Vancomycin Pharmacokinetic Dosing
Analysis of Patient Data & Optimization of Kinetic Parameters
6/2007

Methods:
All patients' data from pharmacokinetic consults was placed in an Excel spreadsheet (age, height, weight, sex, serum creatinine at time of levels, dose and frequency at time of levels, and measured trough). Patients were excluded if they had acute renal failure, unstable renal function, were receiving hemodialysis, or did not have steady state serum levels. Summary date is presented in the table below.

Number of Patients = 107		
	Average (SD)	Range
Age (years)	58.5 (17)	22-90
Male	47%	
Serum Creatinine (mg/dl)	0.98 (0.51)	0.4-4
Creatinine Clearance Calculated at Time of Levels (ml/min)	80 (33)	14.9-173
Height (Inches)	67.8 (4.2)	60-81
Ideal or Actual Body Weight (kg) (which ever was less)	64.9 (11)	43-98.3
Actual Body Weight (kg)	90.9 (25.9)	43-171.8
% of Patients Obese (20% or more above Ideal Weight)	64%	
% Above Ideal Weight (TBW-IBW)*100/IBW	42% (42%)	0-184%
Volume of Distribution = 0.65 * Total Body Weight (liters)	59 (16.8)	27.9-111.7
Dose Administered At Time of Level (mg)	1214 (352)	500-2000
Dosage Interval (hours)	18.5 (8)	8-48
Trough Measured At Time of Level (mcg/ml)	9.6 (3.9)	1.5-22.4
Predicted Trough Using Matzke Elimination Rate Constant (0.00083*creatinine clearance + 0.0044)	11 (3.2)	3.6-19.5
Predicted Trough Using Updated Equation (0.00107*creatinine clearance*1.73/Surface Area) +0.005216005	9.3 (3.2)	1.8-19.9

Ideal body weight and body surface area were calculated for each patient using the Devine and DuBois & DuBois formulas respectively. The program currently uses Cockcroft-Gault equation with ideal body weight and actual serum creatinine to calculate creatinine clearance. The current volume of distribution is 0.65 l/kg of total body weight.

One compartment, open model, pharmacokinetic dosing equations were incorporated into the spreadsheet and were used to calculate the predicted trough for each patient using their individual data. A nonlinear fitting routine to minimize the sum of the square of the errors, sum of $(\text{actual level-predicted level})^2$, was used to optimized pharmacokinetic parameters. The parameters that were optimized are bolded in the equations below. Actual serum creatinine values were used and were not adjusted upward when they were less than 1 mg/dl. The following equations were optimized during the fittings.

Creatinine clearance (ml/min or ml/min/1.73 Meters^2)

$= (140\text{-age})^* [\text{IBW} + ((\text{TBW-IBW})^*\mathbf{Fat\ Factor})]^* \mathbf{(1.73/SA_{patient})^{1\ or\ 0}} / (72 * \text{Serum creatinine}_{mg/dl})$

When the exponent is set to 0 the result for the quantity within the parentheses is equal to 1.

Vd (liters) = $\mathbf{Vd_{l/kg}}$ *total body weight

K (hours-1) = **slope** * $\mathbf{Clcr_{ml/min\ or\ ml/min/1.73\ M^2}}$ + **intercept**

Predicted level (mcg/ml) = $\text{Dose}_{mg} (1-e^{-k*t'}) *e^{-k*(Tau-t')} / [\text{TBW}*\text{Vd}_{l/kg}*k*t'*(1-e^{-k*Tau})]$

k = elimination rate constant (hour^{-1})

t' = infusion period (hours)

Tau = Dosage Interval (hours)

IBW = Ideal Body Weight (kg)

TBW = Total Body Weight (kg)

$SA_{patient}$ = Surface Area (M^2)

When the fat factor was optimized its limits were set to a range of $\geq$ 0 and $\leq$ 1.
When Vd (l/kg) was optimized its limits were set to a range of $\geq$ 0.3 and $\leq$ 1.3.
When surface area was included in the equation the exponent was set to 1.
When the slope of elimination rate was optimized its limits were set to a range of $\geq$ 0.0001 and $\leq$ 0.002
When the intercept to the elimination rate was optimized its limits were set to a range of $\geq$ 0 and $\leq$ 0.01

Results:

- Data fittings that did not include the patient's body surface area all gave similar results and were an improvement over the current model with the exception of the fitting including a fixed fat factor of 0.4 which made predictions worse. Allowing the fat factor and/or Vd (l/kg) to be included in the fitting did not improve the results.
- When the patient's surface area was included in the equation the data fittings improved and bias related to weight, height, and the patient's body surface area were minimized. Including the fat factor with the surface area factor did not improve the fitting and setting the fat factor to 0.4 made predictions worse.

The selected equation to update the dosing program is bolded below:

K (hours-1) = 0.00107 * $Clcr_{ml/min}$ *(1.73/$SA_{patient}$) + 0.005216005

The programs equation for creatinine clearance will remain unchanged as the surface area factor may be incorporated into the elimination rate constant equation above and will give the same results without impacting the dosage calculations in the aminoglycoside program.

The following equations will remain unchanged.

