Comparison of Vancomycin Dosing Predictions for A One-Compartment Open Model Versus Optimized Goti and Carreno Two-Compartment Open Models

3/2023

Background:
The current pharmacokinetic one-compartment open model vancomycin dosing program's equations for elimination rate constant and distribution volume have been used since 6/2007. A change in the dosing program was implemented at that time due to over prediction of doses for heavy patients and the under-prediction of doses for low-weight patients. The former version used kinetic parameters published by Matzke. Pharmacokinetic analysis of l07 patients with steady-state serum levels was used to optimize the equations for calculating the elimination rate and volume of distribution by minimizing the sum of the square of errors for actual versus predicted levels. Several further analyses at later dates did not demonstrate a need to further refine the equations. The program is implemented in Excel and allows for data fitting of multiple levels with changing doses and intervals under steady-state or non-steady-state conditions using the method of superposition.

Optimized clearance values for the two-compartment Carreno and Goti models were derived in a prior retrospective MUE of 801 patients dosed whose demographic, serum creatinine, dosing and serum level history, and steady-state levels were available.

Two-compartment versus one-compartment models

- One-compartment models have two independent variables, the volume of distribution and clearance. One-compartment models are easier to characterize, understand, implement in dosing tools, less prone to programming errors due to fewer and less complex equations, and data analysis is easier than two-compartmental models.
- Two-compartment models have four independent variables, clearance, interdepartmental clearance, volume of distribution of the central compartment, and volume of distribution of the peripheral compartment. A data-rich sampling scheme is necessary to adequately characterize the four pharmacokinetic parameters with numerous serum levels required during both the distribution and elimination phases. The Goti model was <u>not</u> developed with intensive serum sampling and is better termed a pseudo-two-compartment model or computer-generated two-compartment model. This creates an overly parameterize model, as the parameters have not been determined, but are assumed. The Goti model was derived from critical care patients with 67% of patients having one, 20.8% having two, 7.6% having three, 2.9% having four, and 1.1% having five serum level determinations. The Carreno model was derived from a small data set of twelve obese patients with an average BMI of 45. The patients had five serum levels drawn at the following times post-infusion, 1, 2, 4, 6 hours, and one level at the end of the dosing interval.

Purpose of Present Analysis:
Vancomycin serum level trough predictions for the current one-compartment open model and the optimized Carreno and Goti two-compartment open models will be compared in a retrospective MUE. The population-predicted steady-state levels will be compared with actual steady-state levels. Two separate analyses will be performed, one for patients with a BMI < 30 and one for patients with BMI <u>≥</u> 30. The breakpoint of 30 was picked as the Goti model appeared to perform poorly with higher BMIs during routine clinical use.

Endpoints:

- Primary endpoints: Comparison of the dosing methods prediction error as noted by analysis of the Sum of Square Errors, Root Mean Square Error, and Bias for serum levels and AUCs predictions.
- Secondary endpoints:
    - Comparison of percentages of the population predicted trough levels falling in the categories of less than equal to 5 mcg/ml, greater than or equal to 5 to < 10 mcg/l, and greater than equal to 10 mcg/ml of the actual state levels for the dosing methods.
    - Comparison of percentage of the population predicted AUCs (mg/hour/liter per day) falling in the categories of less than equal to 100, greater than 100 and less than 200, and greater than or equal to 200 of actual AUCs for the dosing methods.
    - Comparison of calculated clearance for each dosing method.
    - Comparison of the dosing methods prediction errors for patients with both and peak and trough
    - Comparison of clearance calculated for one compartment model for peak and trough pair versus trough only.

Methods:

