

T. D. M. S.

Version 6.5

For Windows

THERAPEUTIC

DRUG

MONITORING

SYSTEM

USER MANUAL

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Healthware, Inc.

PO Box 33483

San Diego, CA 92163

Phone/FAX : (858) 452-0297

e-mail: Information@TDMS2000.com

Designed by : Jenn Ting, Pharm.D.

Written by : Philip O. Anderson, Pharm.D.

Jenn Ting, Pharm.D.

Windows Programmer: Anjum Gupta

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Abbreviations and Definitions of Terms Used in the T.D.M.S™. User's Manual

AUIC	Area under the inhibitory curve (Post / MIC)
BSA	Body surface error
CLcr	Creatinine clearance
Crs	Serum creatinine in mg/dL
IBW	Ideal body weight
MIC	Minimum inhibitory concentration of a bacterium
Peak	The extrapolated serum concentration at the exact end of an IV infusion
Post	The serum concentration at a user-specified time after the end of an IV infusion
TBW	Total body weight

CHAPTER 1. SYSTEM OVERVIEW



Figure 1. Title Screen

The Title Screen (Figure 1) displays the program name, version, the name of your institution and today's date as it is set in your computer. There are two choices on this screen:

Configure Database allows you to designate the location of the T.D.M.S.TM database where patient data are stored (*see* Appendix A. T.D.M.S. Installation Procedures for more details). You are required to press this button and designate a database location the first time you run T.D.M.S.TM after it is installed.

Next allows you to proceed to the following screen. Note that you can either click on this **Next** button or press the keyboard combination of Alt-N to proceed. Wherever you see a letter underlined on a button throughout the program, you can use the Alt-letter combination to activate the button.

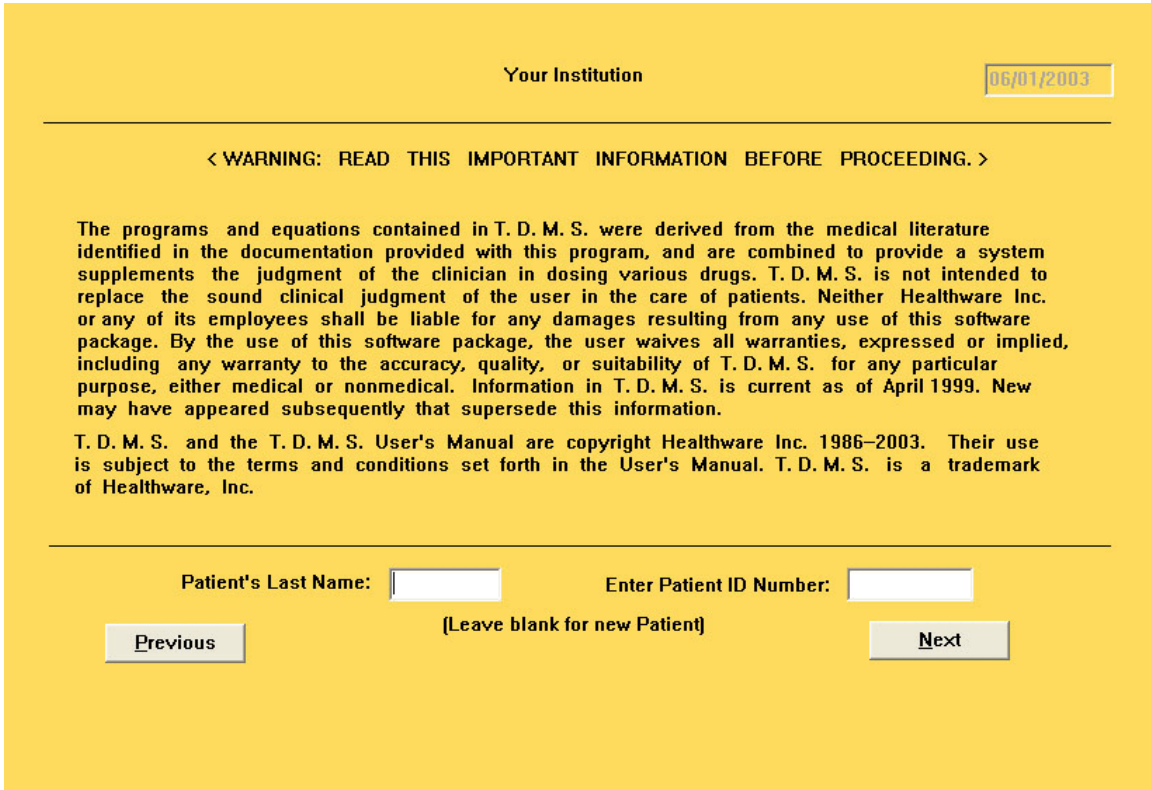


Figure 2. Database Search Screen

This screen displays the legal disclaimer at the top and has two boxes that allow you to search for a patient in the database. You only need to fill in one of the two boxes.

Patient's Last Name allows you to search for a patient by the last name. Partial name searches are possible, so entering the letter "An" will retrieve all patient's whose last name starts with "An".

Enter Patient ID Number allows you to search by the identification number you have stored in the database, such as the patient's medical record number.

Previous takes you back to the Title Screen.

Next allows you to proceed to the following screen. If you entered information into one of the boxes above, you will be taken to the Database Screen (Figure 3) where search results are displayed. If you entered nothing in either box, you will be taken to the Patient Demographics screen.

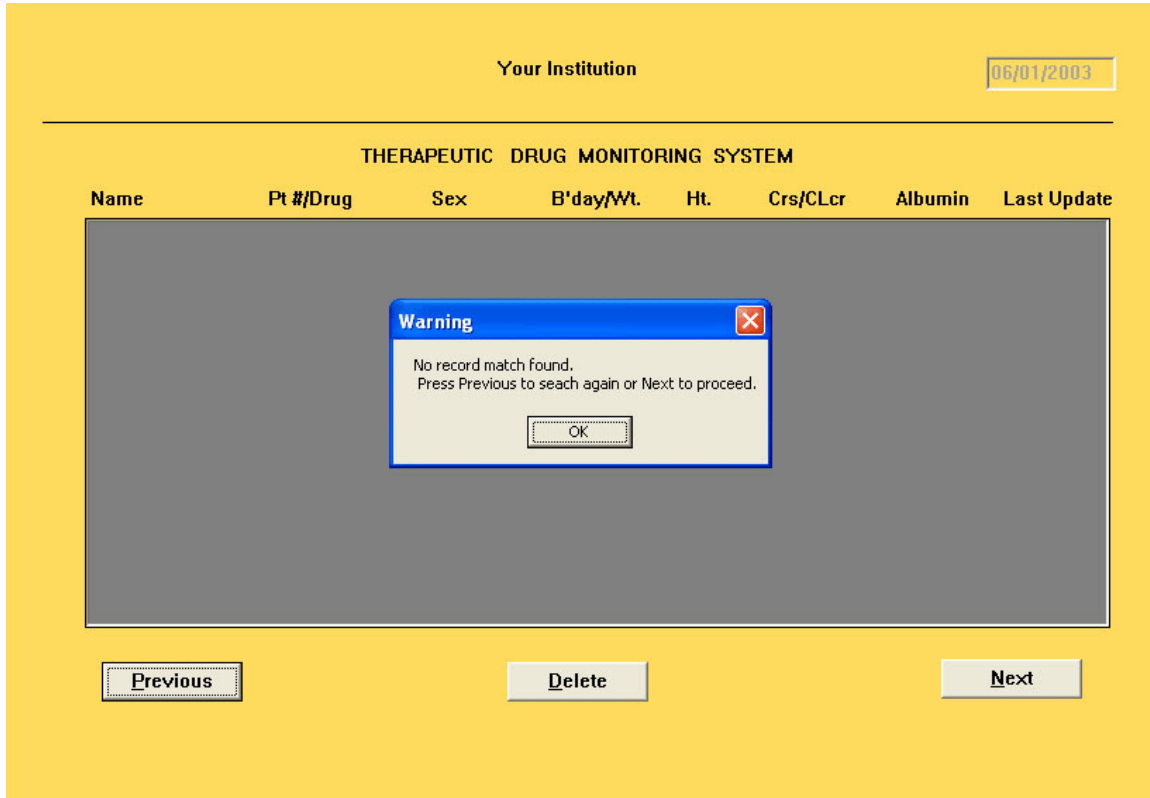


Figure 3. No Match

After clicking the OK button, you may either press the Previous button to reformulate your search or the Next button to continue to the Patient Demographics screen.

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

Patient	Case	
Last: <input type="text" value="Patient"/> First: <input type="text" value="Test"/> Hosp ID: <input type="text" value="12345-A"/> Birthday: <input type="text" value="08/24/1956"/> Sex: <input checked="" type="radio"/> Male <input type="radio"/> Female Updated: <input type="text" value="06/01/2003"/> Patient Note: <input style="width: 100%; height: 40px;" type="text"/>	Drug: <input type="text" value="Gentamicin"/> Weight: <input type="text" value="166"/> <input checked="" type="radio"/> lb <input type="radio"/> kg Height: <input type="text" value="72"/> <input checked="" type="radio"/> in <input type="radio"/> cm <input checked="" type="radio"/> Crs: <input type="text" value="0.9"/> mg/dL <input type="radio"/> CLcr: <input type="text"/> mL/min Albumin: <input type="text"/> g/dL Updated: <input type="text" value="06/01/2003"/> Case Note: <input style="width: 100%; height: 40px;" type="text"/>	
<input type="button" value="Previous"/>	<input type="button" value="Save"/>	<input type="button" value="Next"/>

Figure 4. Patient Demographics Screen

This screen is used to gather information about the patient and drug of interest. In the first three fields of the left (**Patient**) column, you may enter the patient's **Last** and **First** names and any **Hospital Identification** number. These fields are not required, but are used to store and later identify the patient in the database. You may jump between fields with a mouse click, enter key or tab key.

Birthday is entered as mm/dd/yyyy.

Sex is entered by clicking on the appropriate radio button, Male or Female

Patient Note will be stored with the Patient record in the database. Information in this field will be retrieved whenever the Patient or any of the patient's Case records are retrieved. In the right (**Case**) column you enter data about the particular course of drug therapy that you are studying.

Drug is selected from the drop-down menu. You may also type in the name of the drug and the drug name matching what you type will appear as soon as a match occurs.

Weight and **Height** are entered as numbers and the correct units are selected using the buttons to the right of each box. The patient's creatinine clearance (CLcr) can be calculated from serum creatinine (Crs) or it can be entered directly if you have a

measured value. Select either **Crs** or **CLcr** with the radio button and enter the value in the corresponding units in the box to the right of your selection.

Serum **Albumin** is only required when you have selected the drug phenytoin. Otherwise, this entry is skipped. The date that this particular Case was updated is displayed in the field, **Updated**.

Case Note will be stored with the Case record in the database. Information in this field will be retrieved whenever this Case record is retrieved. Buttons at the bottom of this screen allow you to go back to the **Previous** screen, **Save** the information on this screen in the database or proceed with analysis of this case by pressing the **Next** button.

Your Institution

THERAPEUTIC DRUG MONITORING SYSTEM

06/01/2003

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in

Cr_s=1.0 mg/dL Est. CL_{cr}=96.4 mL/min

Gentamicin

Select a Maximum of 2 Applicable Factors:

Is this a critically ill or ICU patient ?

Is this a burn patient ?

Is this a hematology/oncology patient ?

Is this a spinal cord injury patient ?

Is this a cystic fibrosis patient ?

Figure 5 . Factors Screen

The Factors Screen (Figure 5) allows you to enter up to two factors known to affect the pharmacokinetics (by at least 10%) of the drug being used in this Case. Click on the check box to the left of any factor(s) that are applicable. Once the appropriate factors have been checked, click one of the buttons at the bottom of the screen.

Previous takes you back to the Patient Demographics screen where you can change the data you entered.

Dosage Regimen Forecast takes you to the Population Dosage Regimen Forecast screen that allows you to predict the dosage regimen required to achieve given serum drug concentrations that you enter.

Serum Level Forecast takes you to the Population Serum Level Forecast screen that allows you to predict the serum drug concentrations achieved by dosage regimen that you enter.

Serum Level Analysis takes you to the screens for analysis of specific dosage regimen and serum drug concentrations that the patient has received.

Population Pharmacokinetics

The population pharmacokinetics portion of T.D.M.S.TM calculates initial starting dosage regimens for your patient based on their demographic data (age, height, weight, etc.) and any factors that are documented to affect the drugs's pharmacokinetics (drug interactions, diseases, etc.).

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test
47 Years Male 166.0 lb 72.0 in

Population Parameters
Gentamicin
Crs=1.0 mg/dL Est. CLcr=96.4 mL/min

Vd: L (0.31 L/kg)

CL: L/hr kd: /hr

CF: % t1/2: hr

Parameters Saved On 06/01/2003

Vd: L

CL: L/hr Salt: kd: hr

CF: % F: % t1/2: hr

Route - Product
Salt: 1.00 F: 100 %

Steady-State Dosage Regimen Forecast

Desired Post: mg/L Exact Estimate: _____

Time of Post After Infusion: hr Dose: mg

Desired Trough: mg/L Frequency: hr

Infusion Time: hr

Desired Average Concentration: mg/L

Exact Estimate: Rate: mg/24 hr

Loading Dose Forecast

Initial Conc: mg/L

Time Drawn (hr ago): hr

Infusion Time of Loading Dose: hr

If Continuous IV: Infusion Rate Since Level: mg/hr

Exact Estimate: Loading Dose: mg

Previous
Serum Drug Level Forecast
Done

Figure 6 . Population Dosage Regimen Forecast Screen

The population dosage regimen forecast screen (Figure 6) allows you to predict the dosage regimen required to achieve the exact serum drug concentrations that you enter. Results are calculated using population-based pharmacokinetic values from the literature. If you wish to change the population values, you can change those values in the white boxes. If this case was pulled from the database, the parameters stored in the database are displayed in the boxes below the "Parameters Saved On..." heading. You can select the route and specific drug product from the drop-down box in the middle of the screen. After entering the desired serum concentrations and times, the exact dosage regimen required to produce the serum drug concentrations you specify are displayed in the Exact Estimate column. You may enter further information in the Loading Dose Forecast column. If the patient has been on the drug and you have a serum concentration drawn at

a known time, you can enter these. T.D.M.S.TM. will calculate the dose required to produce the Desired Post that you specified after the first dose. Because calculations often result in impractical doses or frequencies, the results obtained on this screen should be considered approximate dosage regimens. The best exact regimens should be determined by using the Population Serum Drug Level Forecast Screen.

