Comparison of Vancomycin Dosing Predictions with A One Compartment Open Model in Excel Versus Two Compartment Open Models in Insight

1/2022

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.

Purpose of Present Analysis:
To compare vancomycin serum level trough predictions with the Excel one compartment open model dosing program versus Insight Software two compartment model for patients previous dosed whose demographic, serum creatine, dosing and serum level history, and steady state levels are available. Two separate analyses will be performed, one for patients with a BMI < 40 and one for patients with BMI greater than equal to 40.

A nonlinear regression analysis to optimize the Goti and Carreno clearance equations will be performed by minimizing the sum of the square of errors for actual versus predicted levels to improve their predictive performance if needed.

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 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 level for the programs.
- Optimization of Goti and Carreno equation clearances to minimize Sum of Square Error, Root Mean Square Error, and Bias of prediction if the current Insight Equation values perform poorly.

Methods:

- Retrospective pharmacokinetic analysis of patients receiving vancomycin from 1/14 to 2/21.
- Subjects are divided into two groups for analysis, one group less than 40 BMI and one group greater than 40 BMI.
- Study participants were identified using the pharmacokinetic dosing and monitoring tool utilized by the pharmacy department.
- Inclusion criteria: patients who were admitted as inpatients from January 2014 to February 2021, 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 compartment open model equations were used to calculate the steady state levels for each patient's dosing regimen. The patient's demographics, dosing history and serum levels were input into a nonlinear one compartment open model data fitting in Excel that uses the method of superposition.
- Excel Program 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/Vd)*Tau) / (((Vd*K*Infusion Period)(1-exp(-K*Tau)))
- Insight 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 (L/hr) = 4.5 L/hr (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 (L/hr) = 0.036 L/hr * creatinine clearance + 0.18 L/hour
  Vcentral (Liters) = 25.76 liters
  Vperipheral (Liters) = Q/K21= 2.29 1/hours * 25.76 Liters / 1.44 1/Hours
  Q (L/hr) = K12*Vc = 2.29 1/hours * 25.76 Liter
  K12 (1/hours) =2.29
  K21 (1/hours) = 1.44
  Cp Steady State Trough = [D*(K21-alpha)(1-exp(-alpha*Infusion Period))*exp(-alpha*Tau) / (Vc * alpha*(beta-Alpha))] *1/(1-exp(-alpha *Tau) +
  [D (beta-K21) *(1-exp(-beta*Infusion Period)*exp(-beta*Tau) / (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 range)		
	BMI less than 40	BMI 40 and above
Number of Patients reviewed	688	113
Age (years)	66.1 (SD 16.6)	57.8 (SD 13.3)
Male	63.3%	54%
Weight (kg)	82.6 (SD 19.7)	140.3 (SD 29.5)
Height (inches)	67.5 (SD 4.4)	67.3 (SD 4.85)
Lean Body Weight (kg)	64.59 kg (SD 11.9)	64.8 (SD 12.53)
BMI (kg/M2)	27.95 (SD 5.58)	47.85 (SD 8.24)
Body Surface Area	1.94 (SD 0.26)	2.44 (SD 0.3)
Serum Creatinine (mg/dL)	1.3 (Range 0.7-5.76)	1.38 (Range 0.7-4.32)
Creatinine Clearance ml/min per 1.73 M2	54 (Range 8-153)	44.4 (Range 10.6-115)

- BMI < 40
    - Vancomycin Total Doses Input: 2368
    - Patient with at least one dose input 100%
    - Patients with at least two doses input 85.9%
    - Patients with at least three doses input 76%
    - Patients with at least four doses input 50.6%
    - Patients with at least five doses input 22.7%
    - Patient with at least six doses input 5.8%
    - Patient with at least at least seven doses input 3.2%
- BMI < 40
    - Vancomycin Total Levels: 925
    - Pre 1st dose 213
    - Post dose levels: 712
        - 116 after 1st dose
        - 137 after second dose
        - 249 after third dose
        - 131 after forth dose
        - 57 after fifth dose
        - 9 after sixth dose
        - 13 after 7 seventh dose
- BMI greater than equal to 40
    - Vancomycin Total Doses Input: 407
    - Patient with at least one dose input 100%
    - Patients with at least two doses input 93.8%
    - Patients with at least three doses input 85.8%
    - Patients with at least four doses input 49.6%
    - Patients with at least five doses input 23.9%
    - Patient with at least six doses input 6.2%
    - Patient with at least at least seven doses input 0.9%
- BMI greater than equal to 40
    - Vancomycin Total Levels: 150
    - Pre 1st dose 33

- Post dose levels: 117
  - 8 after 1st dose
  - 32 after second dose
  - 45 after third dose
  - 18 after forth dose
  - 12 after fifth dose
  - 2 after sixth dose
  - 0 after 7 seventh dose

- 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
Current 1 Compartment Program for patients < 40 BMI	27,725	1	6.35	14.59 (6.73) vrs 15.6 (5.91)	58%	31%	11%
Insight Two Compartment Program for patients BMI < 40 Goti Model	56,709	**6.1**	9.1	14.59 (6.73) vrs 20.7 (6.98)	35.6%	35.3%	29.1%
Current 1 Compartment Program for patient >= 40 BMI	6036	-0.88	7.31	16.08 (7.69) Vrs 15.2 (6.1)	57%	30%	17%
Insight Two Compartment Program for patients >= 40 BMI Carreno	7838	2.79	8.3	16.08 (7.69) Vrs 18.87 (8.07)	45%	39%	16%
Goti Clearance Optimized	24520	-0.485	5.97	14.59 (6.73) Vrs 14.1 (5.05)	62.8%	28%	9.2%
Carreno Clearance Optimized	5839	-0.87	7.19	16.08 (7.69) vrs 15.21 (6.2)	53%	29%	18%

Conclusions

- The current one compartment Excel program is 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 as noted above than Insight's Goti and Carreno two compartment models for obese and non-obese patients.
- Optimization of the Goti and Carreno equations to minimize the SSE, Bias and Root Mean Squared error required changes to the clearance formulas as following:
    - The Goti equation was optimized with a clearance multiplier value of 6.04 l/hour up from the current value of 4.5 l/hour, a 34% increase.
    - The Carreno equation was optimized with a clearance slope of 0.038151 and an intercept of 0.4339 versus the current value for slope of 0.036 l/hour and intercept of 0.18 l/hr.
- Insight's Goti model over predicts levels on average by 6.1 mcg/ml and will cause a delay in reaching therapeutic levels and AUC. As the programs clearance values are used in Bayesian calculations this too may skew dosage calculations and serum level predictions resulting in prolonged underdosing.
- The Carreno model does not perform as well as the current one compartment model and over predicts levels on average by 2.8 mcg/ml.
- Published pharmacokinetic models should be validated in the target patient population before they are implemented, and revisions should be made if needed.