	Volume of Distribution (L/Kg)	Total body Clearance L/h/kg	Kel (1/h)	T1/2 (h)
Smokers Non-smokers	0.3 – 0.7 0.3 – 0.7	0.072 0.054	0.144 0.108	4.8 6.4
CHF	0.48 -1.20	0.0216	0.0257	26.7
Cirrhosis	0.45 – 0.64	0.0216	0.0396	17.5

1) Schumacher, G.E., Therapeutic Drug Monitoring, Appleton& Lange,Norwalk 1995
2) Mungall, D.R., Applied Clincal Pharmacokinetics, Raven Press, New York 1983

Population	Volume of Distribution (L/Kg)	Total body Clearance L/h/kg	Ka (1/h)	Kel (1/h)	T1/2 (h)
Non-smokers (Caucasian)	0.3 – 0.7	0.054		0.108	6.4
Japanese (Tanigawa et al.,)	0.320	0.0539	0.0773	0.168	4.13
Japanese (Yano et al.,)	0.485	0.061		0.126	5.5
South Indians (Present study)	**0.28**	**0.0398**	**2.02**	**0.142**	**4.88**

Earlier work

- The obtained parameters are

  ka(h-1) = 0.223, ke(h-1) = 0.047 (p.o.) & 0.076 (i.v.)

  Vd(1/kg) = 0.733 (p.o.) & 0.830 (i.v.).

  CL(l/h) = 0.0345 (p.o) & 0.061 (i.v.).
- The results suggest that TDM of theophylline should be assessed in terms of clinical effects and also that it should be kept monitored from the viewpoint of the prevention of toxic effects in the theophylline therapy.

Tanikawa et al., Yakugaku Zasshi. 1999 Nov;119(11):861-7

- 2772 serum theophylline concentrations obtained from 131 normal subjects and 306 patients of chronic asthma or COPD, participated in the phase I, II, and III clinical trials in Japan.
- Ka for a 200-mg tablet in a fasting condition was obtained as 0.0773 (1/h), smaller than Kel (0.168 1/h), indicating the flip-flop characteristic.
- The 400-mg tablet showed a Ka value 19% smaller.
- Food indigestion increased the Ka by 17% and the absorption lag time by 5-fold but did not affect the extent of absorption.
- The total body clearance (CL) was related to hepatic function, smoking habits, age and severity of illness.

Tanigawara et al., Biol Pharm Bull. 1995 Nov;18(11):1590-8

- In a retrospective study in 204 asthmatic and COPD patients, with a total of 517 serum concentrations, population pharmacokinetic analysis was performed with the MULTI(ELS) according to a one-compartment model.
- Significant factors produced a final model in which CL was based on IBW (kg) and age (years), and was reduced by 25% in moderate CHF and increased by 28% in smokers

  (CL(L/h) = (0.037 IBW-0.006 age) x 1.284 smoke x 0.751 CHF).

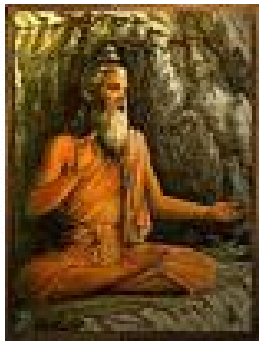
- Otero et al., J Clin Pharm Ther. 1996 Apr;21(2):113-25

- In adult non-smoker and non-CHF patients, application of a maintenance dosing regimen calculated from IBW and age using the final model for CL would theoretically afford only 1.5% of patients with potentially toxic concentrations.
- Thus, measurement of serum theophylline concentrations would only be required when other conditions known to alter theophylline metabolism exist, such as smoking or disease factors.

Conclusion

- Both CL & Vd of theophylline are relatively lower in Indian population, the half-life is shorter than in Caucasians.
- From the conventional formulation the absorption is fairly rapid (higher Ka).
- TBW influences CL & V in the Indian subjects and maintenance dose predictions can be made using this model for the purpose of Target Concentration Intervetion.

Ancient Wisdom



(SNP) which constitutes just 0.1%. Importance of such individual variations in health and disease is an important basic principle of ayurveda and was underlined by Charaka some time 4000 years ago as follows: 'Every individual is different from another and hence should be considered as a different entity. As many variations are there in the Universe, all are seen in Human being'[56].

Acknowledgement:

- Doctors and nurses at MGM Hospital, Warangal, Govt. Hospital, Kothagudem Coal mines.
- Dr.Mark Sale
- Organizers of ECPAG 2006