- Retrospective pharmacokinetic analysis of patients receiving vancomycin from 8/8/22 to 1/22/23.
- Subjects are divided into two groups for analysis, BMI less than 30 and BMI greater than or equal to 30.
- Study participants were identified using the pharmacy department's pharmacokinetic dosing and monitoring tool.
- Inclusion criteria:
    - patients who were admitted as inpatients, who received vancomycin with at least one trough drawn.
    - Patients were included in the study more than once if they had multiple hospital stays during the study review period.
- Exclusion criteria: amputation, malnutrition, continuous renal replacement therapy, and hemodialysis.
- De-identified data collected: patient demographics, serum creatinine(s), dosing, and serum level history.
- Pharmacokinetic Models:
    - One and two-compartment open model equations were used to calculate the steady-state levels for each patient's dosing regimen using population parameters and fit parameters based on serum levels. The patient's demographics, dosing history, and serum levels were input into one and two-compartment open models, and nonlinear data fittings were performed in Excel using the method of superposition.
    - Population Prediction Equations for One Compartment Open Model
      Ideal Weight(kg) =
        Males = 2.3* (Height Inches - 60) + 50 kg
        Female = 2.3* (Height Inches - 60) + 45.5 kg
      Creatinine Clearance (ml/min/1.73 meters squared)
        Males = [(140-Age(years)) * (Lesser of Ideal Weight or Actual Weight) / (72*Serum Creatinine(mg/dl))] *1.73/ Body Surface Area
        Female = 0.85 * above
      K(1/hours) = 0.00107*Creatinine Clearance per 1.73 Meters Squared + 0.0052
      Vd(Liters) = 0.65 L/kg * Total Body Weight
      Cp Steady State Trough(mg/L) = MD*(1-exp(-K*Infusion Period)) * Exp(-(K*(Tau-T')) / ((Vd*K*Infusion Period)(1-exp(-K*Tau)))
    - Optimize Parameter Population Prediction Equations for Two Compartment Open Model with Central Compartment Elimination
      Creatinine Clearance (ml/min)
        Males = ((140-Age(years))*(Total Body Weight if less than 1.2 * Lean Body Weight or Adjusted Body Weight if Total Body Weight >= 1.2*Lean Body Weight) / (72*Serum Creatinine(mg/dl))

Female = 0.85 * above

Goti Equations (clearance optimized in prior MUE)

Clearance (L/hr) = 6.4 L/hour (creatinine clearance/120)$^{0.8}$

Vd central (Liters) = 58.4 liters * (weight(kg)/70)

Vd peripheral (Liters) = 38.4 liters * (weight(kg)/70)

Q (L/hr) = 6.5

Carreno Equations (clearance optimized in prior MUE)

Clearance (L/hr) = 0.043292 L/hour * creatinine clearance + 0.331123 L/hour

Vd central (Liters) = 25.76 liters

Vd peripheral (Liters) = Q/K21= 2.29 1/hour * 25.76 Liters / 1.44 1/hour = 40.97 Liters

Q (L/hr) = K12*Vc = 2.29 L/hour * 25.76 Liter

K12 (1/hour) =2.29

K21 (1/hour) = 1.44

Cp Steady State Trough = [D*(K21-alpha)(1-exp(-alpha*Infusion Period))*exp(-alpha*(Tau-T')) / (Vc * alpha*(beta-alpha))] *1/(1-exp(-alpha *Tau) +

[D (beta-K21) *(1-exp(-beta*Infusion Period)*exp(-beta*(Tau-T')) / (Vc*beta(beta-alpha))] * 1/(1-exp(-beta*Tau)

- Statistical Analysis
  - Sum of Square of Errors = $\sum_{1 \text{ to } N}$ (Steady State Predicted Level for Population-Based Dosing Method – Patient Steady State Level)^2
  - Bias = $\sum_{1\text{-}N}$ (Steady State Predicted Level for Population-Based Dosing – Patient Steady State Level) / N
  - Root Mean Squared Error = ($\sum_{1\text{-}N}$ (Steady State Predicted Level for Population-Based Dosing Method – Patient Steady State Level)^2 / N)$^{0.5}$
- Primary and secondary outcomes will be analyzed using descriptive statistics.

Demographic Date (average (Standard Deviation or numeric range)	
Total Patients	173
Total Levels	334
Age (Years)	65.6 (15.6)
Male	54.8%
Weight (kg)	91.4 (28.6)
Height (Inches)	67.4 (4.4)
Lean Body Weight (kg)	64.2 (12.5)
BMI (kg/M2)	30.9 (8.5)
Body Surface Area (Meters2)	2.0 (0.33)
Serum Creatinine (mg/dL)	1.3 (0.22-9.54)
Creatinine Clearance ml/min per 1.73 m^2)	51.8 (4.9-129)

