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

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Background:
The current pharmacokinetic one compartment open model vancomycin dosing program's equations for elimination rate constant and volume of distribution has been in use since 6/2007. A change in the dosing program was implemented at that time due to over prediction of doses for high weight patients and under prediction of doses for low weight patients. The former version used kinetic parameters published by Matzke. A pharmacokinetic analysis of l07 patients with steady state serum levels was used to optimize the equations for calculating 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 previous dosed whose demographic, serum creatine, dosing and serum level history, and steady state levels were available.

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 prospective 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 $\geq$ 30. The break point 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 programs prediction error as noted by analysis of the Sum of Square Error, Root Mean Square Error, and Bias.
- Secondary endpoints: Comparison of percentages of population predicted 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.

Methods:

- Prospective pharmacokinetic analysis of patients receiving vancomycin from 2/15/21 to 3/30/22.
- 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 pharmacokinetic dosing and monitoring tool utilized by the pharmacy department.
- 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: patient with amputation, malnutrition, patient receiving 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/Surface Area

  Female = 0.85 * above

  K(1/hours) = 0.000107*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) = 6.04 L/hour (creatinine clearance/120)$^{\wedge 0.8}$

  Vcentral (Liters) = 58.4 liters * (weight(kg)/70)

  Vperipheral (Liters) = 38.4 liters * (weight(kg)/70)

  Q (L/hr) = 6.5

  Carreno Equations (clearance optimized in prior MUE)

  Clearance (L/hr) = 0.038151 L/hour * creatinine clearance + 0.4339 L/hour

  Vcentral (Liters) = 25.76 liters

  Vperipheral (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	110	
Age (Years)	66.1 (15)	
Male	51.8%	
Weight (kg)	89.8 (26.6)	
Height (Inches)	67 (4.2)	
Lean Body Weight (kg)	63.3 (11.3)	
BMI (kg/M2)	31 (8.6)	
Body Surface Area (Meters2)	2.0 (0.28)	
Serum Creatinine (mg/dL)	1.2 (0.36-5.31)	
Creatinine Clearance ml/min per 1.73 m2)	53.4 (5-126)	
BMI < 20	3.6%	
BMI 20-25	24.5%	
BMI >25-30	27.3%	
BMI >30-35	14.6%	
BMI > 35	29.1%	

Demographic Date (average (Standard Deviation or numeric range)		
	BMI less than 30	BMI $\underline{\geq}$ 30
Number of Patients reviewed	62	48
Serum Levels	118	96
Age (years)	69.1 (15.7)	62.2 (13.2)
Male	56.5 %	45.8 %
Weight (kg)	73.3 (13.9)	111.3 (21)
Height (inches)	67.3 (4.2)	66.6 (4.3)
Lean Body Weight (kg)	63.7 kg (11.4)	62.8 (11.3)
BMI (kg/M2)	24.9 (3.1)	38.9 (6.7)
Body Surface Area	1.85 (0.22)	2.2 (0.24)
Serum Creatinine (mg/dL)	1.02 (0.36-3.75)	1.3 (0.37-5.1)
Creatinine Clearance ml/min per 1.73 M2	58 (11.7-126.2)	47.8 (4.5-107.8)

- Analysis of Pharmacokinetic Models:

