Developed By Marshall Pierce PharmD https://pkineticdrugdosing.com/

Population Based Dosing Using One Compartment Pharmacokinetic Equations, Dosage Individualization with Serum Level Analysis and Non-Linear Data Fitting Using Bayesian or Non-Bayesian Methods.

Vancomycin

Volume of Distribution (liters) = 0.65 l/kg of total body weight, 1.172 l/kg of total body weight in hemodialysis patients

Elimination Rate Constant (1/hours) = 0.00107 * Creatinine $Clearance_{IBW}$ * 1.73/BSA + 0.0052

HD dosing is not implemented in current version

Elimination Rate Constant (1/hours)hemodialysis= [6.9/(1.172*$Weight_{kg}$)]during dialysis , {0.3348/(1.172*$weight_{kg}$)]non dialysis period

Aminoglycosides

Volume of Distribution (liters) = 0.25 l/kg of adjusted body weight

Elimination Rate Constant (1/hours) = 0.026 * Creatinine $Clearance_{IBW}$ + 0.014

Ideal body weight ($IBW_{(kg)}$) Adults

Males(kg) = $50_{(kg)}$ + $2.3_{(kg)}$ * (height in inches - 60)

Females(kg) = $45.5_{(kg)}$ + $2.3_{(kg)}$ * (height in inches - 60)

Lean Body Weight for Children or height < 48 inches (Peck Formula)

Female < 18 years = -77.55796 + (6.93728 * Height in inches) -(0.171703 * Height in $Inches^2$) + (0.001726* Height in $Inches^3$)

Male < 18 years = -59.6035 + (5.2878 * Height in Inches) - (0.123939 * Height in $Inches^2$) + 0.00128936 * Height in $Inches^3$)

If height < 22 inches, lean weight = total weight

Adjusted body weight, aminoglycosides only, if actual weight > IBW.

Adjusted $Body\ Weight_{(kg)}$ = $LBW_{(kg)}$ + 0.4 * (Actual $Weight_{(kg)}$ – $IBW_{(kg)}$)

Creatinine Clearance Equations

Adults Cockcroft Gault Equation

Males(ml/min) = (140-$age_{(years)}$) * (Use Ideal Body $Weight_{(kg)}$ or actual weight if less than $IBW_{(kg)}$) / (Serum Creatinine *72)

Females(ml/min): above x 0.85

Pediatric Schartz Equation

ClCr(ml/min/1.73 m2) = Factor* $Height_{(Centimeters)}$ / Serum Creatinine

Factor: 0.45 < 1 year, 0.55 1-12 years, > 12 years 0.55 female, > 12 years males 0.7

Amputation and Paralysis Serum Creatinine Multiplication Factors

Entire Leg Amputation (1.2269), AKA (1.1764), BKA (1.0638), Entire Arm Amputation (1.0695), AEA (1.0526), BEA (1.0309), Functional Palegia (1.4), Paraplegia (1.4), Quadriplegia (1.6)

Minimal Serum Creatinine used in calculations: 0.5 mg/dL in patients with functional, para or quadriplegia, or malnutrition; 0.7 in other adults.

AUC Calculation

Non dialysis: (((Peak + Trough)*Infusion Period/2) * 24/Tau) + (((Peak - Trough)/K)*24/Tau)

Hemodialysis: (((Peak + Trough afterHD)*Infusion Period/2) * 24/Tau) + (((Peak - Trough before dialysis) /Krenal)*24/Tau) + ((Trough before dialysis - trough after dialysis)/Kdialysis)*24/Tau

Creatinine Clearance Calculation

How is creatinine clearance calculated when the serum creatinines is changing?

Most creatinine clearance equations assume stable renal function.

Creatinine clearance individualized Cockcroft Gault equation:

Males(ml/min) = (140-age) * (Use Ideal Body Weight(kg) or actual weight if less than IBW(kg)) / (Serum Creatinine *72)

Females(ml/min): above x 0.85

In the simplified form: Creatinine Clearance = Creatinine rate of production / Serum Creatinine

Rate of production is constant for a patient and is determined by age, height, weight, and sex. The rate of production is built into the Cockcroft Gault equation and other creatinine clearance equations. When renal function has changed the following equation may be used to calculate creatinine clearance before steady state serum creatinine levels are achieved. This is the most accurate method of numerous published equations. An iterative method is used to determine clearance as there is no direct solution to the equation.