Demographic Date (average (Standard Deviation or numeric range)		
	BMI less than 30	BMI $\geq$ 30
Number of Patients reviewed	87	86
Serum Levels		
Age (years)	67.2 (16.3)	64 (14.8)
Male	62.1 %	54.7%
Weight (kg)	71.7 (16.4)	111.3 (24.2)
Height (inches)	67.2 (4.2)	67.7 (4.5)
Lean Body Weight (kg)	62.7 kg (12.7)	65.8 (12.3)
BMI (kg/M2)	24.4 (4.1)	37.5 (6.4)
Body Surface Area	1.83 (0.25)	2.2 (0.28)
Serum Creatinine (mg/dL)	1.25 (0.22-9.45)	1.39 (0.36-4.9)
Creatinine Clearance ml/min per 1.73 M^2	57.3 (11.9-129)	46.2 (4.9-115.5)

- Analysis of Pharmacokinetic Models:

Model & Patient Group	**Sum of Square of Errors**	**Bias**	**Precision Root Mean Squared Error**	Predicted versus Actual Trough means (SD)	Absolute (Predicted - Actual) <= 5	Absolute (Predicted- Actual) >5 - <10	Absolute (Predicted - Actual) >= 10
All Patients **N**=173 Total Fittings =333 1st Fitting =173							
1 compartment Model				13.7 (6) Vrs			
All Fitting	13,102	**1.3**	**6.3**	12.4 (5.5)	62.5%	26.4	11.1
1st Fitting	6,446	**2.47**	**6.09**	13.6(5.9) Vrs 11.2(5.4)	65.7%	21.1%	13.2%
Goti Optimized 2 Compartment				12.5 (4.2) Vrs			
All Fittings	321, 907	**-10.9**	**31.1**	23.3 (29.5)	48.2%	27.3%	24.6%
1st Fitting	253,588	**-14.4**	**38.2**	12.4(4) Vrs 26.7 (36)	52.9	30.7	16.5
Carreno Optimized 2 Compartment Optimized				14.48(5.5) Vrs			
All Fittings	64,134	**0.26**	**13.86**	14.2 (13.9)	59.3%	29%	11.7%
1st Fitting	32,390	**1.03**	**13.8**	14.4(5.5) Vrs 13.4(14)	66.5%	24.3%	9.2%
BMI < 30 Patients =86 Total Fitting =166 1St Fitting =86							
1 Compartment Model BMI < 30				14(7.1) Vrs			
All Fittings	7633	**2.52**	**6.8**	11.5(5.5)	63%	22.3%	14.5%
1st Fitting	3454	**3.37**	**6.35**	13.6(6.8) Vrs 10.3(5.1)	65.1%	18.6%	16.3%

Model & Patient Group	**Sum of Square of Errors**	**Bias**	**Precision Root Mean Squared Error**	Predicted versus Actual Trough means (SD)	Absolute (Predicted - Actual) <= 5	Absolute (Predicted- Actual) >5 - <10	Absolute (Predicted - Actual) >= 10
Goti Optimized 2 Compartment BMI < 30				11.8 (4.3) Vrs			
All Fittings	107,394	**-7.94**	**25.4**	19.7(24.8)	50.%	28.3%	21.7%
1st Fitting	79,011	**-10.2**	**30.3**	11.4(4.1) Vrs 21.6(29.5)	56.1%	29.1%	14.9%
Carreno Optimized 2 Compartment BMI < 30				14.7(6) Vrs			
All Fittings	32,640	**0.47**	**14**	14.2(14.2)	60.8%	26.5%	12.7%
1st Fitting	29,342	**-0.25**	**18.5**	14.2(5.7) Vrs 14.5(19)	71%	20.4%	8.6%
BMI >=30 Patients =85 Total Fittings =165 1St fitting=85							
1 Compartment Model BMI >= 30				13.4(4.6)			
All Fittings	5459	**0.11**	**5.75**	Vrs 13.3(5.3)	61.2%	30.9%	7.9%
1st Fitting	2981	**1.64**	**5.9**	13.5(4.8) Vrs 11.9(5.3)	64.7%	24.7%	10.6%
Goti Optimized 2 Compartment Model BMI >=30				13.1(3.8) Vrs			
All Fittings	214,514	**-14**	**36**	27.1(33.4)	45.5%	26.7%	27.8%
1st Fitting	174,568	**-19.2**	**45.3**	13.2(4) Vrs 32.3	49.1%	32.7%	18.2%
Carreno Optimized 2 Compartment Model BMI >=30				14.23(4.9) vrs			1
All Fittings	31,494	**0.04**	**13.8**	14.19(13.6)	56.7%	32.1%	10.9%
1st Fitting	3,587	**2.37**	**6.5**	14.39(5.2) Vrs 12 (5.6)	60.7%	29.2%	10.1%