Model & Patient Group	**Sum of Square of Errors**	**Bias**	**Precision Root Mean Squared Error**	Actual versus Predicted Trough means (SD)	Absolute (Predicted - Actual) <= 5	Absolute (Predicted- Actual) >5-<10	Absolute (Predicted - Actual) >= 10
All Patients N=110 Levels = 214							
1 compartment Model	8548	**0.84**	**6.3**	14.3 (5.6) Vrs 13.4 (6)	65.9%	23.8%	10.3%
Goti Optimized 2 Compartment	479557	**-16.5**	**47.3**	13.1 (4.3) Vrs 29.6 (45.7)	45.8%	25.7%	28.5%
Carreno Optimized 2 Compartment Optimized	13725	**0.54**	**8**	15.2 (5.2) Vrs 14.6 (8)	65.9%	22.4%	11.7%
BMI < 30 Patients =62 Levels = 118							
1 Compartment Model BMI < 30	4534	**1.64**	**6.2**	14.1 (6.3) vrs 12.5 (4.8)	67%	22.9%	10.2%
Goti Optimized 2 Compartment BMI < 30	8568	**-4.8**	**8.5**	12.3 (4.5) vrs 17 (7.8)	50.9%	27.1%	22%
Carreno Optimized 2 Compartment BMI < 30	3867	**1.23**	**5.7**	15.2 (5.6) Vrs 13.9 (5.2)	69.5%	19.5%	11%
BMI >=30 Patients = 48 Levels = 96							
1 Compartment Model BMI >= 30	4013	**-0.14**	**6.5**	14.5 (4.8) Vrs 14.6 (7)	64.6%	25%	10.4%
Goti Optimized 2 Compartment Model BMI >=30	47,0989	**-31**	**70**	14.1 (3.9) Vrs 45.1 (64.5)	39.6%	24%	36.5%
Carreno Optimized 2 Compartment Model BMI >=30	9858	**-0.32**	**10.1**	15.2 (4.7) Vrs 15.5 (10.4)	61.5%	26%	12.5%

Conclusions

- The Optimize Goti model:
  - is less accurate than the 1 compartment and optimized Carreno models in patients with BMI < 30. During data fitting of levels, it produces more variability in predicted levels than the other models. Inaccurate low clearance values may be calculated with unrealistically high-level predictions when levels are fit after a load and/or a load and one MD or when there are large changes in levels in a short time frame when only troughs are used.
  - is less accurate than the 1 compartment and optimized Carreno Models in patients with BMI >= 30 during data fitting of levels and has large prediction discrepancies compared to the other models. The model should not be used in patients with a BMI greater than or equal to 30.
- The Optimized Carreno model:
  - The one compartment and two compartment optimized Carreno models are similar in accuracy, bias, and prediction of levels regardless of BMI.
- The current one compartment and optimized Carreno models are more accurate in predicting trough serum levels as demonstrated by lower values for Sum of the Square of Errors, Bias, Root Mean Squared Error, and higher percentage of levels closer to actual level than the Goti model for obese and non-obese patients.

Recommendations for Insight

- A large population data analysis (>=500 patients per equation) should be performed to optimize the Goti and Carreno equations either prospective or by retrospective using data in the Insight data base.
  - A non-Bayesian analysis should be performed to determine population mean and standard deviation for the clearance equations to populate the Bayesian model.
  - Patients selected should have stable renal function, serum creatinine 0.7 mg/dL or higher, no amputations, without malnutrition (BMI >= 18.5 for Goti), and not receiving RRT.
  - The optimal BMI break points for Goti and Carreno equations should be determined.
  - A separate analysis should be performed for patients with serum creatinine less than 0.7 mg/d due to over prediction of creatinine clearance and BMI < 18.5.

Future MUE

Compare 1 compartment, Goti and Carreno models using dosing history and serum levels of peak and trough versus trough only

- AUCs calculated for peak/trough versus trough only
- Calculated dose and interval for AUC of 500 mg*hour/Liter per 24 hours for peak/trough versus trough only
- Vd calculated for a peak and trough versus trough only
- Clearance calculated for peak and trough versus trough only

Compare population predicted steady state levels versus calculated steady state levels for each method

- Within 5 mcg/ml of predicted
- 5-10 mcg/ml of predicted
- 10 mcg/ml of predicted

Compare the three dosing methods for population predicted values versus calculated values using a peak and trough

- AUC population predicted versus obtained
- Calculated dose and interval for AUC of 500 mg*hour/Liter per 24 hours
- Clearance calculated
- Population predicted level versus obtain steady state level

Fit vrs predicted levels for all models using just trough and pk and trough & compare all models to each other and values for one versus two levels

Fit Vd and Clearance to levels

Consistence of Vd across time for each method

Consistency of Cl across time for each method

Comparison of AUC calculated for each method with pk and trough and within method using pop vd and only trough

Comparison of pop parameters versus fit parameters (cl, Vd) and optimize equations

LD one day of MD then PK/Tr, then 72 hours late PK/Tr