Previous takes you back to the Factors screen where you can change the factors entered.

Serum Level Forecast takes you to the serum level forecast screen that allows you to predict the serum drug concentrations achieved by dosage regimen that you enter.

Done takes you to the Mode screen which provides several further options.

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in

Population Parameters Gentamicin Cr_s=1.0 mg/dL Est. CL_{cr}=96.4 mL/min

Parameters Saved On 06/01/2003

Vd: <input type="text" value="23.278"/> L (0.31 L/kg)	Vd: <input type="text"/> L	CL: <input type="text"/> L/hr	Salt: <input type="text"/>	kd: <input type="text"/> hr
CL: <input type="text" value="5.241"/> L/hr	kd: <input type="text" value="0.225"/> /hr	CF: <input type="text" value="100"/> %	F: <input type="text"/> %	t _{1/2} : <input type="text"/> hr
t _{1/2} : <input type="text" value="3.078"/> hr				

Route - Product Salt: 1.00 F: 100 %

Steady-State Serum Level Forecast

Intermittent IV Infusion	Steady-State Levels	Continuous IV Infusion
Dose: <input type="text" value="200"/> mg	Peak: <input type="text" value="8.2"/> mg/L	Infusion Rate: <input type="text"/> mg/hr
Interval: <input type="text" value="12"/> hr	Trough: <input type="text" value="0.7"/> mg/L	
Time of Post: <input type="text" value="0.5"/> hr	Post: <input type="text" value="7.4"/> mg/L	Steady-State Level
Infusion Time: <input type="text" value="1"/> hr	Average: <input type="text" value="0.0"/> mg/L	Average Level: <input type="text"/> mg/L
MIC: <input type="text" value="0.5"/>	Post/MIC: <input type="text" value="14.7"/>	
	Time Above MIC: <input type="text" value="24.0"/> hr	
	AUIC: <input type="text" value="153"/>	

Figure 7. Population Serum Level Forecast Screen

The Serum Level Forecast Screen (Figure 7) allows you to predict the serum drug concentrations achieved by dosage regimen that you enter. Results are calculated using population-based pharmacokinetic values from the literature. If you wish to change the population values, you can change those values in the white boxes. If this case was downloaded from the database, the parameters stored in the database are displayed in the boxes below the “Parameters Saved On...” heading.

You can select the route and specific drug product from the drop-down box in the middle of the screen. For intermittent administration, enter the dosage regimen that you desire and the steady-state serum levels predicted to be produced by this regimen are displayed. For administration by continuous infusion, simply enter the desired serum and T.D.M.S.™ will calculate the infusion rate needed to achieve this concentration. For antimicrobial agents, enter the minimum inhibitory concentration (MIC) of the organism to calculate pharmacodynamic values (Post/MIC, Time Above MIC and AUIC) at steady-state which are displayed at the bottom of the second column. See Appendix B for an explanation of these values.

Previous takes you to the Factors screen where you can change the factors you entered.

Report takes you to the Population Report Screen (Figure 8).

Done takes you to the Mode screen which provides several further options.

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in
Crs=1.0 mg/dL Est. CLcr=96.4 mL/min

Gentamicin

Population Parameters: 06/01/2003

Vd: 23.278 L (0.31 L/kg)	F: 100.00 %
CL: 5.241 L/hr	kd: 0.225 hr
CF: 100.0 %	t1/2: 3.078 hr

Dosage Recommendation - Population Parameters

Dose: 200.0 mg every: 12.0 hours Infused Over: 1.0 hr

Levels (mg/L) at Steady-State Average: 0.0 Post (0.5 hr): 7.4 Peak: 8.2 Trough: 0.7

Case Note: We recommend a dosage of 200 mg every 12 hours.

Report Printing Options

Print Graphics

Print Population Parameters

Previous
Print

Figure 8. Population Report Screen

This screen displays the Patient's demographic data, population pharmacokinetic parameters and the last dosage regimen that you evaluated on the Population Serum Level screen. The Case Note box allows you to enter optional free text that you would like printed on the written report. This free text can later be saved in the database in the Case record. There are two options:

Previous takes you back to the Serum Level Forecast Screen where you can change the data you entered.

Print takes you to the Windows print utility where you can designate the printer of your choice to print a written report. After printing, the program takes you to the Mode screen to work on the next patient.

Serum Level Analysis Pharmacokinetics

Once serum drug concentrations are available for your patient, the part of T.D.M.S.TM uses standard pharmacokinetic equations to help you create an individualized dosage regimen for the patient. These equations are listed in Appendix C.

06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test
47 Years Male
166.0 lb 72.0 in

Gentamicin
 Crs=1.0 mg/dL Est. CLcr=96.4 mL/min

Initial Pharmacokinetic Parameters :

	Value		Range	
F :	100.000	+/-	5.000	%
Vd:	23.278	+/-	6.983	L (0.309 L/kg)
CL:	5.241	+/-	2.620	L/hr
CF:	100.0	+/-	50.000	%
kd:	0.225			/hr
t1/2:	3.078			hr

Route - Product

Intermittent IV - Injection Salt: 1.00 F: 100 %

Previous
No Fitting
Next

Figure 9. Parameters Adjustment Screen

Prior to analysis of a specific dosage regimen, you may adjust the population parameters used as a starting point for the fitting routine. You may also need to specify a route of administration and drug product from the dropdown menu for some drugs.

Previous takes you to the Factors screen where you can change the factors you entered.

No Fitting takes you to the Mode screen which provides several further options.

Next takes you to the History Spreadsheet Screen where you enter the dosage and serum level histories of the patient.

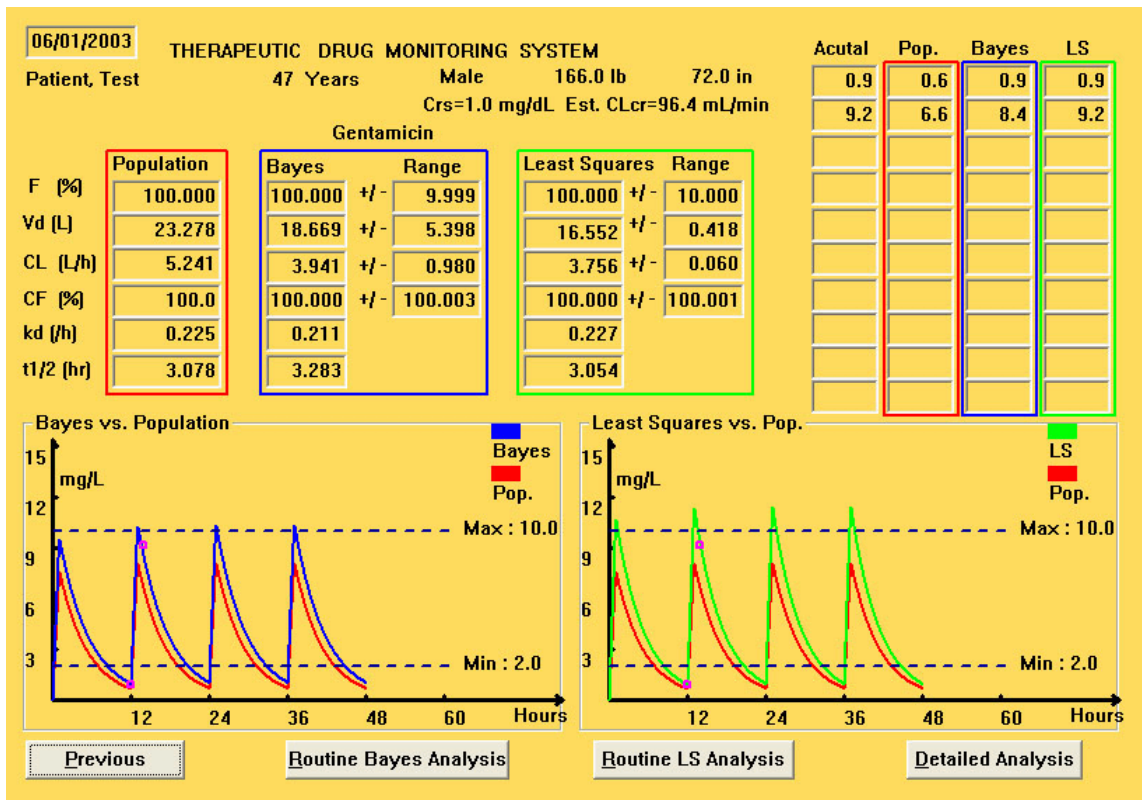


Figure 11. Analysis Results Screen.

The Analysis Results screen (Screen 11) displays the results of the curve fittings which are grouped in three parts of the screen. Throughout this screen, red denotes Population values calculated from patient demographic factors, blue denotes the results obtained from Bayesian curve fitting, and green denotes the results obtained from nonlinear Least-Squares curve fitting.

In the upper left, pharmacokinetic parameters are displayed. Bayesian and Least-Squares values also display the Range (standard deviation) of each value. In the upper right, the serum concentration value at each point in time when a serum level was entered is displayed. The actual measured values are followed by the values calculated using the Population, Bayesian, and Least Squares pharmacokinetic values for that time point. At the bottom of the screen, graphical representations of the serum concentrations versus time plots are displayed, with Bayesian and Least-Squares plots compared to Population plots in each case. These graphs provide a visual method of checking for correct entry of the dosage and serum level history on the previous screen. If only one serum level was obtained, only the Population and Bayesian values and plots are displayed because there is no valid mathematical meaning to a Least-Squares fitting of one point.

Previous takes you to the History Spreadsheet Screen where you can change the data you entered.

Routine Bayes Analysis takes you to the Individualized Routine Dosage Regimen Forecast Screen (Screen 12) that allows you to predict the dosage regimen required to achieve given serum drug concentrations that you enter. Results are calculated using Bayesian pharmacokinetic values.

Routine LS Analysis takes you to the Individualized Routine Dosage Regimen Forecast Screen (Screen 12) that allows you to predict the dosage regimen required to achieve given serum drug concentrations that you enter. Results are calculated using Least Squares pharmacokinetic values.

Detailed Analysis takes you to the Detailed Analysis Screen that allows you to predict the serum drug concentrations achieved by dosage regimen that you enter using both Bayesian and Least Squares values.

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in

Bayes Parameters Gentamicin Crs=1.0 mg/dL Est. CLcr=96.4 mL/min

Parameters Saved On 06/01/2003

Vd: <input type="text" value="18.669"/> L (0.25 L/kg)	Vd: <input type="text"/> L
CL: <input type="text" value="3.941"/> L/hr kd: <input type="text" value="0.211"/> /hr	CL: <input type="text"/> L/hr Salt: <input type="text"/> kd: <input type="text"/> hr
CF: <input type="text" value="100.000"/> % t1/2: <input type="text" value="3.283"/> hr	CF: <input type="text"/> % F: <input type="text"/> % t1/2: <input type="text"/> hr

Route - Product: Salt: 1.00 F: 100.000

<p style="text-align: center;">Steady-State Dosage Regimen Forecast</p> <p>Desired Post: <input type="text" value="7"/> mg/L Exact Estimate:</p> <p>Time of Post After Infusion: <input type="text" value="1"/> hr Dose: <input type="text" value="162"/> mg</p> <p>Desired Trough: <input type="text" value="1"/> mg/L Frequency: <input type="text" value="11.2"/> hr</p> <p>Infusion Time: <input type="text" value="1"/> hr</p> <hr/> <p>Desired Average Concentration: <input type="text"/> mg/L</p> <p>Exact Estimate: Rate: <input type="text"/> mg/24 hr</p>	<p style="text-align: center;">Loading Dose Forecast</p> <p>Initial Conc: <input type="text" value="0.0"/> mg/L</p> <p>Time Drawn (hr ago): <input type="text" value="0.0"/> hr</p> <p>Infusion Time of Loading Dose: <input type="text"/> hr</p> <p>If Continuous IV:</p> <p>Infusion Rate Since Level: <input type="text" value="0.0"/> mg/hr</p> <p>Exact Estimate: Loading Dose: <input type="text"/> mg</p>
---	---

Figure 12. Individualized Dosage Regimen Forecast Screens

The Individualized Bayesian and Least Squares Dosage Regimen Forecast Screens allow you to predict the dosage regimen required to achieve the exact serum drug concentrations that you enter. Results are calculated using either Bayesian or Least-Squares pharmacokinetic values, indicated just below the patient's ID number and name. On this screen, you may select the Route and specific drug product in the dropdown box in the middle of the screen. The exact dosage regimen required to produce the serum drug concentrations you specify are displayed in the Exact Estimates column. You may enter further information in the Loading Dose Forecast column to calculate the dose required to produce the Desired Post after the first dose. Because calculations often result in impractical doses or frequencies, the results obtained on this screen should be considered approximate dosage regimens and the best exact regimens should be determined by using the Serum Drug Level Forecast Screen (Figure 13).

Previous takes you to the History Spreadsheet Screen where you can change the data.

Serum Level Forecast takes you to the serum level forecast screen that allows you to predict the serum drug concentrations achieved by dosage regimen that you enter.

Done takes you to the Mode screen which provides several further options.

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in

Bayes Parameters Gentamicin Crs=1.0 mg/dL Est. CLcr=96.4 mL/min

Parameters Saved On 06/01/2003

Vd: <input type="text" value="18.669"/> L (0.25 L/kg)	Vd: <input type="text"/> L
CL: <input type="text" value="3.941"/> L/hr kd: <input type="text" value="0.211"/> /hr	CL: <input type="text"/> L/hr Salt: <input type="text"/> kd: <input type="text"/> hr
CF: <input type="text" value="100.000"/> % t1/2: <input type="text" value="3.283"/> hr	CF: <input type="text"/> % F: <input type="text"/> % t1/2: <input type="text"/> hr

Route - Product: Salt: 1.00 F: 100.000

Steady-State Dosage Regimen Forecast	Loading Dose Forecast
Desired Post: <input type="text" value="7"/> mg/L Exact Estimate: _____	Initial Conc: <input type="text" value="0.0"/> mg/L
Time of Post After Infusion: <input type="text" value="1"/> hr Dose: <input type="text" value="162"/> mg	Time Drawn (hr ago): <input type="text" value="0.0"/> hr
Desired Trough: <input type="text" value="1"/> mg/L Frequency: _____	Infusion Time of Loading Dose: <input type="text"/> hr
Infusion Time: <input type="text" value="1"/> hr <input type="text" value="11.2"/> hr	If Continuous IV: _____
Desired Average Concentration: <input type="text"/> mg/L	Infusion Rate Since Level: <input type="text" value="0.0"/> mg/hr
Exact Estimate: _____ Rate: <input type="text"/> mg/24 hr	Exact Estimate: Loading Dose: <input type="text"/> mg

Figure 13. Individualized Serum Level Forecast Screens

The Individualized Bayesian and Least Squares Serum Level Forecast Screen (Figure 13) allows you to predict the serum drug concentrations achieved by dosage regimen that you enter. Results are calculated using Bayesian or Least Squares pharmacokinetic values, indicated just below the patient's ID number and name. On this screen, you may select the Route and Product and enter the dosage regimen that you desire. The steady-state serum levels predict to be produced by this regimen are displayed. For antimicrobial agents, enter the minimum inhibitory concentration (MIC) of the organism to calculate pharmacodynamic values (i.e., Post/MIC, Time Above MIC and AUC) at steady-state which are displayed at the bottom of the second column (see Appendix B for an explanation of these values).