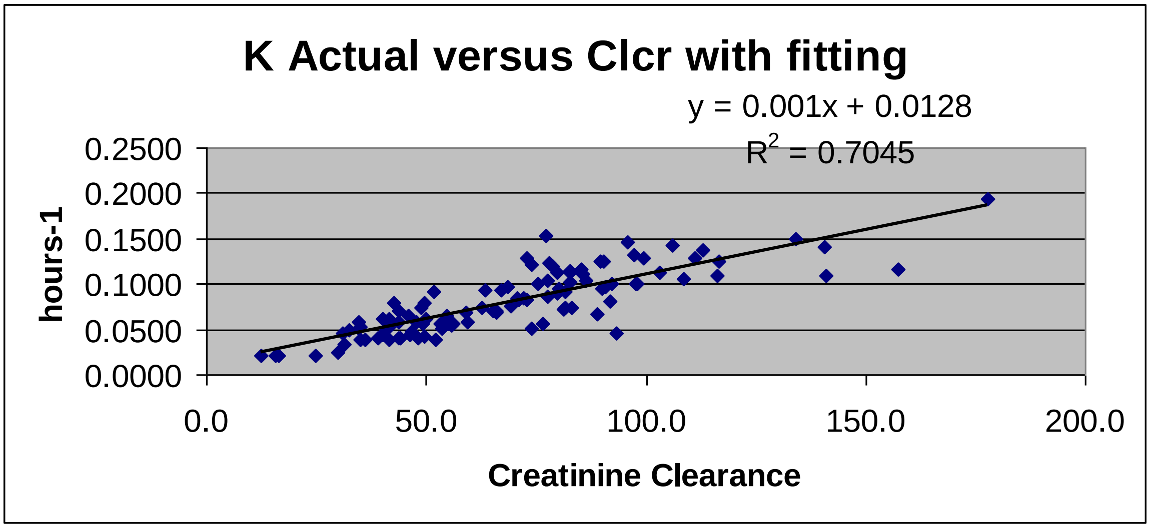
Clcr (ml/min) = [(140-age)* Ideal Body Weight / (72 * Serum creatinine)] , * 0.85 if female

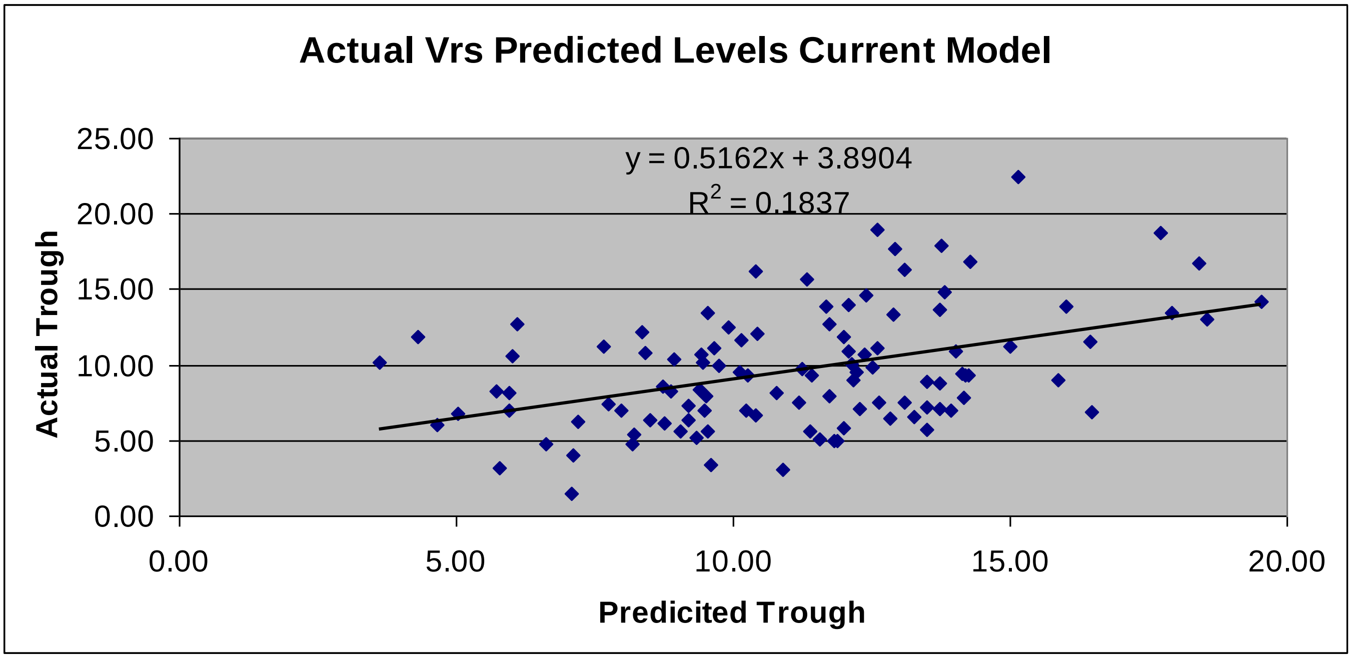
Vd (liters) = 0.65 l/kg *total body weight