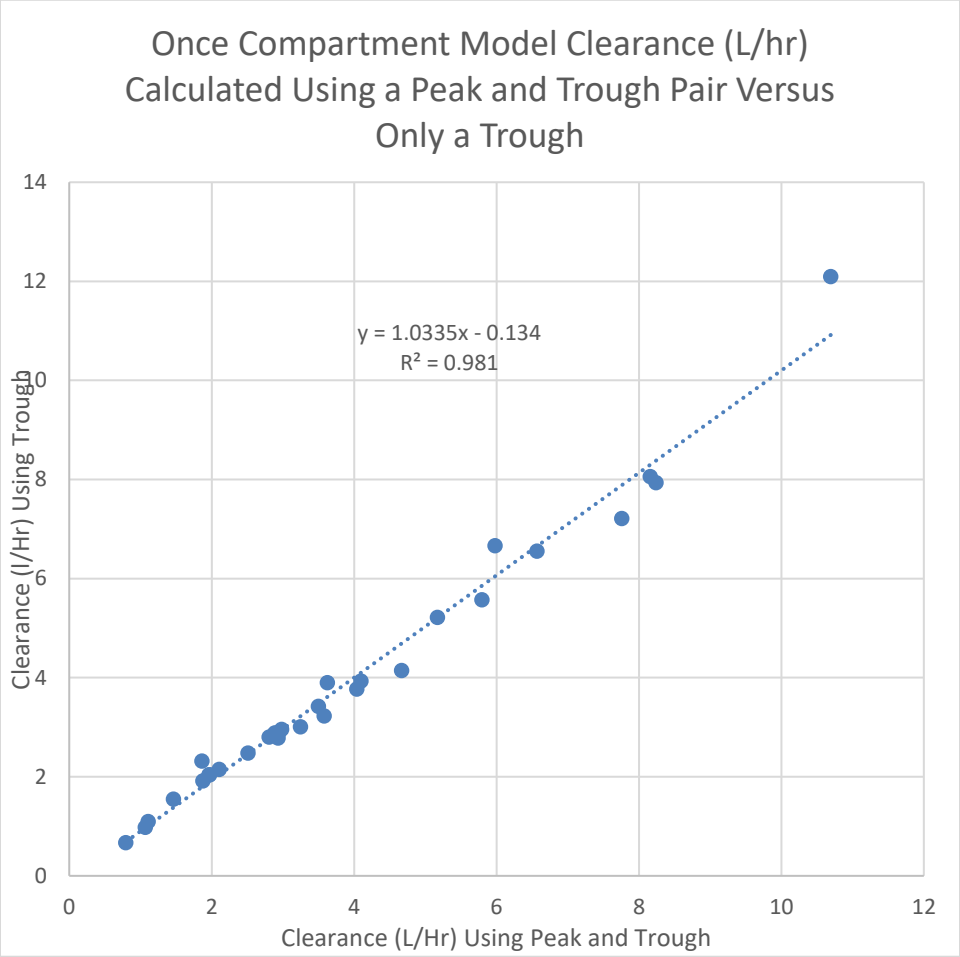
Average Clearance (L/hr) (SD) Calculated by Model at Each Data Fitting					
Model	Cl 1st Fitting	Cl 2nd Fitting	Cl 3rd Fitting	Cl 4th Fitting	Cl 5 Fitting
Number of Patients	174	97	43	17	3
One Compart.	4.08 (2.23)	4.2 (2.49)	3.62 (1.91)	3.71 (1.28)	3.12 (0.37)
Goti Two Compt.	3.56 (2.54)	4.05 (2.54)	3.57 (2.09)	3.86 (1.4)	2.63 (1.26)
Carreno Two Compt.	4.0 (2.12)	4.17 (2.36)	3.54 (1.87)	3.69 (1.24)	2.66 (0.62)
Creatinine Clearance ml/min/1.73 M^2	51.8	56.8	54.1	62.4	66.7
Paired T-Test Two-tailed Clearance Comparison for All Fitting					
One Compt Vrs Carreno	P=0.035	One Compt Vrs Goti	P=5.99 E-08		