For oral or intramuscular drugs you may enter an uneven daily dosage regimen of up to 4 doses per day. Enter the dose and hour on each line, then the time of day that you wish to know the serum level that is predicted. Steady-state peak, trough and average levels will be calculated in addition to the serum level at the time you specified.

Previous takes you to the History Spreadsheet Screen where you can change the data.

Report takes you to the Individualized Report Screen (Figure 15). The parameters reported there depend on whether you select Routine Bayes or Routine L.S. Analysis on the previous screen.

Done takes you to the Mode screen which provides several further options.

Your Institution
THERAPEUTIC DRUG MONITORING SYSTEM

06/01/2003

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in
Cr_s=1.0 mg/dL Est. CL_{cr}=96.4 mL/min

Gentamicin

	Population	Bayes	Range	Least Squares	Range
F (%)	100.000	100.000 +/-	9.999	100.000 +/-	10.000
Vd (L)	23.278	18.669 +/-	5.385	16.552 +/-	0.397
CL (L/hr)	5.241	3.941 +/-	0.985	3.756 +/-	0.072
CF (%)	100.0	100.000 +/-	100.003	100.000 +/-	100.001
kd (/h)	0.225	0.211 +/-		0.227 +/-	
t _{1/2} (hr)	3.078	3.283 +/-		3.054 +/-	

Steady-State Level Predictions (mg/L)

Route - Product: Intermittent IV - Injection Salt: 1.00

Intermittent IV Infusion Oral/IM Continuous IV Infusion

Dose: 200 mg Time of Post: 1 hr Dose: mg Rate: mg/hr
Interval: 12 hr Infusion Time: 1 hr Interval: hr

	Population	Bayes	95% CI	Least Sq.	95% CI
Peak:	8.25	10.49	8.22 - 12.76	11.57	11.34 - 11.80
Trough:	0.69	1.03	0.23 - 1.83	0.95	0.91 - 1.00
2nd Post:	6.58	8.49	6.84 - 10.15	9.22	9.06 - 9.38
Average:					

Figure 14. Detailed Analysis Screen

The Detailed Analysis Screen (Figure 14) allows you to predict the serum drug concentrations achieved by dosage regimen that you enter. Results are calculated using both Bayesian and Least-Squares values and provide both mean serum concentration values and the 95% confidence intervals around each level.

Previous takes you to the Analysis Results Screen where you can change the data you entered.

Bayes Report and **LS Report** both take you to the Individualized Report Screen (Figure 15). The parameters reported there depend on whether you select Bayes or L.S. Report on this screen.

Done takes you to the Mode screen which provides several further options.

Your Institution 06/01/2003

THERAPEUTIC DRUG MONITORING SYSTEM

123456-A Patient, Test 47 Years Male 166.0 lb 72.0 in
Crs=1.0 mg/dL Est. CLcr=96.4 mL/min

Gentamicin

Bayes Parameters: 06/01/2003

Vd: 18.669 L (0.25 L/kg)	F: 100.00 %
CL: 3.941 L/hr	kd: 0.211 hr
CF: 100.0 %	t1/2: 3.283 hr

Dosage Recommendation - Bayes Parameters

Dose: 200.0 mg every: 12.0 hours Infused Over: 1.0 hr

Levels (mg/L) at Steady-State Average: 0.0 Post (1.0 hr): 8.5 Peak: 10.5 Trough: 1.0

Case Note:

Report Printing Options

Print Graphics

Print Population Parameters

Previous
Print

Figure 15. Individualized Report Screen

The Individualized Report Screen (Figure 15) displays the Patient's demographic data, Bayesian or Least Squares pharmacokinetic parameters and the last dosage regimen that you evaluated on the previous screen. The Case Note box allows you to enter optional free text that you would like printed on the written report. This free text can later be saved in the database in the Case record. In the Report Printing Options box, you can uncheck the Print Graphics and Print Population Parameters options to simplify the report that is printed.

Previous takes you back to the Bayesian, Least Squares or Detailed Serum Level Analysis Screen, depending on where you came from, where you can change the data you entered.

Print takes you to the Windows print utility where you can designate the printer of your choice to print a written report.

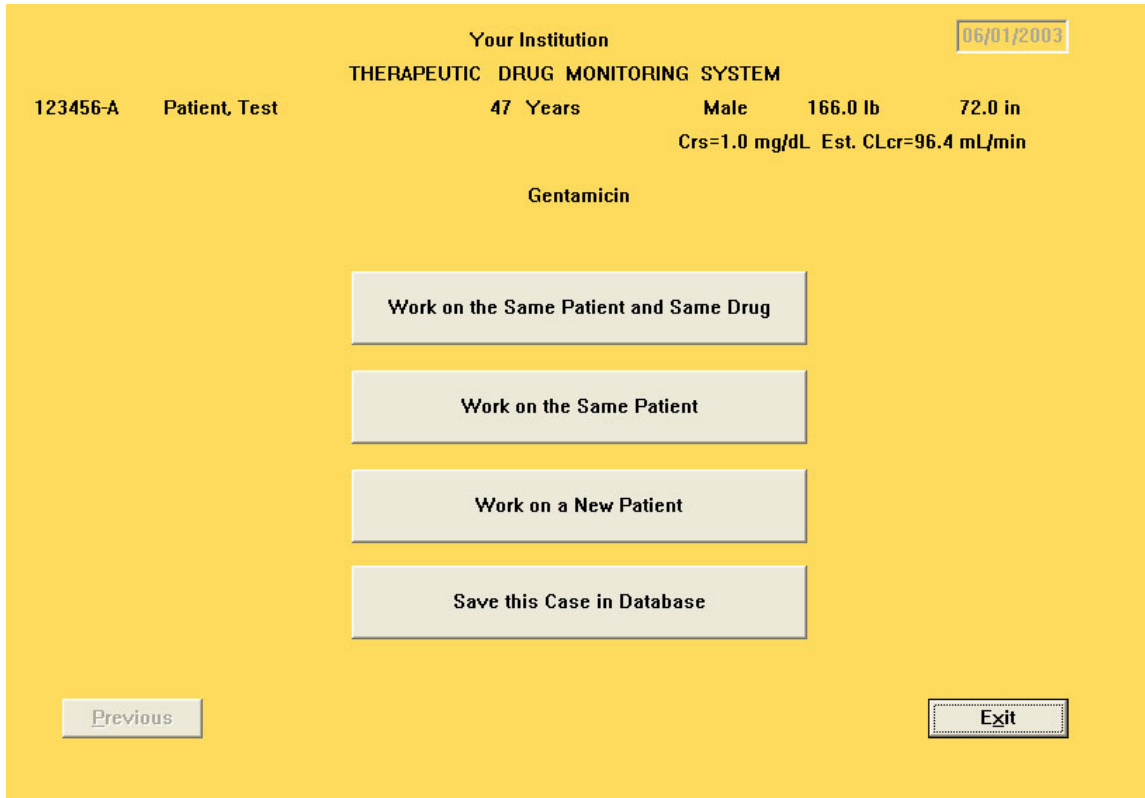


Figure 16. Mode Screen

The Mode Screen gives you several options:

Work on the Same Patient and Same Drug saves all the Patient and Case data. You can only work on the same drug that you have been analyzing.

Work on the Same Patient saves all the Patient data. You can work on any drug with a new patient.

Work on a New Patient deletes all Patient and Case data.

Save this Case in Database saves all data you have entered in the database.

Previous takes you back to the last screen you were working on.

Exit ends T.D.M.S.™

PHYSIOLOGIC PARAMETERS

This chapter provides documentation of the formulas and methods used to estimate various physiologic parameters of the patient. These, in turn, are used to estimate the pharmacokinetic parameters used in dosage regimen and serum level forecasts as well as starting points for the curve fitting routines.

Body Surface Area

The body surface area (BSA) is calculated by the formula of Haycock GB et al. J Pediatr 1978;93:62-6.

Formula:

$$\text{BSA} = \text{weight}^{0.5378} \times \text{height}^{0.3964} \times 0.024265$$

where BSA is in M², weight is in kg and height is in cm.

Adjusted Weight

The adjusted weight of adults over 18 years of age is defined in T.D.M.S.TM as the 1.2 times the ideal body weight (Devine BJ. Drug Intell Clin Pharm 1974;8:650-5) if the patient's actual weight is greater than 1.2 times the ideal weight. Otherwise, the adjusted weight is equal to the patient's total body weight. The adjusted weight of children aged 1 to 16 years is defined as the ideal body weight (Traub SL, Kitchen L. Am J Hosp Pharm 1983;40:107-10 and Traub SL, Johnson CE. Am J Hosp Pharm 1980;37:195-201.) if the actual weight exceeds 1.2 times the ideal body weight, otherwise the adjusted weight is the actual weight. In adolescents aged 16 to 18 years of age who are over 5 ft, the adjusted weight is the average of the ideal body weights calculated by the adult and pediatric formulas. In infants under the age of 1 year, the adjusted weight is the total body weight.

Formulas for IBW in kg:

Adults over 18:

$$\text{IBW (male)} = 50.0 + 2.3 \times \text{height in inches over 5 ft.}$$

$$\text{IBW (females)} = 45.5 + 2.3 \times \text{height in inches over 5 ft.}$$

Children 18 or under:

height under 5 ft.:

$$\text{IBW in kg} = 2.396 \times e^{0.01863 \times \text{height in cm}}$$

height 5 ft or over:

$$\text{IBW in kg (male)} = 39.0 + 2.27 \times \text{height in inches over 5 ft.}$$

$$\text{IBW in kg (female)} = 42.2 + 2.27 \times \text{ht in inches over 5 ft.}$$

Lean Body Mass

Lean body mass (LBM) is calculated by the James formula (Hallynck TH et al. Br J Clin Pharmacol 1981;11:523-6). Lean body mass is defined as the weight of the body minus the weight of all body fat. This is in contrast to ideal body weight which includes a normal amount of body fat weight. The lean body mass calculation is used to "denormalize" the Hallynck creatinine clearance calculations which are normalized to 50 kg lean body mass. The lean body mass calculation is invoked only if the patient's actual body weight is greater than the LBM.

Formulas:

$$\text{LBM (males)} = 1.10 \times \text{weight} - 128 \times \frac{\text{weight}^2}{\text{height}^2}$$

$$\text{LBM (females)} = 1.07 \times \text{weight} - 148 \times \frac{\text{weight}^2}{\text{height}^2}$$

where LBM and weight are in kg and height is in cm.

Creatinine Clearance

The creatinine clearance (Clcr) calculation used depends on the age of the patient. One of two formulas is used. In patients 18 years of age or older, the method of Cockcroft and Gault (Cockcroft DW and Gault MH. Nephron 1976;16:31-41) is used. Ideal body weight (IBW) is used because it is a simple and widely accepted measurement with relatively good predictive ability (Rosborough TK et al Pharmacotherapy 2005;25:823-30). In children from age 0.5 years to 18 years the method of Traub and Johnson (Traub SL and

Johnson CE. Am J Hosp Pharm 1980;37:195-201) is used. In children less than 0.5 years of age, no calculation is made.

Formulas:

Adults over 18:

$$\text{CLcr (males)} = \frac{(140 - \text{age}) \times \text{IBW}}{72 \times \text{SCr}}$$

$$\text{CLcr (females)} = 0.85 \times \text{above value}$$

where CLcr is in mL/min, adjusted weight is in kg and Crs is in mg/dL.

Children 18 or Under:

$$\text{CLcr (mL/min/1.73 M}^2\text{)} = 0.48 \times \text{height/SCr}$$

where height is in cm and Crs is in mg/dL.

PHARMACOKINETIC FORMULAS

This chapter provides the user with the equations used to calculate various serum level and dosage regimen data throughout the program.

ONE COMPARTMENT

Peak Serum Concentration

This equation calculates the steady-state peak serum concentration for intravenously administered drugs that results from infusing a dose (D) over time (t) with a dosage interval (τ), a starting concentration (cp), a Clearance (Cl) and a volume of distribution (Vd).

Formula:

$$\text{Peak}_{ss} = \frac{S \times F \times K_0 \times (1 - e^{-K_d \times t})}{Cl \times (1 - e^{-K_d \times \tau})}$$

where $K_0 = \text{dose}/t$ and $K_d = Cl/Vd$.

Trough Serum Concentration

This formula calculates the minimum serum concentration at steady-state during an intravenous dosage regimen with a dosage interval of τ .

Formula:

$$\text{Trough}_{ss} = \text{Peak}_{ss} \times e^{-K_d \times (\tau - t_{inf})}$$

where $K_d = Cl/Vd$ and t_{inf} is the infusion time.

Average Concentration

This equation is used to calculate the average steady-state serum concentration with all routes of administration.

Formula:

$$\text{Ave}_{ss} = \frac{S \times F \times K_0}{Cl}$$

where K_0 is either the infusion rate or the daily dosage as appropriate.

Loading Dose

This formula calculates the loading dose needed to achieve a specified peak of an intravenous drug infused over time (t) given clearance (Cl), initial serum concentration (cp), volume of distribution (Vd), salt fraction (S) and bioavailability (F).

Formula:

$$\text{loading dose} = \frac{\text{Cl} \times t \times (\text{peak} - [\text{cp} \times e^{-\text{Kd} \times t}])}{\text{S} \times \text{F} \times (1 - e^{-\text{Kd} \times t})}$$

where $\text{Kd} = \text{Cl}/\text{Vd}$ and t is the duration of the infusion with IV dosage or time to peak after a single dose with PO and IM administration.

Dosage Interval

This formula calculates the dosage interval needed to achieve a desired trough given a desired peak, an elimination rate constant of Kd and an infusion time of t.