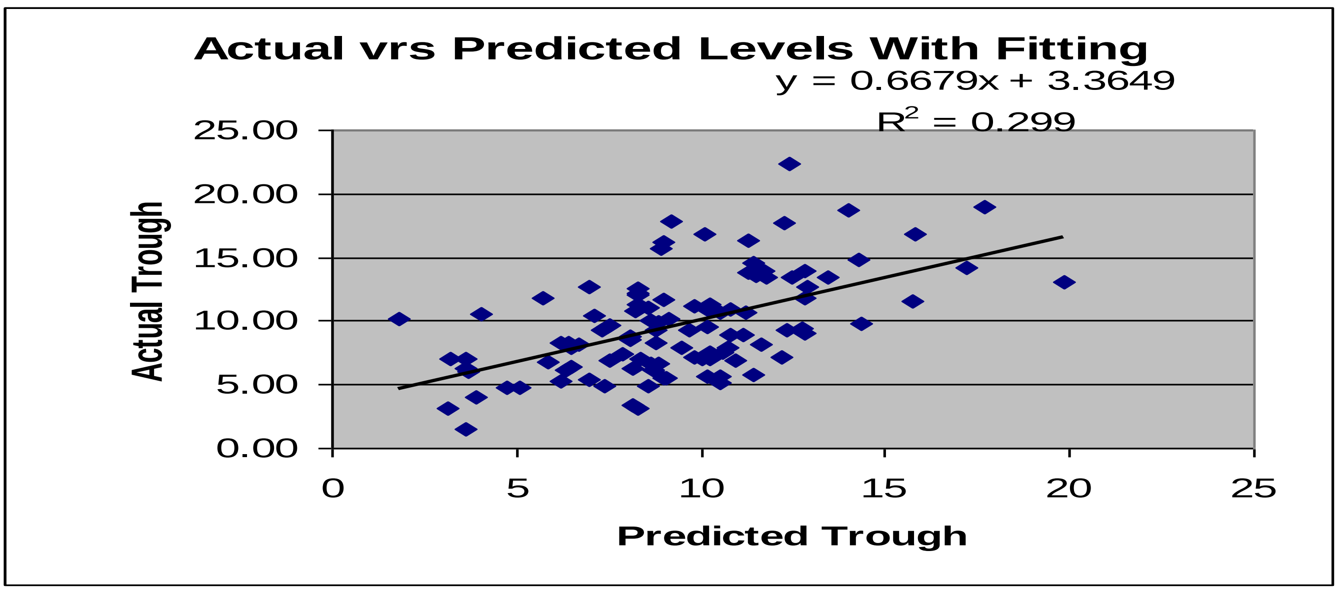
The results of data fitting 6 will not be used to optimize the program as incorporating a Vd of 1.3 l/kg would cause the loading dose calculated to double from 20-25 mg/kg to 40-50 mg/kg, which is unreasonable. The vast majority of studies have found a Vd of around 0.65 l/kg. The Vd value of 1.3 l/kg could potentially cause the user to select a large maintenance dose to be given at long dosing intervals.

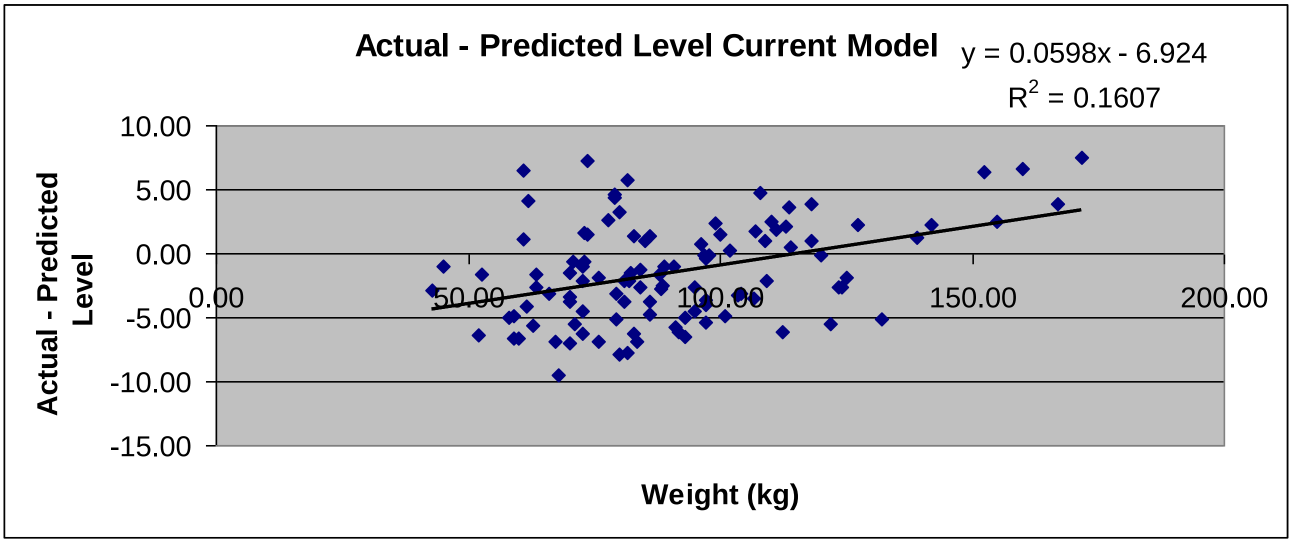
Data Fittings:
The following data fitting were performed. The fit results for the parameters are noted.