Data Fittings for Patients with a Peak and Trough Pair (Populations Predicted Versus Actual Level Levels) For Current One Compartment and Optimized Goti and Carreno Two Compartment Models.					
	Clearance	SSE	RMSE	Bias Peak	Bias Trough
One Compartment Model N =33 Mixed BMI	Cl (l/hr/kg) =0.0006955*Clcrper1.73M2 - 0.00338	3262	13.8	2.3	0.21
One Compartment Model N =14 BMI < 30		1886	15.7	7.4	3.8
One Compartment Model N =19 BMI > 30		1377	12	-1.4	-2.4
Goti N=33 Mixed BMI	Cl L/hr= (6.4*Creatinine Clearance/120)$^{0.8}$	29325	42	-11.4	-7.1
Goti N=14 BMI < 30		1897	16	-7.2	-3.5
Carreno N=33 Mixed BMI	Cl L/hr=0.043292*Creatinine Clearance + 0.331123	3524	14.6	3.4	3.2
Carreno N=14 BMI < 30		1831	16.2	4.3	5.6
Carreno N =19 BMI >=30		1698	13.2	2.3	1.04

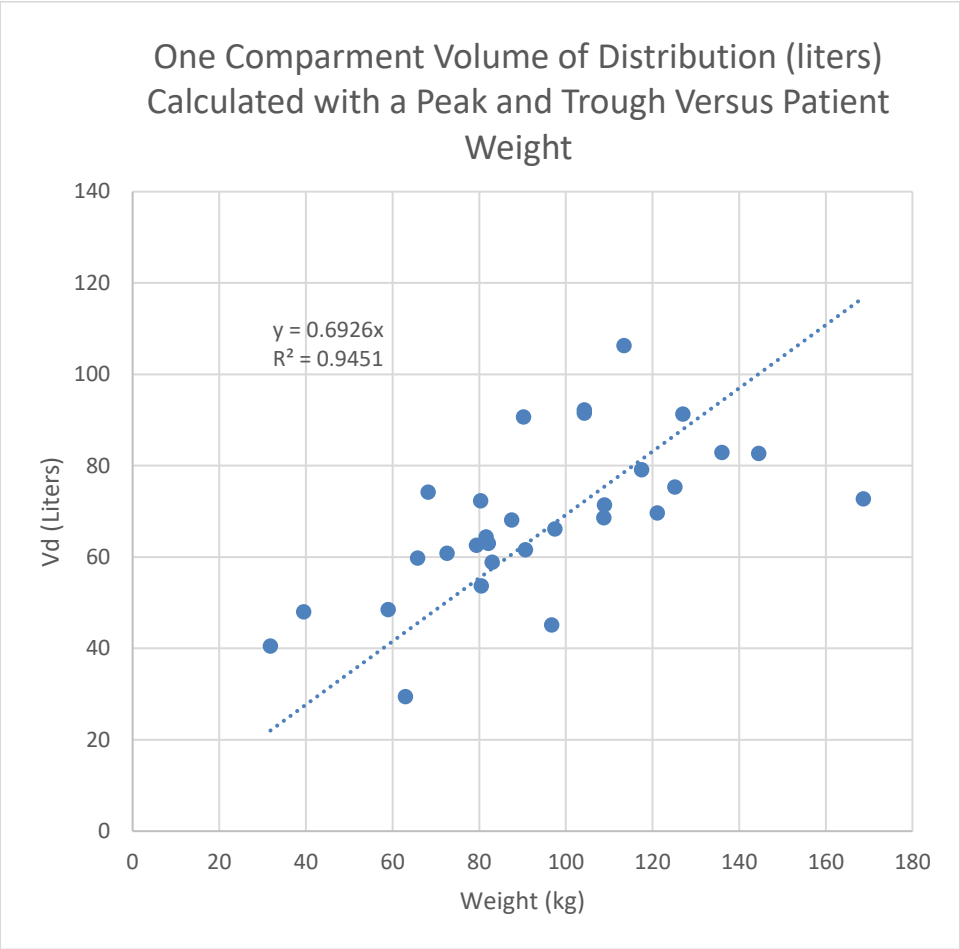
Model & Patient Group	**Sum of Square of Errors**	**Bias**	**Precision Root Mean Squared Error**	Predicted Versus Actual AUC Means (SD)	Absolute (Predicted -Actual) AUC <=100	Absolute (Predicted -Actual) AUC 100 - <200	Absolute (Predicted -Actual) AUC >= 200
All Patients N=173 Fittings = 333							
1 Compartment Model 1st Fitting	4,262,985	64	157	490 (160) Vrs 425 (144)	53%	27.4%	19.4%
All Fittings	8,658,671	36.4	161	493(166) Vrs 457(146)			
Goti Optimized 2 Compartment 1st Fitting	147,127,119	-349	920	398(106) Vrs 748(866)	59.3%	15.9%	24.9%
All Fittings	187,163,938	-266	749	403(109) Vrs 639(706)			
Carreno Optimized 2 Compartment 1st Fitting	19,649,865	28.6	335	486(138) Vrs 457(335)	51.5%	28.3%	20.2%
All Fittings	37,861,668	8.7	337	490(139) Vrs 481(333)			
BMI < 30 N=86 Fitting 166							
1 Compartment Model 1st Fitting	2.321,113	88.5	164	508(182) Vrs 421(145)	57%	20.9%	22.1%
All Fittings	5,183,719	67.7	177	508(181) Vrs 421(146)			