Formula:

$$\text{Interval} = t + \frac{\ln(\text{peak}/\text{trough})}{\text{Kd}}$$

where t is the infusion time with IV doses, and the time to peak at steady-state for IM and oral doses.

Time to Peak - Single Dose

This formula calculates the time of the peak serum concentration following a single dose of a drug given PO or IM with an absorption rate constant of Ka and an elimination rate constant of Kd. This time is used in the above formulas to approximate an "infusion time (t)" for IM and oral doses.

Formula:

$$T_{\text{peak}} = \frac{\ln(\text{Ka}/\text{Kd})}{\text{Ka} - \text{Kd}}$$

where Ka is the absorption rate constant and Kd is Cl/Vd.

Dose Requirement

These formulas calculate the dose required to achieve a desired peak given a clearance (Cl), volume of distribution (Vd), salt fraction (S), bioavailability (F), and dosage interval (τ).

IV Formula:

$$\text{Dose} = \frac{\text{peak} \times \text{Cl} \times \tau \times (1 - e^{-K_d \times \tau})}{S \times (1 - e^{-K_d \times t_{\text{inf}}})}$$

where $K_d = \text{Cl}/V_d$ and t_{inf} is the infusion time.

PO/IM Formula:

$$\text{Dose} = \frac{\text{peak} \times V_d \times (1 - e^{-K_d \times \tau})}{F \times S \times e^{-K_d \times T_{\text{Max}}^{\text{SS}}}}$$

where $K_d = \text{Cl}/V_d$ and $T_{\text{Max}}^{\text{SS}}$ is the time to peak at steady-state as calculated below under Steady-State Levels With First-Order Absorption.

Steady-State Levels with First-Order Absorption

These equations calculate the steady-state peak (Peak_{ss}) and trough ($\text{Trough}_{\text{ss}}$) concentrations for orally and intramuscularly administered doses (D) of drugs with a bioavailability fraction (F), salt fraction (S), volume of distribution (Vd) and absorption and elimination rate constants (K_a & K_d , respectively) at a given dosage interval (τ). The time to peak at steady-state ($T_{\text{Max}}^{\text{ss}}$) is calculated as an intermediate step for calculating Peak_{ss} .

Formulas:

$$\text{Peak}_{\text{ss}} = \frac{S \times F \times D}{V_d} \times \frac{e^{-K_d \times T_{\text{Max}}^{\text{ss}}}}{1 - e^{-K_d \times \tau}}$$

$$\text{Ave}_{\text{ss}} = \frac{S \times F \times D}{\text{Cl} \times \tau}$$

$$TMax_{ss} = \frac{\ln (Ka \times [1 - e^{-Kd \times \tau}] / Kd \times [1 - e^{-Ka \times \tau}])}{Ka - Kd}$$

$$Trough_{ss} = \frac{S \times F \times D \times Ka}{Vd \times (Ka - Kd)} \times \left[\frac{e^{-Kd \times \tau}}{1 - e^{-Kd \times \tau}} - \frac{e^{-Ka \times \tau}}{1 - e^{-Ka \times \tau}} \right]$$

Concentration at Time t

These equations are used to calculate the serum concentration (cp) at a given time (t) after a dose where S is the salt fraction, D is the dose, CF is the compliance factor, F is the bioavailability, K_0 is the infusion rate, t_{inf} is the infusion time, Vd is the volume of distribution, Cl is the clearance and Kd is Cl/Vd. They are used in both the curve fitting routines and in the graphics calculations. The concentration during a multiple dose regimen is calculated by superposition (i.e., addition of the contributions of all prior doses). The superposition method is used in both the curve fitting and graphics portions of T.D.M.S.TM to determine the serum concentration at times of interest.

IV Formulas:

IV Bolus:

$$Cp_t = \frac{CF \times S \times D}{Vd} \times e^{-Kd \times t}$$

During IV Infusion:

$$Cp_t = \frac{CF \times S \times K_0}{Cl} \times (1 - e^{-Kd \times t})$$

After the End of an Infusion:

$$C_{p_t} = \frac{CF \times S \times K_0}{Cl} \times (1 - e^{-K_d \times t_{inf}}) \times e^{-K_d \times (t - t_{inf})}$$

PO/IM Dosage:

$$C_{p_t} = \frac{CF \times S \times F \times K_a \times \text{dose}}{V_d \times (K_a - K_d)} \times (e^{-K_d \times t} - e^{-K_a \times t})$$

TWO COMPARTMENT

Micro-Rate Constants

The following equations are used to calculate micro-rate constants after establishment of clearance (Cl), volume of distribution of the peripheral compartment (V_{d_b}), volume of distribution of the central compartment (V_c) and the transfer rate constant between the peripheral and central compartments (K_{21}) by population estimates.

Formulas:

$$K_{10} = Cl / V_c$$

$$\beta = Cl / V_{d_b}$$

$$\alpha = K_{21} \times K_{10} / \beta$$

Steady-State Concentration at Time t

This equation is used to predict the serum concentration at steady-state ($C_{p_{ss}}$) at time (t) during a dosage interval of drugs with a salt fraction (S) given IV at an infusion rate of K_0 over an infusion time of (t_{inf}) and at a dosage interval of (τ). During the infusion, t_{inf} and t are equal.

Formula:

$$C_{p_{ss}} = \frac{K_0 \times S \times (K_{21} - \alpha) \times (1 - e^{-\alpha \times t_{inf}}) \times e^{-\alpha \times t}}{V_c \times \alpha \times (\alpha - \beta) \times (1 - e^{-\alpha \times \tau})} + \frac{K_0 \times S \times (\beta - K_{21}) \times (1 - e^{-\beta \times t_{inf}}) \times e^{-\beta \times t}}{V_c \times \beta \times (\alpha - \beta) \times (1 - e^{-\beta \times \tau})}$$

Nonsteady-State Concentration at Time t

This equation is used to predict the serum concentration (C_p) at time (t) during a dosage interval of drugs with a salt fraction (S) given IV at an infusion rate of (K_0) over an infusion time of (t_{inf}) and a dosage interval (τ). During the infusion, $t_{inf} = t$.

Formulas:

$$C_{p_t} = \frac{K_0 \times S \times (K_{21} - \alpha) \times (1 - e^{-\alpha \times t_{inf}}) \times e^{-\alpha \times t}}{V_c \times \alpha \times (\alpha - \beta)} + \frac{K_0 \times S \times (\beta - K_{21}) \times (1 - e^{-\beta \times t_{inf}}) \times e^{-\beta \times t}}{V_c \times \beta \times (\alpha - \beta)}$$

MICHAELIS-MENTEN FORMULAS

Steady-State Serum Concentration

This formula calculates the steady-state serum concentration of a drug eliminated by capacity-limited (Michaelis-Menten) pharmacokinetics (e.g., phenytoin)

$$C_{pss} \text{ (mg/L)} = \frac{K_m \times \text{Dosage Rate}}{(V_{max} - \text{Dosage Rate})}$$

where,

$$\text{Dosage Rate} = S \times F \times \text{Dose} / \text{Dosage Interval}$$

Dosage at Steady-State

$$\text{Dosage} = \frac{V_{max} \times C_{pss} \times \text{Interval}}{S \times F \times (K_m + C_{pss})}$$

Calculation of Vmax from One Steady-State Level

$$V_{max} = \frac{\text{Dosage Rate} \times (K_m + C_{pss})}{C_{pss}}$$

where,

Dosage Rate = $S \times F \times \text{Dose} / \text{Dosage Interval}$
Km = Population value for Km with 0 or 1 steady-state level and from the formula below with 2 steady-state levels

Calculation of Km from Two Steady-State Levels

$$K_m = \frac{\text{Rate 1} - \text{Rate 2}}{(\text{Rate 1}/C_{pss 1}) - (\text{Rate 2}/C_{pss 2})}$$

DRUG-SPECIFIC PARAMETERS

In this chapter, the formulas used to calculate the estimated pharmacokinetic parameters for individual patients are provided. In addition, certain assumptions made in the program are mentioned. Literature references are provided to document the formulas and values used.

Aminoglycosides

All of the aminoglycosides are assumed to have the same clearance and apparent volume of distribution. Parameters that are associated with aminoglycosides in the program are as follows: salt fraction = 1; bioavailability = $100 \pm 5\%$; and the IM absorption rate constant is 1.9 hr^{-1} in patients 75 and under and 2.7 hr^{-1} in patients over 75.¹⁻³

Formulas:

Clearance (L/hr):

Cl (over 6 months) =

$$([0.82 \times \text{CLcr}] + 0.11) \times \text{dosing weight} \times 0.06$$

Where dosing weight = $\text{IBW} + 0.4 \times (\text{TBW} - \text{IBW})$

Reference: 4

Cl (over 6 months with cystic fibrosis) =

$$([0.82 \times \text{CLcr}] + 0.24) \times \text{adjusted weight} \times 0.06$$

References: 5-7

Cl (under 6 months) =

$$(0.05 + [0.17 \times \text{age in years}]) \times \text{total body weight}$$

(calculation made only if Crs is less than 0.8-1.2 mg/dL,
depending on the age of the infant)

References: this equation written to smooth transition between age groups in references 5-11

Volume of Distribution (L):

$$V_d (\text{over 6 months}) = 0.3 \times \text{dosing weight}$$

$$\text{Where dosing weight} = \text{IBW} + 0.4 \times (\text{TBW} - \text{IBW})$$

$$V_d (\text{6 months} - 1 \text{ yr}, < \text{IBW}) = 0.3 \times \text{total body weight}$$

References: 4, 12

$$V_d (\text{1 month to 6 months}) = (0.52 - [0.44 \times \text{age in yr}]) \times \text{total body weight}$$

References: this equation written to smooth transition between age groups above and below

$$V_d (\text{1 month and under}) = 0.52 \times \text{total body weight}$$

Reference: 15

$$V_d (\text{1 month and under receiving ECMO [extracorporeal membrane oxygenation]}) = 0.58 \times \text{total body weight}$$

Reference: 16

$$V_d (\text{1 month and under with uncorrected patent ductus arteriosus}) = 0.63 \times \text{total body weight}$$

Reference: 15

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 5%, Cl - 50%, Vd - 30% in patients 65 and under and 50% in those over 65, CF - 50%; the time weighting factor is 1.005.^{15,16} In cystic fibrosis, inpatient variability may be increased, tending towards more normal values as infection resolves.¹⁷⁻²⁰ In these patients, the time weighting factor is increased to 1.01 in T.D.M.S.TM to more heavily weight the most recent serum levels. Time weighting is also increased to 1.01 in critically ill and ICU patients.^{21,22}

Modifying Factors

Many factors have been found to alter aminoglycoside pharmacokinetics. However, only a few have been reliably quantified and confirmed. Only those that have been well quantified are included in T.D.M.S.TM

Critically Ill or ICU Patients. Numerous studies have documented that critically ill and ICU patients have a larger volume of distribution than other patients and their variability over time is greater. Vd is increased by 13% to 0.34 L/kg in patients over 1 month of age and time weighting is increased to 1.01.^{21,22}

Burn Patients. Burn patients often have higher dosage requirements than other patient groups. A major reason for this is that glomerular filtration rate is dramatically increased in some burn patients.²³ T.D.M.S.TM allows creatinine clearance to range as high as 265 mL/min in this patient group and calculates aminoglycoside clearance as for other patients. If a burn patient is critically ill, the "Critically Ill or ICU Patient" factor should also be selected.

Hematology/Oncology Patients. These patients have an expanded Vd which is modeled as an increase of 17% to 0.35 L/kg.²⁴⁻²⁶

Spinal Cord Injury. These patients have a larger Vd which is increased in T.D.M.S.TM by 10% to 0.33 L/kg.²⁷

Cystic Fibrosis. Data are conflicting between studies on whether there are alterations in pharmacokinetic parameters in cystic fibrosis. One factor may be that inpatient parameters change as therapy progresses. T.D.M.S.TM increases the nonrenal clearance by 118% and increases the time weighting factor to 1.01.^{5-7,18,20,28}

Patent Ductus Arteriosus. Newborns with uncorrected or recently treated patent ductus arteriosus have a larger volume of distribution than normal. This factor is taken into account as noted above under Volume of Distribution.¹⁴

ECMO. This procedure increases the volume of distribution as noted above under Volume of Distribution.¹⁵

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Ciprofloxacin

The salt fraction for ciprofloxacin is 1 for both the oral and injectable product. Oral bioavailability is $70 \pm 20\%$ for patients 60 and younger and $87.5 \pm 20\%$ in those over 60 yr.¹⁻³ The absorption rate constant is 1.5.¹ Parenteral bioavailability is $100 \pm 5\%$.

Formulas:

Clearance (L/hr):

$$Cl (18 \text{ years and over}) = (1.97 \times CLcr \times 0.06) + 13.23$$

Reference: 4

Volume of Distribution (L):

$$Vd (18 \text{ years and over}) = 2.1 \times \text{adjusted wt.}$$

Reference: 5

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: Oral F - 20%, IV F - 5%, Cl - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005, assay error is 10% and FE is 0.25.

Modifying Factors

The absorption of oral ciprofloxacin is quite susceptible to interference by divalent cations. The amount of interference varies by product and amount contained. These products generally should be taken 6 hours before or 2 hours after ciprofloxacin.

Aluminum and Magnesium Antacids. Concurrent ingestion of these antacids reduces ciprofloxacin bioavailability by 60% per Nix DE et al. Clin Pharmacol Ther 1989;46:700-5, Shiba K et al. Antimicrob Agents Chemother 1992;36:2270-4, Flor S et al. Antimicrob Agents Chemother 1990;34:2436-8, Höffken G et al. Rev Inf Dis 1988;(suppl):S138-9.

Cancer Chemotherapy. Patients receiving cancer chemotherapy have ciprofloxacin bioavailability reduced by 47% per Johnson EJ et al. J Antimicrob Chemother 1990;25:837-42.

Cystic Fibrosis. Cystic fibrosis patients have ciprofloxacin bioavailability increased by 40% per Cristensson BA et al. Antimicrob Agents Chemother 1992;25:12-7.

Oral Didanosine. This product has buffering agents included which decrease ciprofloxacin bioavailability by 98% per Sahai J et al. Clin Pharmacol Ther 1993;53:292-7.

Oral Iron. Oral iron decreases ciprofloxacin bioavailability by 50% per Polk RE. Antimicrob Agents Chemother 1989;33:1841-4, Shiba K et al. Antimicrob Agents Chemother 1992;36:2270-4, Lehto P et al. Br J Clin Pharmacol 1994;37:82-5.