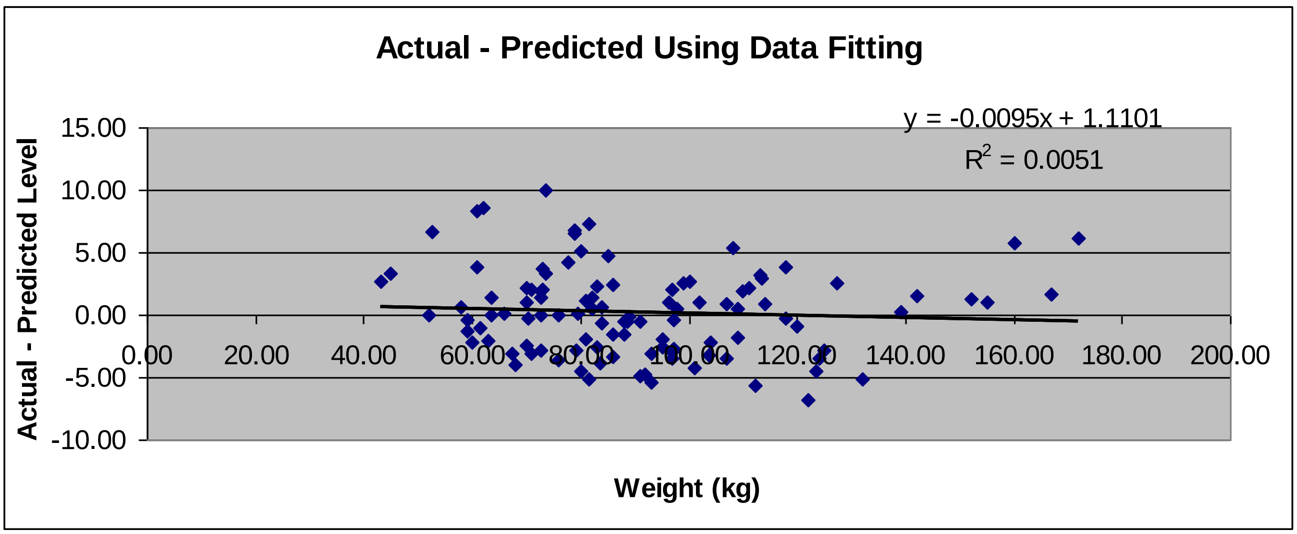
Fittings	Vd (l/kg)	Elimination Rate Constant Slope	Elimination Rate Constant Intercept	Fat Factor	Surface Area Factor	(Actual-Predicted) Average **Bias**	(Actual-Predicted) Standard Deviation	Sum of (Actual-Predicted) *Bias*	Absolute of (Actual-Predicted) Average	Absolute of (Actual – Predicted) Standard Deviation	**RMSE Accuracy**	Sum of Absolute (Actual - Predicted) *Precision*	Sum of Square of Errors (Actual – Predicted)^2
Current Model	0.65	0.00083	0.0044	Not Used	No Used	-1.49	3.86	-159	3.5	2.2	4.10	374	1821
1	0.65 Fixed	Fit Value 0.000896	Fit Value 0.00663531	Not Used	Not Used	0.26	3.7	27.7	3.1	2.1	3.679	327	1461
2	0.65 Fixed	Fit Value 0.000896	Fit Value 0.00663531	Fit Value 0	Not Used								
3	Fit Value 1.3	Fit Value 0.000565	Fit Value 0.003907852	Fit Value 0	Not Used	0.18	3.6	19.4	3	2.1	3.615	319	1410
4	0.65 Fixed	Fit Value 0.001053	Fit Value 0.005126106	Fit Value 0.039709	1.73/SA	0.24	3.4	25.6	2.74	2.1	3.413	294	1257
5	0.65 Fixed	Fit Value 0.00107	Fit Value 0.005216005	Fit Value 0	1.73/SA	0.23	3.4	24.4	2.72	2.1	3.419	291	1261
6	Fit Value 1.3	Fit Value 0.000674	Fit Value 0.002908673	Fit Value 0	1.73/SA	0.14	3.2	15.3	2.68	2	3.294	287	1171
7	0.65 Fixed	Fit Value 0.000772	Fit Value 0.008617933	0.4 Fixed	Not Used	0.52	4.2	55.7	3.37	2.54	4.2	360	1902
8	0.65 Fixed	Fit Value 0.000926	Fit Value 0.005627497	0.4 Fixed	1.73/SA	0.33	3.7	34.9	2.92	2.3	3.64	312	1436