Model & Patient Group	**Sum of Square of Errors**	**Bias**	**Precision Root Mean Squared Error**	Predicted Versus Actual AUC Means (SD)	Absolute (Predicted -Actual) AUC <=100	Absolute (Predicted -Actual) AUC 100 - <200	Absolute (Predicted -Actual) AUC >= 200
Goti Optimized 2 Compartment							
1st Fitting	45,952,480	-249	731	383(107) Vrs 631(708)	60.8%	15.4%	23.3%
All Fittings	62,562,098	-195	614	394(115) Vrs 589(594)			
Carreno Optimized 2 Compartment							
1st Fitting	17,094,420	-3.4	446	473(139) Vrs 476(449)	54.7%	25.6%	19.8%
All Fittings	19,152,274	13	340	476(452) Vrs 472(140)			
BMI >= 30 N=85 Fitting =165							
1 Compartment							
1st Fitting	1,941,871	43.8	151	467(132) Vrs 423(141)	47.1%	35.8%	17.6%
All Fittings	3,474,953	5.6	145	466(128) Vrs 460(141)			
Goti Optimized							
1st Fitting	101,174,639	-463	1091	409(104) Vrs 872(1000)	57.1%	16.5%	26.3%
All Fittings	124,601,840	-341	869	411(102) Vrs 752(800)			
Carreno Optimize							
1st Fitting	2,375,445	61.8	167	495(134) Vrs 433(147)	47.1%	31.8%	21.2%
All Fittings	18,709,394	4.5	337	494(128) Vrs 490(331)			

28 Data Fittings



28 Data Fittings



Conclusions

- The current one-compartment model is recommended as vancomycin pharmacokinetics are adequately described and it performs better than the Goti and Carreno two-compartment models.
- The one-compartment model outperformed the two-compartment models when both a peak and trough were drawn as noted by lower values for Root Mean Squared Error for predicted versus actual levels.
- The one-compartment model's calculated clearance values were similar using either a peak and trough pair or a trough as noted by linear regression analysis R^2 value of 0.981 for twenty-eight patients.
- The current one-compartment and optimized Carreno models are more accurate in predicting AUCs and serum levels regardless of BMI as demonstrated by lower values for the Sum of the Square of Errors, Bias, Root Mean Squared Error, and a higher percentage of AUCs and levels closer to the actual AUC and actual levels than the Goti model.
- The Goti model:
    - Is not recommended for use as is less accurate than the 1 compartment and optimized Carreno models in patients with BMI < 30 and BMI $\underline{\geq}$ 30. During data fitting of levels, it produces more variability in predicted levels and AUC than the other models. Inaccurate low clearance values may be calculated with unrealistically high predicted levels and AUCs when levels are fit after a load and/or a load and one or two maintenance doses or when there are large changes in levels in a short time frame.