Serum Creatinine2 = Serum Creatinine1 * exp((-Vd/Clearance of Creatinine)*T) + Rate of Production (1-exp((-Vd/Clearance of creatinine)T)) / Clearance of Creatinine

T is the time between serum two known creatinines (creatinine1 and creatinine2).

K is the elimination rate constant for creatinine.

Vd is the volume of distribution for creatinine

This equation accounts for the elimination of creatinine already present, and the fraction of steady state achieved during the time between the creatinines.

Assumptions of the non-steady state equation:

All of the change in renal function has occurred at or before the time of the oldest creatinine (creatinine1).

The change in creatinines is due to renal function changes and is not due to tissue destruction or hydration changes.

The serum creatinines are accurately determined and the time between them is known.

Monitoring of serum levels

Vancomycin peaks: are usually drawn > 2 hours after the end of the infusion in the post-distribution phase. Levels drawn in the distribution phase will cause erroneous calculations, increased K and decreased Vd.

Aminoglycoside peaks: are usually drawn 0.5 hours after the end of the infusion for traditional dosing

Pulse dosing: a level is drawn 14 hours after the end of the infusion. True troughs are not drawn or useful in monitoring.

Vancomycin & aminoglycoside troughs: are drawn 0.5-1 hour before a dose. Hemodialysis troughs are drawn before dialysis.

Peak and trough monitoring for AUC or traditional aminoglycoside dosing should be drawn after the same dose and should not drawn around a dose. Dose at xx:xx with both levels drawn after xx:xx dose.

The calculations are more accurate if both levels are drawn after the same dose and this is the preferred method of drawing peaks and troughs.

Vancomycin hemodialysis peaks and troughs: Levels should not be drawn any sooner than 6 hours after dialysis even if dose is given during dialysis. The following is recommended for vancomycin when dosing post dialysis: dialysis dose 4-6 hours post dialysis infused over 2 hours, peak 2 hours after infusion complete.

Data Fitting: The program utilizes non-steady state one compartment open model equations with the method of superposition to calculate the expected level(s) from the input dosing history, initial serum level, measured levels, and estimated pharmacokinetic parameters.

Cp Total at time T = $Cpoexp(-K(T-to)) + \sum_{1-N} [D1(1-exp(-KT'))*exp(-K(T-Td1-T'))/(VKT')] + [D2(1-exp(-KT'))*exp(-K(T-Td2-T'))/(VKT')]$…….for all doses before the level.

The expected levels, displayed in the data fitting section, are calculated using the population elimination rate constant (C26) and volume of distribution (C22) before the data is fit. Once the data (dosing and serum levels) is fit the patient specific values of elimination rate constant and volume of distribution, D26 and E26 are used to calculate the levels.

Objective Function to Minimize

Non-Bayesian

Sum of the Square of Errors $=\sum_{1 \text{ to } N}$ (Predicted Level1 – Actual Level1)^2 + (Predicted Level2 – Actual Level2)^2 for all input levels

Bayesian

Sum of the Square of Errors $=\sum_{1 \text{ to } N}$ (Predicted Level1 – Actual Level1)^2/(CV*Actual Level)^2 + (Predicted Level2 – Actual Level2)^2/(CV*Actual Level)^2 for all input levels + (Vdpop - Vdfit)^2/(CV*Vdpop)^2 + (Clpop – Cl fit)^2/(CV*Clpop)^2

CV = Coefficient of variation for parameter

Instructions For Use

In general, it is better to enter a starting level, then the dosing and serum level history, rather than assuming steady state as it is rare for doses to be given uniformly and on time.

1. Enter the data required in the blue colored cells in column C, (C1-C16).

2. Select the patient type non hemodialysis or intermittent hemodialysis vancomycin in cell E5.

3. Select the values in cells E8 through G8, E11 through F11, and E14 if the patient has amputation(s), paralysis, or malnutrition.

4. Press the "Calculate Creatinine Clearance or Dose" button. This will calculate the patient's creatinine clearance and suggested dose and frequency.

5. Enter a rounded dosage interval and rounded dose in cells C34 and C36 respectively.

6. Population based parameters (elimination rate constant and volume of distribution) are used to calculate the peak, trough, and AUC in C37, C38, and C 39 respectively.

7. Change the input frequency and dose in C34 and C36 to obtain your desired predicted peak, trough, and AUC in cells C37, C38 and C39.