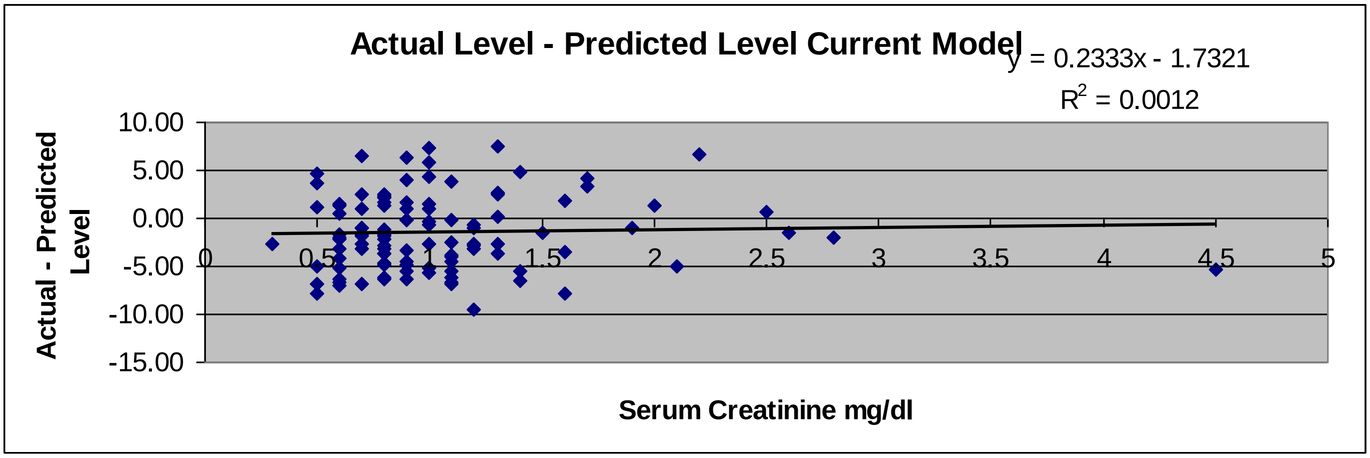

K Actual versus Clcr with fitting
y = 0.001x + 0.0128
R2 = 0.7045
hours-1
0.2500
0.2000
0.1500
0.1000
0.0500
0.0000
0.0
50.0
100.0
150.0
200.0
Creatinine Clearance

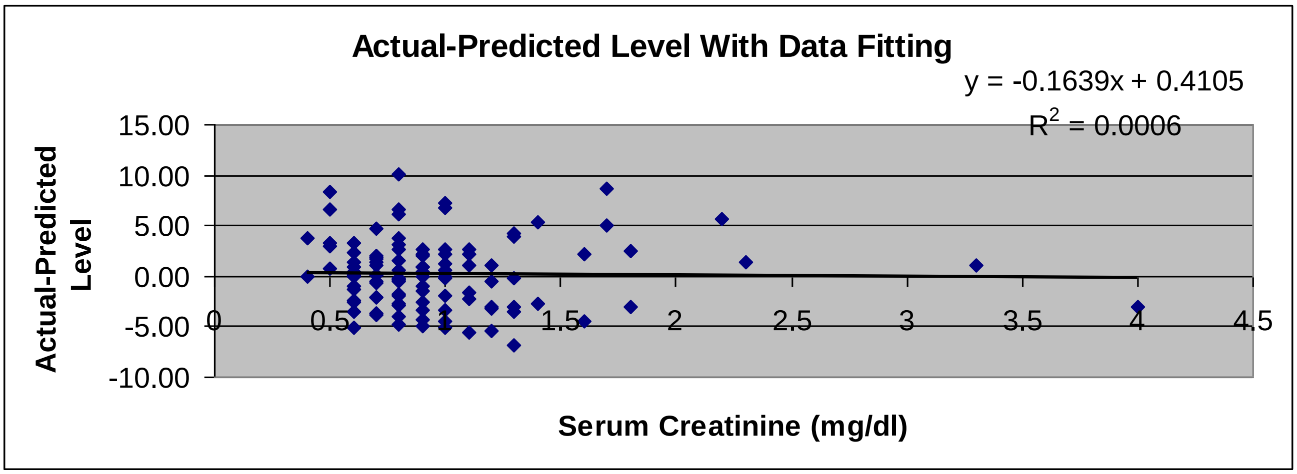

Actual Vrs Predicted Levels Current Model
y = 0.5162x + 3.8904
R2 = 0.1837
Actual Trough
25.00
20.00
15.00
10.00
5.00
0.00
0.00
5.00
10.00
15.00
20.00
Predicited Trough