Sucralfate. Sucralfate decreases ciprofloxacin bioavailability by 60% per Garrelts JC et al. Antimicrob Agents Chemother 1990;34:931-3, Nix DE et al. Pharmacotherapy 1989;9:377-80, VanSlooten AD et al. DICP Ann Pharmacother 1991;25:578-82.

Zinc. Zinc alone or in multivitamins decreases ciprofloxacin bioavailability by 50% per Polk RE et al. Antimicrob Agents Chemother 1989;33:1841-4.

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Digoxin

The various dosage forms of digoxin have different bioavailabilities and coefficients of variation associated with their absorption. The values used are as follows:^{1,2}

<u>Bioavailability</u>	
Tablets	70 ± 14%
Capsules	95 ± 5%
Elixir	77.5 ± 9.6%
IV Injection	100 ± 5%

The oral absorption rate constant (k_a) is set at 1.5 hr⁻¹. It should be noted that this rate constant has its primary use in determining the shape of curves plotted in the graphics portion of T.D.M.S.TM Although k_a is used during curve fitting, serum digoxin levels should not be drawn before 6-8 hours after an oral dose when using a one-compartment simulation. Since absorption is complete by 6-8 hours after the dose, the exact value of the absorption rate constant is not important during curve fitting.

Formulas:

Clearance (L/hr):

$$Cl \text{ (CHF over 10 yr)} = (0.88 \times CL_{Cr} + 0.33 \times TBW) \times 0.06$$

$$Cl \text{ (nonCHF over 10 yr)} = (1.02 \times CL_{Cr} + 0.8 \times TBW) \times 0.06$$

Reference: 3

$$Cl \text{ (6 months - 10 yr)} = (1.4 \times CL_{Cr} + 0.7 \times TBW) \times 0.06$$

References: 4-8

$$Cl \text{ (under 6 months)} = (3.24 - [2.88 \times \text{patient age in yr}]) \times TBW \times 0.06$$

This equation was written to make a smooth transition between a neonatal clearance of 0.18 x total body weight and the clearance at six months.

$$Cl \text{ (under 1 month)} = 0.18 \times TBW$$

$$Cl \text{ (under 1 month, premature)} = 0.12 \times TBW$$

(calculation made only if C_{Cr} is less than 0.8-1.2 mg/dL, depending on the age of the infant)

Reference: all data for children under 6 months from reference 9.

Volume of Distribution (L)

$$Vd (10 \text{ yr and over}) = (3.12 \times CLcr) + (3.84 \times TBW)$$

Reference: 3

$$Vd (2 \text{ yr} - 10 \text{ yr}) = 16 \times TBW$$

$$Vd (1 \text{ month} - 2 \text{ yr}) = (8.44 + [\text{age in yr} \times 3.78]) \times \text{total body weight}$$

$$Vd (\text{under 1 month, full-term}) = 8.75 \times \text{total body weight}$$

$$Vd (\text{under 1 month, premature}) = 7.5 \times \text{total body weight}$$

Reference: all pediatric data from reference 9. Equation for age group between 1 month and 2 years of age was derived to make a smooth transition between groups above and below.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - specified by product above, Cl - 52%, Vd - 30%, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

A number of factors are known to affect digoxin bioavailability, clearance and apparent volume of distribution. These are used to modify the calculated population values for F, Cl and Vd if they are selected as being present. The factors that are used and the references are given below:

Congestive Heart Failure. CHF decreases digoxin renal and nonrenal clearance as noted above.

Thyroid Dysfunction. Hyperthyroidism increased digoxin clearance by 30% and volume of distribution by 30%. Hypothyroidism decreases digoxin clearance by 30% and volume of distribution by 30%.¹⁰

Amiodarone. Amiodarone decreases digoxin clearance by an average of 28% and the volume of distribution by 12%.^{11,12} It also appears to increase oral bioavailability of digoxin by an average of 25%.¹³ The increased bioavailability factor is applied to the tablets and elixir only and not to the capsules.

Diltiazem. Diltiazem decreases the clearance of digoxin by 15%.¹⁴⁻¹⁸

Quinidine. Quinidine decreases the volume of distribution of digoxin by 30% and decreases the clearance by 50%.^{19,20}

Verapamil. Oral verapamil decreases the nonrenal clearance by 43% during long-term use.^{21,22} During the first 4 weeks of therapy, renal digoxin clearance is also decreased.²³ Therefore, total digoxin clearance will be less initially than predicted by this correction.

Amiloride or Triamterene. Amiloride and triamterene decrease nonrenal digoxin clearance by an average of 85% and increase renal clearance by 20%.^{24,25}

Spirolactone. Spirolactone decreases digoxin clearance by 30%.^{20,25-26}

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Flucytosine

The salt fraction for flucytosine is 1 for both the oral and injectable (investigational) product. Oral bioavailability is $84 \pm 15\%$ and the absorption rate constant is 1.1.¹ Parenteral bioavailability is $100 \pm 5\%$.

Formulas:

Clearance (L/hr):

$$Cl \text{ (6 months and over)} = (0.79 \times CLcr) + (0.01 \times \text{adjusted wt.})$$

References: 1-3

Volume of Distribution (L):

$$Vd \text{ (6 months and over)} = 0.71 \times \text{adjusted wt.}$$

References: 1-4

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 15%, Cl - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

There are no well-documented factors that affect flucytosine pharmacokinetics other than renal function which is accounted for in the clearance calculation above. However, it has been observed by our consultants that flucytosine serum levels of infants in intensive care units are somewhat unpredictable and are often quite low. It is not known if this is due to erratic oral absorption, instability of extemporaneously compounded flucytosine suspensions, or both. Since there are no published pharmacokinetic studies on flucytosine in infants, T.D.M.S.TM should be used with caution in this age group.

References

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Lithium

The various dosage forms of lithium salts have different bioavailabilities and absorption rate constants. The absorption rate constant has its primary relevance in determining the shape of curves plotted in the graphics portion of T.D.M.S.TM Although it is used during curve fitting, serum lithium levels are usually drawn 12 hours after a dose. Since absorption is complete by about 10 hours after the dose, the exact value of the absorption rate constant is not important during curve fitting when using a one-compartment simulation.

Lithium Dosage Form Parameters

Dosage Form	F	SD	Ka	Refs.
Syrup	1.0	0.1	3.6	1
Fast-Release Capsules	1.0	0.1	1.2	1
Fast-Release Tablets	1.0	0.1	1.2	1
Eskalith CR	0.97	0.1	0.5	1

Formulas:

Clearance (L/hr):

$$Cl (12 \text{ yr or over}) = 0.14 \times CL_{Cr} + 0.006 \times \text{adjusted weight}$$

References: 3-8

Volume of Distribution (L)

$$Vd (12 \text{ yr} - 70 \text{ yr}) = 0.73 \times \text{adjusted weight}$$

References: 3-5

$$Vd (\text{over } 70 \text{ yr}) = 0.59 \times \text{adjusted weight}$$

References: 6,7

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - specified by product above, Cl - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005. The time weighting factor is 1.005.

Modifying Factors

Acetazolamide or Sodium Bicarbonate. Acetazolamide and sodium bicarbonate increase lithium clearance by about 30% per Pepin SM, in Taylor WJ, Caviness MHD, eds. A textbook for the clinical application of therapeutic drug monitoring. Irving, TX. Abbott Laboratories, Diagnostics Division 1986:435-65.

Angiotensin Converting-Enzyme (ACE) Inhibitors. Numerous case reports of lithium toxicity have occurred with concurrent use of these agents. However, the cause of the toxicity has not been defined and it seems to happen only sporadically. Monitor lithium serum levels especially carefully when administering an ACE inhibitor concurrently.

Ibuprofen or Piroxicam. Average clearance is decreased by 33% and the coefficient of variation is increased to 43% per Ragheb M. J Clin Psychiatr 1987;48:161-3. Ibuprofen decreases lithium clearance erratically. Data on piroxicam are limited to case reports and changes in clearance are difficult to quantify. It appears that clearance is decreased by at least 33% with piroxicam, possibly more, per Walbridge DG et al. Br J Psychiatr 1985;147:206-7 and Harrison TM et al. Br J Psychiatr 1986;149:124-5.

Diclofenac, Indomethacin or Naproxen. Diclofenac, indomethacin and naproxen decrease lithium clearance by an average of 25% per Reimann IW et al. Arch Gen Psychiatr 1983;40:283-6., Frolich JC et al. Br Med J 1979;28:1115-6 and Ragheb M et al. J Clin Psychopharmacol 1986;6:150-4.

Low Sodium Diet. A low sodium diet decreases lithium clearance by up to 50% per Atherton JC et al. Kidney Int 1990;37(suppl 28):S36-8.

Theophylline. The clearance of lithium is increased proportionately to theophylline serum concentration. An increase in lithium clearance of 50% corresponds approximately to a theophylline level of 15 mg/L per Holstad SG et al. Psychiatry Res 1988;25:203-11.

Thiazide Diuretics. Thiazides in typically used doses decrease lithium clearance by an average of 29% per Petersen V et al. Br Med J 1974;2:143-5., Himmelhoch JM et al. Clin Pharmacol Ther 1977;22:225-7 and Jefferson JW et al. JAMA 1979;241:1134-6.

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Levofloxacin and Ofloxacin

The salt fraction for ofloxacin is 1 for both the oral and injectable product. Oral bioavailability is $100 \pm 10\%$. The absorption rate constant is 3.0.^{1,2} Parenteral bioavailability is $100 \pm 5\%$.

Formulas:

Clearance (L/hr):

$$Cl \text{ (18 years and over)} = [(1.21 \times CLcr) + 36] \times 0.06$$

Reference: 3

Volume of Distribution (L):

$$Vd \text{ (18 years and over)} = 1.36 \times \text{adjusted wt.}$$

References: 4-8

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: Oral F - 10%, IV F - 5%, Cl - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005, assay error is 10% and FE is 0.15.

Modifying Factors

The absorption of oral levofloxacin and ofloxacin is susceptible to interference by divalent cations. The amount of interference varies by product and amount contained. These products generally should be taken 6 hours before or 2 hours after levofloxacin or ofloxacin.

Aluminum and Magnesium Antacids. Concurrent ingestion of these antacids reduces ofloxacin bioavailability by 45% per Flor S et al. *Antimicrob Agents Chemother* 1990;34:2436-8, Höffken G et al. *Rev Infect Dis* 1998;(suppl):S138-9 (abstract) and decreases the K_a to 0.67/hr per Akerele JO, Okhamafe AO. *J Antimicrob Chemother* 1991;28:87-94.

Oral Iron. Oral iron decreases ofloxacin bioavailability by 17.5% and increases the SD to 15% per Lehto P et al. *Br J Clin Pharmacol* 1994;37:82-5, Martinez Cabarga M et al. *Antimicrob Agents Chemother* 1991;35:2102-5.

Sucralfate. Sucralfate decreases ofloxacin bioavailability by 61% per Lehto P et al.

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Procainamide

Procainamide Dosage Form Parameters

Dosage Form	F	SD	Ka	Refs.
Fast-Release Capsules	0.83	0.166	2	1,2
Slow-Release Capsules	0.83	0.166	0.4	1,3,4

Formulas:

Clearance (L/hr):

$$\text{Cl (over 12 yr)} = [(2.7 \times \text{CLcr}) + (3.9 \times \text{adjusted weight})] \times 0.06$$

Reference: 2

$$\text{Cl (7 - 12 yr)} = 19.4 \times \text{patient age}$$

Reference: 5

$$\text{Cl (6 months - 7 yr)} = 7.3 + [1.86 \times (\text{patient age} - 0.5)] \times \text{total body weight}$$

Reference: this equation was written to make a smooth transition between age groups above and below.

$$\text{Cl (under 6 months)} = 7.3 \times \text{total body weight}$$

Reference: 6

Volume of Distribution (L)

$$\text{Vd (18 yr and over)} = 1.9 \times \text{adjusted weight}$$

References: 2

$$\text{Vd (12 - 18 yr)} = \{2.9 - [(\text{patient age} - 12) \times 0.166]\} \times \text{adjusted weight}$$

References: this equation was written to make a smooth transition between age groups above and below.

$$\text{Vd (12 yr and under)} = 2.9 \times \text{total body weight}$$

References: 5,6

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 20%, Cl - 50%, Vd - 30%, CF - 50%. The time weighting factor is 1.005, assay error is 10% and FE is 0.35.

Modifying Factors

Amiodarone. Amiodarone decreases total drug clearance by 23% per Windle J et al. Clin Pharmacol Ther 1987;41:603-10 and Saal AK et al. Am J Cardiol 1984;53:1264-7.

Cimetidine. Cimetidine decreases renal clearance by 40% per nonrenal clearance per Bauer LA et al. JAGS 1990;38:467-9, Somogyi A et al. Eur J Clin Pharmacol 1983;25:339-45, Rodvold KA. Ther Drug Monit 1987;9:378-83, Lai, MY et al. Int J Clin Pharmacol Ther Toxicol 1988;26:118-21 and Christian CD et al. Clin Pharmacol Ther 1984;36:221-7.

Trimethoprim or Septra. Trimethoprim decreases procainamide renal clearance by 46% per Vlasses PH et al. Arch Intern Med 1989;149:1350-3, Kosoglou T et al. Clin Pharmacol Ther 1988;44:467-77.

Impaired Cardiac Output. Decreased cardiac output decreases total drug clearance by 35% per Winter M. Basic clinical pharmacokinetics, 2nd ed, Vancouver, WA. Applied Therapeutics. 1988.

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Phenobarbital

The salt fraction is 1 for the oral product and 0.91 for the injectable product. Oral bioavailability is $100 \pm 10\%$, while parenteral bioavailability is $100 \pm 5\%$. Absorption rate constants are 1.5 hr^{-1} for tablets, 7.2 hr^{-1} for the elixir and 1.1 hr^{-1} for IM injections.^{1,2}

Formulas:

Clearance (L/hr):

$$\text{Cl (over 13 yr)} = 0.004 \times \text{total body weight}$$

Reference: 3-6

$$\begin{aligned} \text{Cl (10 - 13 yr)} = \\ (0.0077 - [(\text{age in yr} - 10) \times 0.00123]) \times \text{total body weight} \end{aligned}$$

Reference: this equation was written to make a smooth transition between age groups above and below as suggested by data in reference 7.

$$\text{Cl (10 yr and under)} = 0.0077 \times \text{total body weight}$$

References: 6-10

Volume of Distribution (L)

$$\text{Vd (over 1 month)} = 0.6 \times \text{total body weight}$$

References: 10-13

$$\begin{aligned} \text{Vd (under 1 month)} = \\ (0.91 - [3.7 \times \text{age in years}]) \times \text{total body weight} \end{aligned}$$

Reference: this equation was written to make a smooth transition between Vd of 0.6 L/kg above and neonatal Vd of 0.91 L/kg per references 10-13.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 10%, Cl - 20% in adults and 40% in children under 13 and in those taking valproate,^{3,6,14} Vd - 10% in adults and 20% in children under 13, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

Liver Disease. Severe cirrhosis decreases phenobarbital clearance by one-third while hepatitis decreases clearance by 17%.¹⁵

Pregnancy. Pregnancy increases clearance by an estimated 35% from data of reference 16.