Analyzing steady state levels using a trough drawn after a known steady state dose.

8. Steps 1-7 must be completed, enter the current frequency and dose in C34 and C36.

9. Enter the date therapy was started in cell C44.

10. Enter the steady state trough in cell G46 and the date and time of the trough in G47.

11. Enter the time of the dose which was given before the trough in E42.

12. Press the "Assume Steady State: Trough drawn after dose 1". This will copy the entered trough to cell D46, place the calculated time of the pre-dose trough in cell D47, and the dose to E41.

This is for your convenience, if you choose to you can enter the data manually without pressing the "Assume Steady State" button.

By placing the same trough around a single dose you are creating steady state conditions. This is the definition of steady state, levels are unchanging dose to dose.

13. Press "Fit Data (Elimination Rate Constant Optimization)" button. The program will determine the elimination rate constant that minimizes the difference between the actual and predicted level.

14. The calculated patient specific elimination rate constant is displayed in cell D26 after data fitting.

15. The predicted state levels using the patient specific elimination rate constant are displayed in cells D37 and D38 respectively.

16. You may adjust the dosage frequency and dose in D34 and D36 to obtain your desired levels.

Explanation of program when assuming steady State where the trough is drawn past the time the next dose was due and next dose was held.

Trough at time of Dose1 displayed in E50 = Trough PredoseD46*Exp(-K*(Time of Dose1 E42 - Time of Predose Trough D47)*24)

The trough in D46 will show a time in D47 that is after the time of the dose1 in E42, but the equation above back extrapolates the calculated trough displayed in E50 to the time of Dose 1.

The programs calculations are correct though the displayed values in D46 and D47 look incorrect. The value in E50 is the value used in the further calculations.

Note: the predicted levels for input dosage regimens in column C (population) and D (patient specific) are independent from one another after data fitting.

Analyzing steady state levels using a trough drawn before a known steady state dose. This will be rarely used but is included for flexibility.

8. Steps 1-7 must be completed, enter the current frequency and dose in C34 and C36.

9. Enter the date therapy was started in cell C44.

10. Enter the steady state trough in cell D46 and the date and time of the trough in D47.

11. Enter the date and time of the dose which was given in E42.

12. Press the "Assume Steady State: Trough drawn before dose 1". This will copy the entered trough to cell G46, place the calculated time of the post dose trough in cell G47, and the dose to E41.

This is for your convenience, if you choose to you can enter the data manually without pressing the "Assume Steady State" button.

By placing the same trough around a single dose you are creating steady state conditions. This is the definition of steady state, levels are unchanging dose to dose.

13. Press "Fit Data (Elimination Rate Constant Optimization)" button. The program will determine the elimination rate constant that minimizes the difference between the actual and predicted level.

14.The calculated patient specific elimination rate constant is displayed in cell D26 after data fitting.

15. The predicted state levels using the patient specific elimination rate constant are displayed in cells D37 and D38 respectively.

16. You may adjust the dosage frequency and dose in D34 and D36 to obtain your desired levels.

Note: the predicted levels for input dosage regimens in column C (population) and D (patient specific) are independent from one another after data fitting.

Analyzing steady state levels using a peak and trough both drawn after a steady state dose (Traditional Dosing for Aminoglycosides or Vancomycin AUC dosing)

Note: this is the recommended method for drawing levels. Both levels should be drawn after the same dose.

8. Steps 1-7 must be completed, enter the current frequency and dose in C34 and C36.

9. Enter the date therapy was started in cell C44.

10. Enter the steady state trough in cell G46 and the date and time of the trough in G47.

11. Enter the steady state peak in cell F46 and time of the peak in F47.

12. Enter the date and time of the dose which was given in E42.

13. Press the "Assume Steady State: Trough drawn after dose 1". This will copy the entered trough to cell D46, place the calculated time of the post dose trough in cell D47, and the dose to E41.

This is for your convenience, if you choose to you can enter the data manually without pressing the "Assume Steady State" button.

By placing the same trough around a single dose you are creating steady state conditions. This is the definition of steady state.

14. Press "Fit Data (Elimination Rate Constant & Vd Optimization)" button. The program will determine the elimination rate constant and volume of distribution that minimizes the difference

between the actual and predicted levels.

15. The calculated patient specific elimination rate constant is displayed in cell D26 and volume of distribution in cell E26 after data fitting.