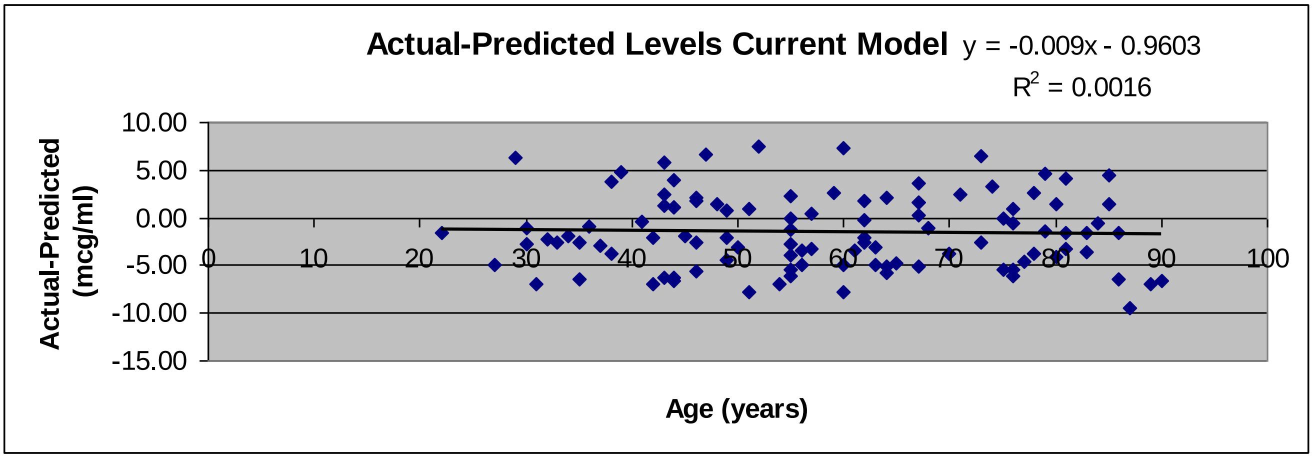

Actual vrs Predicted Levels With Fitting
y = 0.6679x + 3.3649
R2 = 0.299
Actual Trough
25.00
20.00
15.00
10.00
5.00
0.00
0
5
10
15
20
25
Predicted Trough


Actual - Predicted Level Current Model
y = 0.0598x - 6.924
R2 = 0.1607
10.00
5.00
0.00
-5.00
-10.00
-15.00
0.00
50.00
100.00
150.00
200.00
Actual - Predicted Level
Weight (kg)

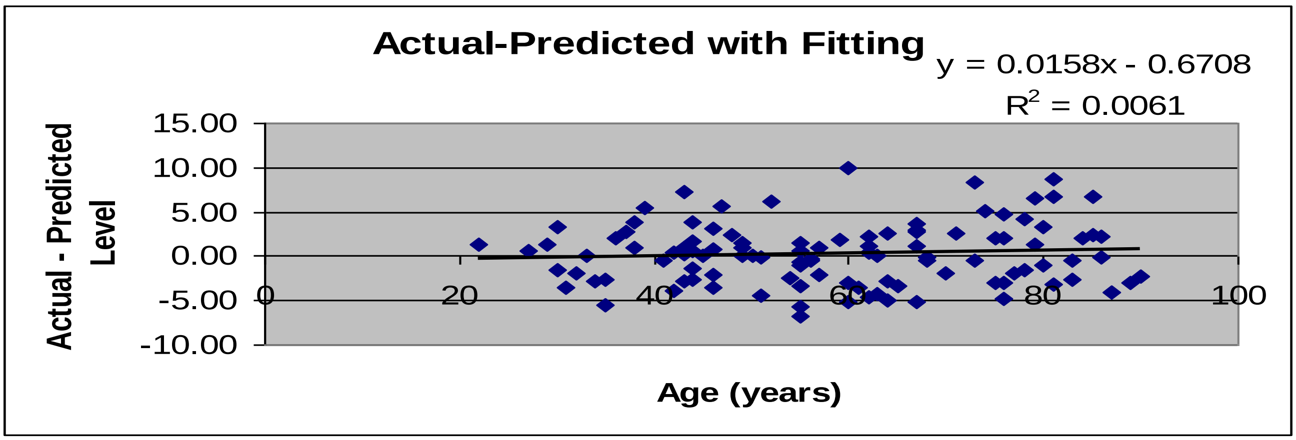

Actual - Predicted Using Data Fitting
y = -0.0095x + 1.1101
R2 = 0.0051
15.00
10.00
5.00
0.00
-5.00
-10.00
0.00
20.00
40.00
60.00
80.00
100.00
120.00
140.00
160.00
180.00
200.00
Actual - Predicted Level
Weight (kg)


Actual Level - Predicted Level Current Model
y = 0.2333x - 1.7321
R2 = 0.0012
Actual - Predicted Level
Serum Creatinine mg/dl
10.00
5.00
0.00
-5.00
-10.00
-15.00
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

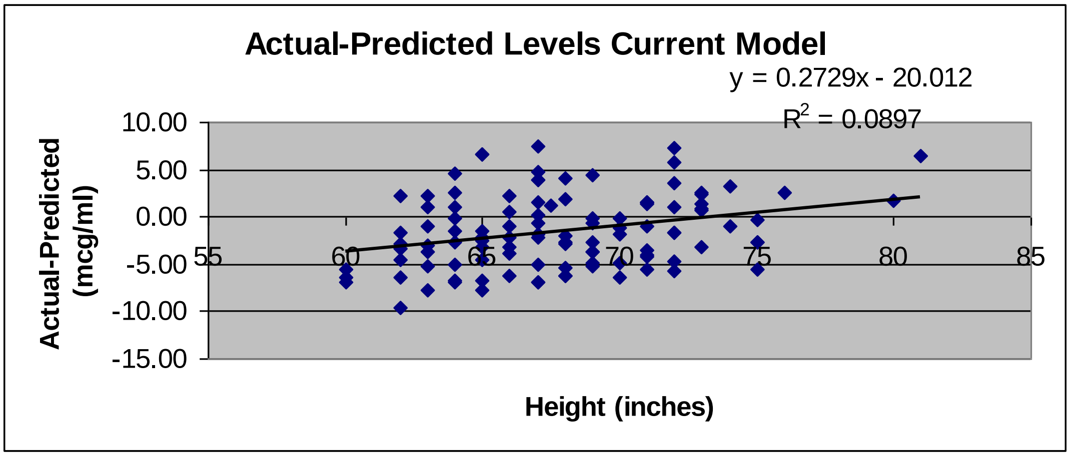

Actual-Predicted Level With Data Fitting
y = -0.1639x + 0.4105
R2 = 0.0006
Actual-Predicted Level
Serum Creatinine (mg/dl)
15.00
10.00
5.00
0.00
-5.00
-10.00
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5