Valproic Acid. Concurrent valproic acid use decreases phenobarbital clearance by 35% in adults and 55% in children under 16.^{3,6,14}

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Phenytoin

Phenytoin exhibits slow and erratic (although usually complete) oral absorption, variable plasma protein binding, and capacity-limited (Michaelis-Menten) elimination pharmacokinetics. All of these factors contribute to the great difficulty in predicting an individual patient's phenytoin dosage requirements. Various condition and drugs are known to affect phenytoin's pharmacokinetics, although the exact changes in parameters is often not known. Because of these many factors and their uncertainty, T.D.M.S.TM groups some of these factors together and makes a single approximate change in pharmacokinetic parameters. It is always important to measure serum phenytoin levels during therapy, especially if there are complicating factors. Obtaining free (unbound) phenytoin levels are particularly recommended in the presence of drugs or conditions that affect protein binding. Phenytoin injection should not be given intramuscularly because of its poor absorption and tissue toxicity. Only the phenytoin prodrug fosphenytoin is allowed to be given IM by T.D.M.S.TM It is converted to phenytoin in the body by a first-order process.

Phenytoin Dosage Form Parameters

Dosage Form	S	F	SD	Refs.
Fosphenytoin (IM)	1*	1	0.1	1
Fosphenytoin (IV)	1*	1	0.1	2
Phenytoin Injection (IV)	0.92	1	0.1	3
Phenytoin Capsules	0.92	1	0.1	3
Phenytoin Suspension	1	1	0.1	3
(neonates <1 month)	1	0.9	0.2	4
Phenytoin Tablets	1	1	0.1	3

*Dosage expressed in phenytoin equivalents (PE)

Oral phenytoin absorption in adults is modeled as a constant 50 mg/hour. In children, the rate is reduced in proportion to the body surface area of the child.

Intramuscular fosphenytoin absorption (ref. 1) has a K_a of 2.5 and intravenous fosphenytoin absorption has a K_a of 3.6 (ref. 2) which represents conversion to phenytoin.

Phenytoin Plasma Protein Binding

Group	Unbound Fraction	Refs.
Adults and Children	0.1	3
Neonates <1 month	0.2	5
CLcr 10-25 mL/min	*	6,7

CLcr <10 mL/min 0.25 6,7

* $0.35 - (0.01 \times \text{CLcr})$ equation to smooth transition between normal and uremic values

Correction of Levels and Vd to Normal Albumin Concentration and Affinity

For CL_{cr} < 25 mL/min:

$$\text{Corrected parameter} = \frac{\text{Uncorrected Parameter}}{0.48 \times (1 - \alpha) \times \text{serum albumin}/4.4 + \alpha}$$

For CL_{cr} ≥ 25

$$\text{Corrected parameter} = \frac{\text{Uncorrected Parameter}}{[(1 - \alpha) \times \text{serum albumin}/4.4 + \alpha]}$$

Correction of Levels and Km for Altered Albumin Concentration and Affinity

For CL_{cr} < 25 mL/min:

$$\text{Corrected parameter} = \text{Uncorrected Parameter} \times 0.48 \times (1 - \alpha) \times \text{serum albumin}/4.4 + \alpha$$

For CL_{cr} ≥ 25 mL/min:

$$\text{Corrected parameter} = \text{Uncorrected Parameter} \times [(1 - \alpha) \times \text{serum albumin}/4.4 + \alpha]$$

Time to Reach New Level after Dosage Change

$$\text{Time} = \frac{K_m \times [\ln(C_{p_0}/C_{p_t}) + (C_{p_0} - C_{p_t})]}{V_{\max}/V_d}$$

Time to Reach 90% of Steady-State Level

$$\text{Time}_{90\%} = \frac{K_m \times V_d \times (2.3 \times V_{\max} - 0.9 \times \text{Dosage Rate})}{(V_{\max} - \text{Dosage Rate})^2}$$

where,

$$\text{Dosage Rate} = S \times F \times \text{Dose} / \text{Dosage Interval}$$

Population Formulas:

V_{max} (mg/day):

$$V_{\max} (<6 \text{ months}) = 11.5 \text{ mg/kg/day}$$

Reference: Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

$$V_{\max} (6 \text{ months} - 15 \text{ yr}) = 415 \times (\text{total body weight}/70 \text{ kg})^{0.6}$$

Reference: Grasela TH et al. Clin Pharmacokinet 1983;8:355-64.

$$V_{\max} (15 \text{ yr} - 20 \text{ yr}) = 415 + (29 \times [\text{age} - 15]) \times (\text{total body weight}/70 \text{ kg})^{0.6}$$

Reference: Equation written to smooth transition between upper and lower age groups.

$$V_{\max} (>20 \text{ yr}) = 560 - (2.8 \times [\text{age} - 20]) \times (\text{total body weight}/70 \text{ kg})^{0.6}$$

Reference: Grasela TH et al. Clin Pharmacokinet 1983;8:355-64 modified to attain a value of 560 mg (8 mg/kg/day) for a 70 kg person at age 20 and decreasing with increasing age per Bauer LA, Bluin RA. Clin Pharmacokinet 1983;8:545-9.

K_m (mg/L):

$$K_m (<1 \text{ month}) = 5 \text{ mg/L}$$

Reference: Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

$$K_m (1 \text{ month} - 6 \text{ months}) = 5 + (0.3 \times (\text{age} - 0.083))$$

Reference: Equation written to smooth transition between upper and lower age groups.

$$K_m (6 \text{ months} - 15 \text{ yr}) = 6.4 \text{ mg/L}$$

Reference: Bauer LA, Bluin RA. Clin Pharmacokinet 1983;8:545-9. (weighted average of all age groups)

$$K_m (\geq 15 \text{ yr}) = 5.7$$

Reference: Grasela TH et al. Clin Pharmacokinet 1983;8:355-64.

Volume of Distribution (L)

$$V_d (<1 \text{ yr}) = 1 \times \text{TBW} \pm 30\%$$

Reference: Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

$$V_d (\geq 1 \text{ yr}) = 0.65 \times \text{IBW}$$

Reference: Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

$$V_d (\text{Obesity}) = (0.65 \times \text{IBW}) + 1.33 \times (\text{TBW} - \text{IBW})$$

References: Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209 & Abernethy DR, Greenblatt. Arch Neurol 1985;42:468-71.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 10%, V_{max} - 30%, K_m - 50%, V_d - 20%, CF - 50%. The time weighting factor is 1.01, assay error is 10% and FE is 0.75.

Modifying Factors

Ethnic Differences. Metabolism of phenytoin is under genetic control. Various ethnic groups appear to metabolize phenytoin differently. However, it is unclear the extent to which genetic and environmental (e.g., diet, pollution) factors contribute to these differences, which groups are affected and by how much. The best studied group is Japanese patients (in Japan) who have a lower K_m than Europeans; Japanese-Americans have not been studied. Some evidence also exists that Blacks in southern Africa have similarly prolonged elimination. African-Americans appear to have metabolism more similar to Caucasians than to southern Africans. Saudi Arabians' metabolism seems to be similar to Caucasians'. Hvidberg EF. Ethnic differences in reactions to drugs and xenobiotics. Alan R. Liss, Inc. 1986:279-87; Edeki TI, Brase DA. Drug Metab Rev 1995;27:449-69; Botha JH et al. Clin Pharm 1991;10:928-31; Grasela TH et al. Clin Pharmacokinet 1983;8:355-64. T.D.M.S.TM allows selection of a slow metabolism factor for patients who have ethnically slow metabolism; K_m is decreased by 50% if this option is selected.

Highly Protein-Bound Drugs. Drugs that are highly albumin bound can increase the

free (unbound) fraction of phenytoin. The free fraction is increased by 40% in T.D.M.S.TM when one of the following drugs are given concurrently: salicylate (high-dose), tricyclic antidepressants (possibly), and valproic acid. The value arises from the 40% change that occurs with valproic acid per Tozer TN, Winter ME. Chapter 25. Phenytoin. In, Applied pharmacokinetics, 2nd ed. Applied Therapeutics. Vancouver, WA. 1986.

Jaundice. The free fraction is increased by 50% with a serum bilirubin >6 mg/dL. This value is estimated from the fact that a serum bilirubin of 6 mg/dL is over 0.1 mmol/L, per Tozer TN, Winter ME. Chapter 25. Phenytoin. In, Applied pharmacokinetics, 2nd ed. Applied Therapeutics. Vancouver, WA. 1986.

Neurologic Injury. Critically ill patients with head trauma have high phenytoin requirements. This appears to be caused primarily by an increase in predicted V_{max} by 40%. Boucher BA et al. Clin Pharmacol Ther 1988;44:675-83 and O'Mara NB et al. Crit Care Med 1995;23:1418-24. Phenytoin metabolism also appears to change more rapidly with time than in other patients, so the time-weighting factor is increased to 1.01

Tube Feeding. Tube feeding has marked effects on phenytoin levels. In T.D.M.S.TM, it is modeled as a decrease in F to 0.6 and an increase in its SD to 0.3 per the computer program, Phenda.

Other Factors

Many other factors are known to affect phenytoin serum concentrations. However, the exact effects on pharmacokinetic parameters are not known. They probably also increase the variability in the factors they affect. The following factors are not programmed into T.D.M.S.TM, but the user may consider manually adjusting these parameters and/or increasing their SD in patients with one of these conditions.

Antacids or Sucralfate. Antacids or sucralfate may decrease absorption (F) of phenytoin. It is best to separate doses of phenytoin and antacids by 2 or more hours per Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

Cirrhosis/Severe Liver Disease. Liver diseases may reduce phenytoin's metabolism, causing a decrease in V_{max} per Tozer TN, Winter ME. Chapter 25. Phenytoin. In, Applied pharmacokinetics, 2nd ed. Applied Therapeutics. Vancouver, WA. 1986.

Diarrhea. Diarrhea may decrease the absorption (F) of phenytoin per Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209.

Enzyme Inducing Drugs. Drugs that induce hepatic cytochrome P450 metabolism of phenytoin increase V_{max} and/or K_m. Common drugs included in this category include: carbamazepine, phenobarbital (usually an inducer, but sometimes can be a competitive inhibitor), and rifampin. Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209 & Anderson PO. Cytochrome P450 enzyme interactions. In,

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Enzyme Inhibiting Drugs. Drugs that competitively inhibit hepatic cytochrome P450 metabolism of phenytoin, decreasing its Km. Common drugs included in this category include: amiodarone, fluoxetine, fluvastatin (possibly), chloramphenicol, cimetidine, clarithromycin (possibly), disulfiram, fluconazole, isoniazid (especially in slow acetylators), omeprazole, sulfonamides, ritonavir, trimethoprim, valproic acid (possibly), and zafirlukast (possibly) per Winter M. in Murphy J, ed. Clinical Pharmacokinetics Pocket Reference 1993:193-209 & Anderson PO. Cytochrome P450 enzyme interactions. In, Anderson PO, Knoben JE, eds. Handbook of clinical drug data, 8th ed. Stamford, CT. Appleton & Lange; 1997:694-6.

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Quinidine

Quinidine has a number of factors associated with its bioavailability. There are several salt forms each containing different amounts of quinidine base. Each dosage form also has an associated absorption rate constant and bioavailability. Certain factors can also affect these absorption parameters.

Oral Quinidine Parameters

Dosage Form	Salt	F	Ka	Refs.
Quinidine Sulfate (nonsustained-release tablets and capsules)	0.83	0.8 ⁺	1.8 [*]	1-4
Cardioquin	0.6	0.8 ⁺	1.15 [*]	1
Quinaglute	0.625	0.8 ⁺	0.7 [*]	1,5-7
Duraquin	0.625	0.8 ⁺	0.5 [*]	4,8,9
Quinidex	0.83	0.8 ⁺	0.34 [*]	1,10-13

Intramuscular Quinidine Parameters

Quinidine Gluconate	0.625	0.875	0.77 [*]	3
Quinidine Sulfate	0.83	0.875	0.77 [*]	3

⁺Concurrent rifampin use increases the first-pass metabolism of quinidine and decreases oral bioavailability by 41%.¹⁴

^{*}Congestive heart failure decreases the rate of absorption of oral quinidine by 45%;¹⁵ IM quinidine absorption is slowed by 56%.¹⁶

Formulas:

Clearance (L/hr):

$$Cl \text{ (over 60 yr and } > 50 \text{ kg)} = (0.0566 \times CL_{Cr}) + 10$$

References: 5, 17

$$Cl \text{ (12 yr - 60 yr and elderly adults } < 50 \text{ kg)} =$$

$$(0.0566 \times CL_{Cr}) + (0.2 \times \text{adjusted weight})$$

References: 17-20

$$\text{Cl (9 yr - 12 yr)} = \{0.46 - [(\text{age} - 9) \times 0.57]\} \times \text{adjusted weight}$$

References: this equation was written to smooth the transition between values for children age 9 years and under to those of 12 year olds which appear to be equal to weight-adjusted adult values based on data in reference 19.

$$\text{Cl (6 months - 9 yr)} = 0.46 \times \text{adjusted weight}$$

Reference: 19

Volume of Distribution (L):

$$\text{Vd (over 6 months)} = 2.7 \times \text{adjusted weight}$$

Reference: 4

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: F - 15%, Cl - 45%, Vd - 40%, CF - 50%. The time weighting factor is 1.005.

Serum Level Range

The therapeutic serum level range of quinidine is not firmly established and depends to a certain extent on the assay method used. The range used in T.D.M.S.TM (1-4 mg/L) is for *unchanged* quinidine and is most relevant for newer, more specific assay techniques such as HPLC. Older, less specific assays, such as the fluorescent assay, also detect certain metabolites, some of which may have partial activity. The therapeutic range with these latter assays is accordingly higher (2-6 mg/L). The assay method and usual therapeutic range of your laboratory should be taken into account when using T.D.M.S.TM

Modifying Factors

Congestive Heart Failure. CHF decreases the volume of distribution by 32% and decreases nonrenal clearance by 46% or total clearance by an average of 34%.^{17,21} Absorption rates are also affected as noted above.