16. The predicted state levels using the patient specific K and Vd are displayed in cells D37 and D38 respectively.

17. You may adjust the dosage frequency and dose in D34 and D36 to obtain your desired levels.

Note: the predicted levels for input dosage regimens in column C (population) and D (patient specific) are independent from one another after data fitting.

Analyzing steady state levels using a trough drawn before a known steady state dose and a peak after the same dose (Traditional Dosing for Aminoglycosides)

Note: this is not the recommended method for drawing levels. Both levels should be drawn after the same dose.

8. Steps 1-7 must be completed, enter the current frequency and dose in C34 and C36.

9. Enter the date therapy was started in cell C44.

10. Enter the steady state trough in cell D46 and the date and time of the trough in D47.

11. Enter the steady state peak in cell F46 and time of the peak in F47.

12. Enter the date and time of the dose which was given in E42.

13. Press the "Assume Steady State: Trough drawn before dose 1". This will copy the entered trough to cell G46, place the calculated time of the post dose trough in cell G47, and the dose to E41.

This is for your convenience, if you choose to you can enter the data manually without pressing the "Assume Steady State" button.

By placing the same trough around a single dose you are creating steady state conditions. This is the definition of steady state.

14. Press "Fit Data (Elimination Rate Constant & Vd Optimization)" button. The program will determine the elimination rate constant and volume of distribution that minimizes the difference between the actual and predicted levels.

15. The calculated patient specific elimination rate constant is displayed in cell D26 and volume of distribution in cell E26 after data fitting.

16. The predicted state levels using the patient specific K and Vd are displayed in cells D37 and D38 respectively.

17. You may adjust the dosage frequency and dose in D34 and D36 to obtain your desired levels.

Note: the predicted levels for input dosage regimens in column C (population) and D (patient specific) are independent from one another after data fitting.

Analyzing Non-Steady State Levels

8. Steps 1-7 must be completed, enter the current frequency and dose in C34 and C36.

9. Enter the date therapy was started in cell C44.

10. Enter a starting level and time of the level in cells D46 and D47 respectively. This level may be zero if no drug is on board or any known level before the first dose in the series of doses being entered and serum levels you wish to analyze.

11. Enter all doses and the dates and times given from the time of the starting level through the last dose administered before the last level to be analyzed in chronological order, oldest to most recent left to right. The doses are numbered 1-7, chronological after the starting level.

12. Enter all levels and the times drawn to be analyzed in chronological order, oldest to most recent left to right. Levels entered should be placed in a cell after the last dose before the level and before the next dose after the level.

13. Press the appropriate data fitting button, "Fit Data (Elimination Rate Constant Optimization)" if only troughs have been drawn, and "Fit Data (Elimination Rate Constant & Vd Optimization) if a peak(s) and trough(s) have been drawn.

14. The calculated patient specific elimination rate constant is displayed in cell D26 and volume of distribution in cell E26 after data fitting.

15. The predicted state levels using the patient specific K and Vd are displayed in cells D37 and D38 respectively.

16. You may adjust the dosage frequency and dose in D34 and D36 to obtain your desired levels.

17. If the patient's renal function is unstable serum creatinine values may be entered below the serum levels to adjust the elimination rate constant used during data fitting. The entered creatinines in cells C12 and C13 may the same, rising or decreasing, but should be the most recent values. Once data is fit the serum creatinines in C12 and C13 should not be adjusted as erroneous data fitting calculations will result if the data is refit.

Note: the predicted levels for input dosage regimens in column C (population) and D (patient specific) are independent from one another after data fitting.

When to assume levels are Non-Steady State Levels

1. If you are ordering levels before 5 half-lives have passed from the start of therapy for a stable regimen.

2. If you order levels after loading dose or the 1st maintenance dose with or without a loading dose.

3. The patient's doses or dosage intervals are not consistent.

4. The patient's renal function is unstable.

Note: the predicted levels for input dosage regimens in column C (population) and D (patient specific) are independent from one another after data fitting.

Data Storage

The program stores patient demographic information, current dose and frequency, along with calculated values including population and patient specific elimination rate constant and volume of distribution in a separate file. This allows analysis of predicted versus actual levels to optimize the parameters used in the program and MUEs to be performed.

Program Requirements

Excel 2010

A shared drive with copies of the program in separate folders if multiple users will be dosing patients at the same time or the program will have to be installed on multiple computers.

A copy of the program should be placed in individual folders on the shared drive for each functional area of use along with the patient data file.

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