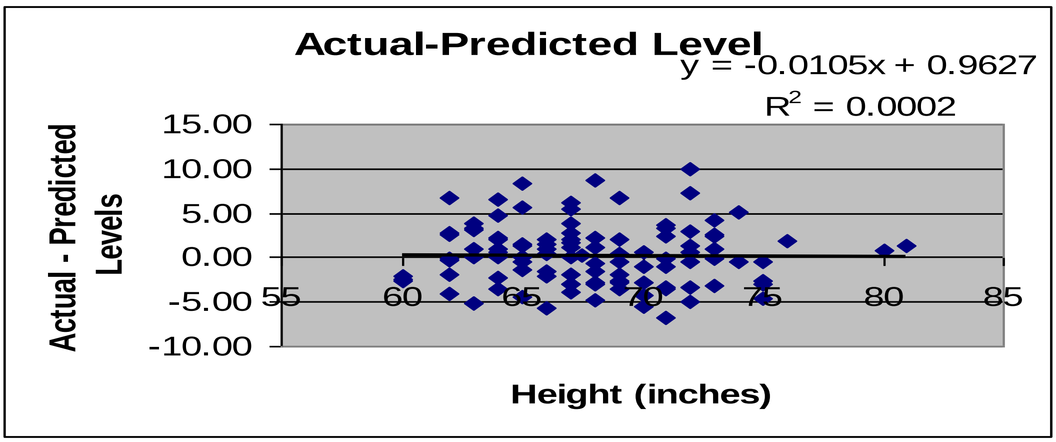


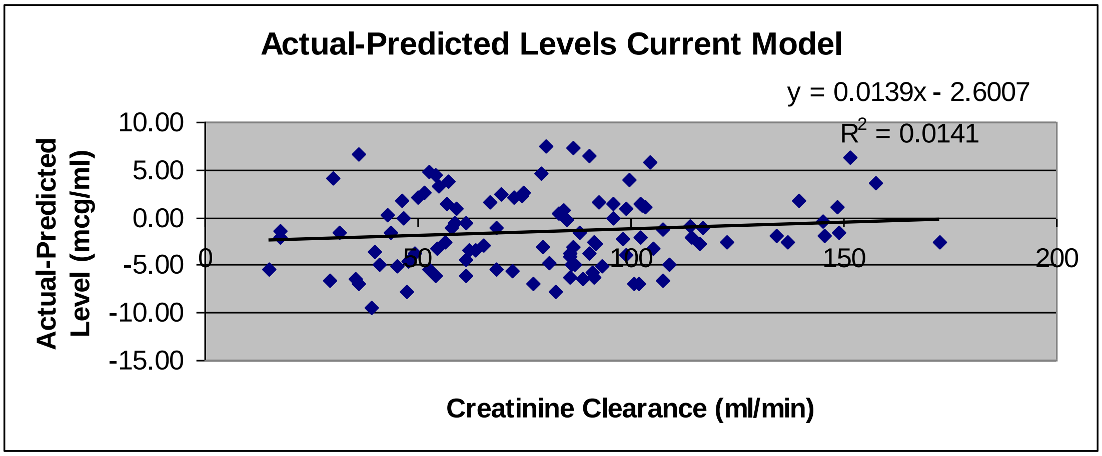
Actual-Predicted Levels Current Model
y = -0.009x - 0.9603
R2 = 0.0016
Actual-Predicted (mcg/ml)
10.00
5.00
0.00
-5.00
-10.00
-15.00
0
10
20
30
40
50
60
70
80
90
100
Age (years)