Cirrhosis. Cirrhosis increases the volume of distribution by 50%.²² Severe cirrhosis may also decrease nonrenal clearance (by 46%),¹⁷ but this factor is not included in T.D.M.S.TM because it was derived in only three patients and older studies found no such decrement.²²

Amiodarone. Amiodarone increases quinidine serum levels by perhaps as much as 100%.²³ The exact mechanism of this interaction is currently unknown. T.D.M.S.TM currently assumes that this is due to a 50% decrease in clearance.

Barbiturates. Barbiturates increase clearance of quinidine by 2.5 times and increase the variability of clearance by 20%.²⁴

Cimetidine. Cimetidine decreases quinidine clearance by 40%.²⁵

Phenytoin. Phenytoin increases clearance of quinidine by 2.5 times and increases the variability of clearance by 20%.²⁴

Rifampin. Rifampin increases clearance by 3.7 times.¹⁴ It also decreases oral bioavailability as noted above.

Verapamil. Preliminary evidence indicates that verapamil decreases quinidine clearance by 35%.^{26,27}

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Theophylline

Absorption parameters for the theophylline derivatives include the salt form (salt), the bioavailability (F) and its coefficient of variation (CV), the absorption rate constant (Ka), and the time to 90% absorption (t_{90}). The values for specific products are listed in the table on page 57. In T.D.M.S.TM, all oral dosage forms are modeled as if absorption were a first-order process (i.e., using Ka). While some of the better slow-release dosage forms approach true zero-order absorption, with the slow absorption rate constants used, differences in predictions between the two models are clinically unimportant.

Absorption rate constants were primarily calculated from data that were visually obtained from Wagner-Nelson absorption plots. Both the time to 50% absorption (1 half-life) and the time to 90% absorption (3.5 half-lives) were read off the plots and the derived constants were averaged to produce the Ka. In a few instances, investigators reported the time to 50% absorption and this value was used to calculate Ka. Whenever possible, several studies and methods were used to derive Ka. Average values of the best data are used for Ka in T.D.M.S.TM. The theophylline pharmacokinetic parameters used in T.D.M.S.TM are presented with references in tabular form below.

The curve fitting routines in T.D.M.S.TM can only accept one oral dosage form; however, if more than one form has been used, additional slow-release dosage forms can be fit by modeling them as a constant IV infusion. The time to 90% absorption (t_{90}) can be used as the duration of the infusion. This method is most accurate for the most slowly released dosage forms. If both a slow and fast dosage form have been used, the most accurate fit is obtained by using the default parameters (first-order absorption) for the fast-release dosage form and modeling the slow-release dosage form as an IV infusion. Realize, however, that subsequent predictions using oral dosage forms are made using the first-order absorption model and the dosage form chosen from the menu. To use other dosage forms, the corresponding pharmacokinetic parameters can be entered into the prediction equations either by selecting User's Choice for the dosage form, or by changing the calculated default parameters in the Dosage or Serum Concentration Forecast screens.

Formulas:

Clearance (L/hr):

$$Cl \text{ (over 60 yr)} = 0.035 \times \text{total body weight}$$

Reference: 12

$$Cl \text{ (18 yr - 60 yr)} = 0.04 \times \text{total body weight}$$

References: 12-17

continued on the bottom of page 57

Theophylline Dosage Form Parameters

Dosage Form	Salt	F	SD	Ka	t ₉₀	Refs.
Elixir/Syrup	1	1	0.1	2.3	-	1,2
Fast-Release Solids	1	1	0.1	2.4	-	1,2
Slo-Phylline Gyrocaps ⁺	1	0.985	0.14	0.41	5.3	3,4
Somophylline-CRT ⁺⁺	1	1	0.15	0.27	7.4	3
Quibron-T/SR	1	0.98	0.15	0.25	8.3	3,5
Theo-dur 100 mg	1	1	0.15	0.17	10.4	3
Theo-dur 200, 300 mg ⁺⁺⁺	1	0.97	0.15	0.125	14.2	1,3
Slo-bid Gyrocaps	1	1	0.11	0.12	19.6	3,6,7
*Theo-dur Sprinkle (fasting)	1	0.95	0.1	0.15	13	3,8
*Theo-dur Sprinkle (meal)	1	0.4-0.8	?	0.13	18	3,8
*Theo-24 (fasting)		1	0.65	? 0.03-0.8	30 ⁺	3,9
*Theo-24 (meal)	1	1	?	0.125	20	9
*Uniphyll (fasting)		1	0.53	? 0.085	35	10
*Uniphyll (meal)	1	0.83	?	0.095	21.4	10

Aminophylline Parameters

Injection	0.79	1	-	-	-	10
Elixir/Syrup		0.86	1	0.1	2.3	- 1,2,11
Fast-Release Tablets	0.8	0.94	0.1	2.4	-	1,2,11
Phyllocontin	0.79	0.95	0.15	0.26	7	1,3,11

⁺Bronkodyl S-R, Elixophylline SR & Theophyl-SR are the same as Slo-Phylline Gyrocaps.³

⁺⁺Aerolate is probably the same as Somophylline-CRT.³

⁺⁺⁺Sustaire is the same as Theo-dur.

*These products are erratically absorbed, with large differences between the fasting and nonfasting states.⁸⁻¹⁰ They are not included as menu selections in T.D.M.S.TM for this reason.

Clearance Formulas, continued

$$Cl (18 \text{ yr} - 60 \text{ yr, obese}) = 0.032 \times \text{total body weight}$$

References: 14-16

$$Cl (10 \text{ yr} - 18 \text{ yr}) =$$

$$(0.084 - [0.0055 \times \{\text{age in years} - 10\}]) \times \text{adjusted weight}$$

Reference: this equation was written to make a smooth transition between age groups above and below as suggested by data in reference 12.

$$Cl (1 \text{ yr} - 10 \text{ yr}) = 0.084 \times \text{adjusted weight}$$

References: 12, 18

$$Cl (\text{under } 1 \text{ yr}) = (0.018 + [0.066 \times \text{age in years}]) \times \text{total body weight}$$

Reference: this equation was written to make a smooth transition between the clearance of the age group above and the clearance of $0.018 \times \text{total body weight}$ at birth, per references 19 and 20.

Volume of Distribution (L):

$$Vd (\text{under } 1 \text{ month}) = 0.77 \times \text{total body weight}$$

Reference: 19

$$Vd (1 \text{ month} - 1 \text{ year}) = (0.8 - [0.31 \times \text{age in yr}]) \times \text{total body weight}$$

Reference: this equation was written to make a smooth transition between age groups above and below.

$$Vd (1 \text{ yr and over, nonobese}) = 0.48 \times \text{total body weight}$$

References: 13-17

$$Vd (1 \text{ yr and over, obese}) = 0.35 \times \text{total body weight}$$

References: 13-17

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are follows: F - specified by product above, Cl - 50%, Vd - 25% , CF - 50%. The time weighting factor is 1.01.²¹

Modifying Factors

Congestive Heart Failure. Congestive heart failure decreases theophylline clearance to 43% of normal.²²

Cirrhosis. Cirrhosis decreases theophylline clearance by 50%²³

Chronic Obstructive Pulmonary Disease. COPD decreases theophylline clearance to 80% of normal.²²

Smoking. Smoking increases theophylline clearance to 1.6 times normal.²²

Cimetidine. Cimetidine use decreases theophylline clearance to 75% of normal.^{24,25}

Ciprofloxacin or Erythromycin. Concurrent ciprofloxacin use decreases theophylline clearance by 25%.²⁶⁻²⁸ Concurrent erythromycin use also decreases theophylline clearance by about 25% after 5 days of use.²⁹⁻³¹

Oral Contraceptives. Oral contraceptives decrease theophylline clearance by 30%.³²

Phenytoin. Concurrent phenytoin use increases theophylline clearance to 1.5 times normal.³³

Rifampin. Rifampin increases theophylline clearance by 45%.³⁴⁻³⁷

Mexiletine or Troleandomycin. Concurrent mexiletine or troleandomycin use decreases theophylline clearance by about 50%.^{38,39}

Cystic Fibrosis. Cystic fibrosis increases theophylline clearance by 1.8 times and increases volume of distribution by 30%.^{40,41}

Phenobarbital. Chronic phenobarbital use increases theophylline clearance by 33%.²⁴

Diltiazem or Verapamil. Diltiazem and verapamil each decrease theophylline clearance by about 15%.⁴²⁻⁴⁴

Thyroid Dysfunction. Theophylline clearance is increased by 40% in hyperthyroidism, while hypothyroidism decreases clearance by 20% and increases volume of distribution by 40%.^{45,46}

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Vancomycin

Vancomycin pharmacokinetics are assumed to conform to a two-compartment open model in T.D.M.S.TM Most appropriately, at least four serum levels would be needed to characterize the drug's pharmacokinetics. To accomplish the fitting with a fewer number of levels during the distribution phase, K_{21} and V_c are fixed and are not allowed to vary once the original population estimate is made. Parameters that are assigned by the program are as follows: salt fraction = 1 and bioavailability = 100%. The microrate constant K_{21} is fixed by age group as follows:

Constants:

$$K_{21} \text{ (over 1 month)} = 0.46$$

References: 1 (as recalculated in reference 2), 3, 4

$$K_{21} \text{ (1 month and under)} = 0.64$$

References: 1 (as recalculated in reference 2)

K_{10} , α and β are calculated from V_c , Vd_B and Cl using the formulas on page 41.

Formulas:

Clearance (L/hr):

$$Cl \text{ (2 years and over)} = ([0.79 \times CLcr] + 0.05) \times \text{dosing weight} \times 0.06$$

Where dosing weight = $IBW + 0.4 \times (TBW - IBW)$

References: 3-13

$$Cl \text{ (under 2 years)} = 0.006 + \text{total body weight} \times ([0.028 / Crs] + [0.046355 \times \text{age in years} \times PNA] + [0.0123 \times GA])$$

where $PNA = 1$ if $Crs \leq 7$ or $PNA = 0$ if $Crs > 7$

and $GA = 1$ if the infant's gestational age < 28 weeks or

$GA = 0$ if the infant's gestational age ≥ 28 weeks

Reference: 19

Volumes of Distribution (L):

Central

$$V_c \text{ (all ages)} = 0.17 \times \text{total body weight}$$

References: 1 (as recalculated in reference 2), 3, 4, 12-14

$$V_c \text{ (adults with CLcr under 10 mL/min)} = 0.45 \times \text{total body weight}$$

Reference: 17

$$V_c \text{ (under 1 month receiving ECMO)} = 0.28 \times \text{total body weight}$$

Reference: 18

Peripheral

$$V_{d_B} = 0.7 \times \text{dosing weight}$$

References: 1 (as recalculated in reference 2), 3, 4, 10-13

$$V_{d_B} \text{ (adults with CLcr under 10 mL/min)} = 1.0 \times \text{dosing weight}$$

$$\text{Where dosing weight} = \text{IBW} + 0.4 \times (\text{TBW} - \text{IBW})$$

Reference: 17

$$V_{d_B} \text{ (under 1 month and either under 1 kg or with PDA)} =$$

$$0.93 \times \text{total body weight}$$

References: 7, 16

where dosing weight is equal to the total body weight or in the case of obese patients (total body weight > 120% of IBW), the dosing weight is equal to the IBW plus 40% of the difference between the ideal and total body weights.

Bayes Parameters

Coefficients of variation of pharmacokinetic parameters are as follows: Cl - 50%, V_{d_B} - 50%, CF - 50%. The time weighting factor is 1.005.

Modifying Factors

Burn Patients. Burn patients often have high creatinine and vancomycin clearances, but the relationship between the two is essentially the same as in unburned patients.^{3,14,15} T.D.M.S.TM allows creatinine clearance to range as high as 265 mL/min in this patient group and calculates vancomycin clearance as for other patients.

Patent Ductus Arteriosus. Limited data (which are consistent with aminoglycoside data) indicate that Vd is increased and clearance is decreased in infants with patent ductus arteriosus. This effect probably persists for a few days after treatment with indomethacin.⁸ Infants weighing less than 1 kg also have an expanded Vd_b.^{7,16}

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Appendix A. T.D.M.S. Installation Procedures

Single Computer

1. Double-click on the dark blue “Setup” icon that looks like a computer screen and disk box. Follow the directions in the setup program.
2. When the setup process is complete, run TDMS2000 from the Start\Programs menu.
3. You will get a warning message, “Your database is not configured. “Please press the Configure Database button on the next screen.” Click the OK button.
4. The opening T.D.M.S.TM screen will appear.
5. Click on the Configure Database button. A dialog box will appear that indicates the T.D.M.S.TM database file called “Patients.mdb” (note: on some systems, the database name will display simply as “patients”) will be placed in the “My Documents” folder by default. You can have the “Patients.mdb” file in any location available to your system, including a network drive to be accessed by more than one computer. For a single computer, it is a good idea to designate the folder, “c:\Program Files\TDMS\TDMS 2000” as the default location for the database.
6. When you locate the folder where you want to store the patient data, press the “Save” button.
7. A dialog box will appear asking, “Do you want to install the TDMS database at ...” If this location is satisfactory, click OK.
8. If you are designating “c:\Program Files\TDMS\TDMS 2000” as the default location for the database, a warning message stating, “Database file already exists and was not overwritten. Configuration successful” will appear. Click OK.
9. The program is now ready to run. Click “Next” to begin.
10. If at any time you wish to change the location of the database, copy the file “Patients.mdb” to the desired location, then press the “Configure Database” button on the T.D.M.S.TM opening screen and repeat steps 5-8 above.

Network Computers

1. Create a folder called “TDMS” on the network drive.
2. Double-click on the dark blue “Setup” icon that looks like a computer screen and disk box.
3. Follow the directions in the setup program and designate the TDMS folder on the network drive as the destination for the program files and database.
4. On each network computer, go to the TDMS folder on the network drive and create a shortcut to the TDMS 2000 program file (red cross on a white background)
5. Cut the shortcut and paste it on the desktop.
6. Follow steps 2-9 above in the single computer instructions, designating the TDMS folder on the network drive as the database location. This installation method allows users at each computer to share the database access and allows for one-step updating as upgrades become available.

Alternate Network Configuration

Alternatively, you can install T.D.M.S.TM on several individual workstations following the

Single Computer installation instructions above. These workstation can share a common database on the network drive by copying the patients.mdb database to the network drive and configuring the database location (steps 2-9) of each workstation version of T.D.M.S.[™] to the network drive. This method will require updating each workstation individually as updates to T.D.M.S.[™] become available.