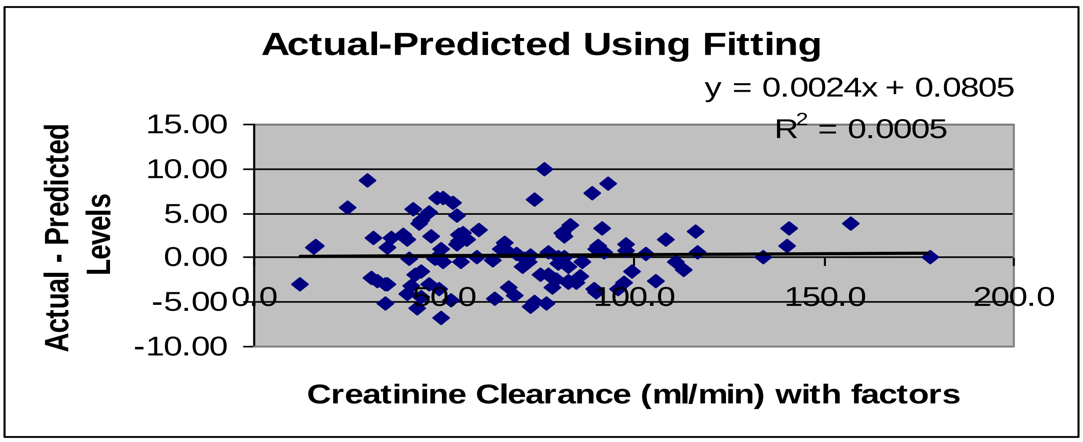


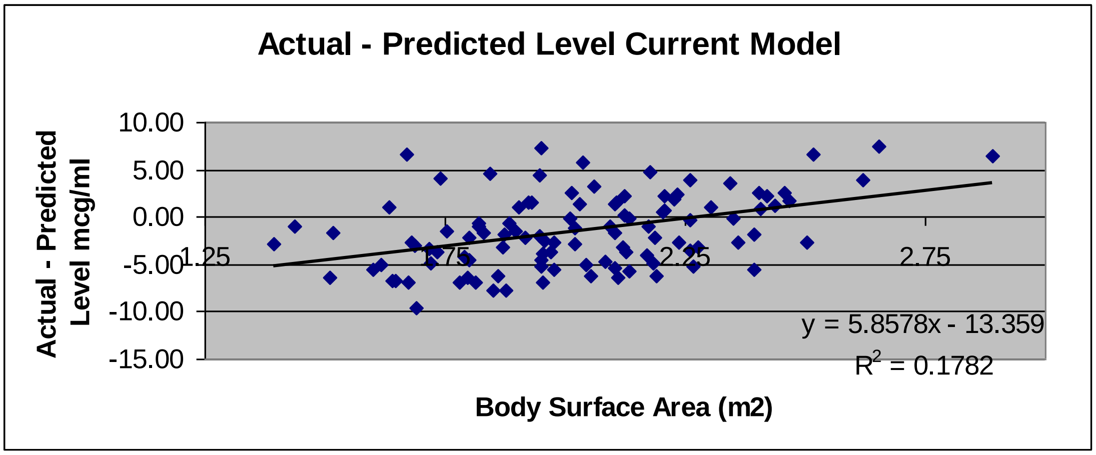
Actual-Predicted with Fitting
y = 0.0158x - 0.6708
R2 = 0.0061
Actual - Predicted Level
15.00
10.00
5.00
0.00
-5.00
-10.00
0
20
40
60
80
100
Age (years)

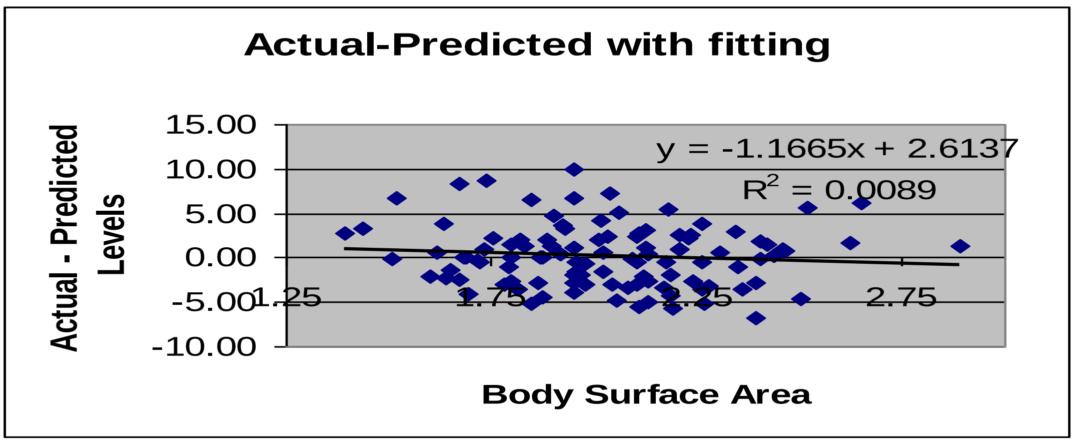

Actual-Predicted Levels Current Model
y = 0.2729x - 20.012
R2 = 0.0897
Actual-Predicted (mcg/ml)
10.00
5.00
0.00
-5.00
-10.00
-15.00
55
60
65
70
75
80
85
Height (inches)


Actual-Predicted Level
y = -0.0105x + 0.9627
R2 = 0.0002
Actual - Predicted Levels
15.00
10.00
5.00
0.00
-5.00
-10.00
55
60
65
70
75
80
85
Height (inches)


Actual-Predicted Levels Current Model
y = 0.0139x - 2.6007
R2 = 0.0141
Actual-Predicted Level (mcg/ml)
10.00
5.00
0.00
-5.00
-10.00
-15.00
0
50
100
150
200
Creatinine Clearance (ml/min)


Actual-Predicted Using Fitting
y = 0.0024x + 0.0805
R2 = 0.0005
Actual - Predicted Levels
15.00
10.00
5.00
0.00
-5.00
-10.00
0.0
50.0
100.0
150.0
200.0
Creatinine Clearance (ml/min) with factors


Actual - Predicted Level Current Model
Actual - Predicted Level mcg/ml
10.00
5.00
0.00
-5.00
-10.00
-15.00
1.25
1.75
2.25
2.75
y = 5.8578x - 13.359
R2 = 0.1782
Body Surface Area (m2)


Actual-Predicted with fitting
Actual - Predicted Levels
15.00
10.00
5.00
0.00
-5.00
-10.00
1.25
1.75
2.25
2.75
y = -1.1665x + 2.6137
R2 = 0.0089
Body Surface Area