APPENDIX B. ANTIBIOTIC PHARMACODYNAMICS

There has been considerable work on the incorporation of microbial sensitivity data together with patient-specific pharmacokinetics in order to optimize antimicrobial therapy. The use of this method of integrating individual patient pharmacokinetics with the MIC of infecting organisms has been termed, "dual individualization". The microbial pharmacodynamic parameter common to almost all methods is the minimum inhibitory concentration (MIC) of the infecting organism. This is value obtained *in vitro* from bacterial cultures. While not a flawless measure of bacterial sensitivity, it is widely used and reported. Potential pitfalls in the use of the MIC have been reviewed.¹ Since there is not currently general agreement on which (if any) value is the best overall, T.D.M.S.TM calculates the three most widely used pharmacodynamic values. These values, their methods of calculation, and the experience with each are described.

Time Above the MIC

This function is used with antibiotics to calculate the amount of time per day that the serum concentration is above the MIC of the organism being treated. For one-compartment drugs (e.g., aminoglycosides), values used include the clearance (Cl), salt fraction (S), bioavailability (F), compliance factor (CF), infusion time (t_{inf}), dose (D), dosage interval (τ) and steady-state trough level (trough_{ss}) based on the on the intermittent infusion model,

where $K_0 = S \times F \times CF \times D / t_{inf}$ and $k_d = Cl/Vd$.

The calculation is made in two phases: an approximation of the time that the serum concentration passes the MIC on the upswing (t_1) is subtracted from the time since the end of the infusion that the serum concentration passes the MIC on the downswing (t_2).² For two-compartment drugs (e.g., vancomycin) an iterative method is used to approximate the time above MIC to the nearest 0.1 hour.

One-Compartment Formulas:

$$t_1 = \frac{\text{MIC-Trough}_{ss}}{\text{Peak}_{ss}\text{-Trough}_{ss}} \times t_{inf}$$

If t_1 is less than 0, t_1 is set to 0

$$t_2 = \frac{\ln(\text{Peak}_{ss}/\text{MIC})}{K_d}$$

$$\text{Time above MIC} = (t_2 + t_{inf} - t_1) \times 24/\tau$$

Post/MIC Ratio

The post/MIC ratio is defined as the ratio of the "peak" serum concentration (drawn up to 1 hour after the end of the infusion) divided by the MIC. The greatest amount of experience with this value has been with the aminoglycoside antibiotics.⁴⁻⁶ The rate of successful aminoglycoside treatment is improved with values over 6 mg/L.⁷ With infections in relatively "protected" or inaccessible sites such as the lung, higher values may prove to be better. Extending these findings, the use of larger doses at longer dosage intervals has been explored. Once daily use of aminoglycosides has been reported and may have equal or greater efficacy and lower toxicity than multiple daily dose regimens.⁷

The time above the MIC appears to be most useful for drugs that act on the bacterial cell wall (e.g., β -lactams, vancomycin). Maximizing time above the MIC with these antibiotics appears to improve their efficacy when used against susceptible organisms.^{1,3} The concentration of drug in plasma should exceed the MIC for all or most of the 24-hour period daily for optimal efficacy with drugs having little or no post-antibiotic effect against the organism (e.g., β -lactams against gram-negative organisms). However, this alone may not be sufficient because some resistant organisms may require high peak levels for optimal killing.¹

AUIC

Several slightly different methods of combining the area under the serum concentration-time curve with the MIC have been reported to correlate with antimicrobial efficacy. The method with the most study in humans is the area under the inhibitory curve (AUIC).^{2,8,9}

The AUIC is a value derived by first calculating the area under the serum concentration-time curve (AUC). AUC is then divided by the MIC of the organism to calculate the AUIC value which technically is dimensionless, although the unit "SIT⁻¹" or "inverse serum inhibitory titer" has been applied to this value. It also is suggested that the time above the MIC should be maintained at 24 hours in seriously ill hospitalized patients while applying the AUIC method.

An AUIC value that appears to predict antimicrobial efficacy is 125. This value may apply across antimicrobial classes.² Clinically a value of over 125 has been associated with success of ciprofloxacin, although higher values appear to offer more rapid eradication of organisms.⁹

The method of calculating AUC has varied, with most of the work published by Schentag and colleagues using a rather complex method that calculated the area only during that the serum drug concentration exceeds the MIC (i.e., between the times where the serum concentration first exceeds the MIC and first drops below the MIC as in the time above the MIC calculation).² However, more recently, most investigators, including Schentag, have standardized on using simpler calculation of the total AUC below:¹⁰

AUIC Calculations:

$$\text{AUC} = \frac{S \times F \times CF \times \text{Dose}}{Cl} \qquad \text{AUIC} = \frac{\text{AUC} \times 24}{\text{MIC} \times \tau}$$

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APPENDIX C. PHARMACOKINETIC FORMULAS

This chapter provides the user with the equations used to calculate various serum level and dosage regimen data throughout the program.

ONE COMPARTMENT

Peak Serum Concentration

This equation calculates the steady-state peak serum concentration for intravenously administered drugs that results from infusing a dose (D) over time (t) with a dosage interval (τ), a starting concentration (cp), a Clearance (Cl) and a volume of distribution (Vd).

Formula:

$$\text{Peak}_{ss} = \frac{S \times F \times K_0 \times (1 - e^{-K_d \times t})}{Cl \times (1 - e^{-K_d \times \tau})}$$

where $K_0 = \text{dose}/t$ and $K_d = Cl/Vd$.

Trough Serum Concentration

This formula calculates the minimum serum concentration at steady-state during an intravenous dosage regimen with a dosage interval of τ .

Formula:

$$\text{Trough}_{ss} = \text{Peak}_{ss} \times e^{-K_d \times (\tau - t_{inf})}$$

where $K_d = Cl/Vd$ and t_{inf} is the infusion time.

Average Concentration

This equation is used to calculate the average steady-state serum concentration with all routes of administration.

Formula:

$$\text{Ave}_{ss} = \frac{S \times F \times K_0}{Cl}$$

where K_0 is either the infusion rate or the daily dosage as appropriate.

Loading Dose

This formula calculates the loading dose needed to achieve a specified peak of an intravenous drug infused over time (t) given clearance (Cl), initial serum concentration (cp), volume of distribution (Vd), salt fraction (S) and bioavailability (F).

Formula:

$$\text{loading dose} = \frac{\text{Cl} \times t \times (\text{peak} - [\text{cp} \times e^{-\text{Kd} \times t}])}{\text{S} \times \text{F} \times (1 - e^{-\text{Kd} \times t})}$$

where $\text{Kd} = \text{Cl}/\text{Vd}$ and t is the duration of the infusion with IV dosage or time to peak after a single dose with PO and IM administration.

Dosage Interval

This formula calculates the dosage interval needed to achieve a desired trough given a desired peak, an elimination rate constant of Kd and an infusion time of t.

Formula:

$$\text{Interval} = t + \frac{\ln(\text{peak}/\text{trough})}{\text{Kd}}$$

where t is the infusion time with IV doses, and the time to peak at steady-state for IM and oral doses.

Time to Peak - Single Dose

This formula calculates the time of the peak serum concentration following a single dose of a drug given PO or IM with an absorption rate constant of Ka and an elimination rate constant of Kd. This time is used in the above formulas to approximate an "infusion time (t)" for IM and oral doses.

Formula:

$$T_{\text{peak}} = \frac{\ln(\text{Ka}/\text{Kd})}{\text{Ka} - \text{Kd}}$$

where Ka is the absorption rate constant and Kd is Cl/Vd.

Dose Requirement

These formulas calculate the dose required to achieve a desired peak given a clearance (Cl), volume of distribution (Vd), salt fraction (S), bioavailability (F), and dosage interval (τ).

IV Formula:

$$\text{Dose} = \frac{\text{peak} \times \text{Cl} \times \tau \times (1 - e^{-K_d \times \tau})}{S \times (1 - e^{-K_d \times t_{\text{inf}}})}$$

where $K_d = \text{Cl}/V_d$ and t_{inf} is the infusion time.

PO/IM Formula:

$$\text{Dose} = \frac{\text{peak} \times V_d \times (1 - e^{-K_d \times \tau})}{F \times S \times e^{-K_d \times T_{\text{Max}_{\text{ss}}}}}$$

where $K_d = \text{Cl}/V_d$ and $T_{\text{Max}_{\text{ss}}}$ is the time to peak at steady-state as calculated below under Steady-State Levels With First-Order Absorption.

Steady-State Levels with First-Order Absorption

These equations calculate the steady-state peak (Peak_{ss}) and trough ($\text{Trough}_{\text{ss}}$) concentrations for orally and intramuscularly administered doses (D) of drugs with a bioavailability fraction (F), salt fraction (S), volume of distribution (Vd) and absorption and elimination rate constants (K_a & K_d , respectively) at a given dosage interval (τ). The time to peak at steady-state ($T_{\text{Max}_{\text{ss}}}$) is calculated as an intermediate step for calculating Peak_{ss} .

Formulas:

$$\text{Peak}_{\text{ss}} = \frac{S \times F \times D}{V_d} \times \frac{e^{-K_d \times T_{\text{Max}_{\text{ss}}}}}{1 - e^{-K_d \times \tau}}$$

$$\text{Ave}_{\text{ss}} = \frac{S \times F \times D}{\text{Cl} \times \tau}$$

$$TMax_{ss} = \frac{\ln (K_a \times [1 - e^{-K_d \times \tau}] / K_d \times [1 - e^{-K_a \times \tau}])}{K_a - K_d}$$

$$Trough_{ss} = \frac{S \times F \times D \times K_a}{V_d \times (K_a - K_d)} \times \left[\frac{e^{-K_d \times \tau}}{1 - e^{-K_d \times \tau}} - \frac{e^{-K_a \times \tau}}{1 - e^{-K_a \times \tau}} \right]$$

Concentration at Time t

These equations are used to calculate the serum concentration (cp) at a given time (t) after a dose where S is the salt fraction, D is the dose, CF is the compliance factor, F is the bioavailability, K_0 is the infusion rate, t_{inf} is the infusion time, V_d is the volume of distribution, Cl is the clearance and K_d is Cl/V_d . They are used in both the curve fitting routines and in the graphics calculations. The concentration during a multiple dose regimen is calculated by superposition (i.e., addition of the contributions of all prior doses). The superposition method is used in both the curve fitting and graphics portions of T.D.M.S.TM to determine the serum concentration at times of interest.

IV Formulas:

IV Bolus:

$$Cp_t = \frac{CF \times S \times D}{V_d} \times e^{-K_d \times t}$$

During IV Infusion:

$$Cp_t = \frac{CF \times S \times K_0}{Cl} \times (1 - e^{-K_d \times t})$$

After the End of an Infusion:

$$Cp_t = \frac{CF \times S \times K_0}{Cl} \times (1 - e^{-Kd \times t_{inf}}) \times e^{-Kd \times (t-t_{inf})}$$

PO/IM Dosage:

$$Cp_t = \frac{CF \times S \times F \times Ka \times \text{dose}}{Vd \times (Ka - Kd)} \times (e^{-Kd \times t} - e^{-Ka \times t})$$

TWO COMPARTMENT

Micro-Rate Constants

The following equations are used to calculate micro-rate constants after establishment of clearance (Cl), volume of distribution of the peripheral compartment (Vd_b), volume of distribution of the central compartment (Vc) and the transfer rate constant between the peripheral and central compartments (K_{21}) by population estimates.

Formulas:

$$K_{10} = Cl / Vc$$

$$\beta = Cl / Vd_b$$

$$\alpha = K_{21} \times K_{10} / \beta$$

Steady-State Concentration at Time t

This equation is used to predict the serum concentration at steady-state (Cp_{ss}) at time (t) during a dosage interval of drugs with a salt fraction (S) given IV at an infusion rate of K_0 over an infusion time of (t_{inf}) and at a dosage interval of (τ). During the infusion, t_{inf} and t are equal.

Formula:

$$Cp_{ss} = \frac{K_0 \times S \times (K_{21} - \alpha) \times (1 - e^{-\alpha \times t_{inf}}) \times e^{-\alpha \times t}}{Vc \times \alpha \times (\alpha - \beta) \times (1 - e^{-\alpha \times \tau})} +$$

$$\frac{K_0 \times S \times (\beta - K_{21}) \times (1 - e^{-\beta \times t_{inf}}) \times e^{-\beta \times t}}{Vc \times \beta \times (\alpha - \beta) \times (1 - e^{-\beta \times \tau})}$$

Nonsteady-State Concentration at Time t

This equation is used to predict the serum concentration (Cp) at time (t) during a dosage interval of drugs with a salt fraction (S) given IV at an infusion rate of (K₀) over an infusion time of (t_{inf}) and a dosage interval (τ). During the infusion, t_{inf} = t.

Formulas:

$$Cp_t = \frac{K_0 \times S \times (K_{21} - \alpha) \times (1 - e^{-\alpha \times t_{inf}}) \times e^{-\alpha \times t}}{Vc \times \alpha \times (\alpha - \beta)} +$$

$$\frac{K_0 \times S \times (\beta - K_{21}) \times (1 - e^{-\beta \times t_{inf}}) \times e^{-\beta \times t}}{Vc \times \beta \times (\alpha - \beta)}$$

MICHAELIS-MENTEN FORMULAS

Steady-State Serum Concentration

This formula calculates the steady-state serum concentration of a drug eliminated by capacity-limited (Michaelis-Menten) pharmacokinetics (e.g., phenytoin)

$$C_{pss} \text{ (mg/L)} = \frac{K_m \times \text{Dosage Rate}}{(V_{max} - \text{Dosage Rate})}$$

where,

$$\text{Dosage Rate} = S \times F \times \text{Dose} / \text{Dosage Interval}$$

Dosage at Steady-State

$$\text{Dosage} = \frac{V_{max} \times C_{pss} \times \text{Interval}}{S \times F \times (K_m + C_{pss})}$$

Calculation of Vmax from One Steady-State Level

$$V_{max} = \frac{\text{Dosage Rate} \times (K_m + C_{pss})}{C_{pss}}$$

where,

$$\text{Dosage Rate} = S \times F \times \text{Dose} / \text{Dosage Interval}$$

K_m = Population value for K_m with 0 or 1 steady-state level and from the formula below with 2 steady-state levels

Calculation of Km from Two Steady-State Levels

$$K_m = \frac{\text{Rate 1} - \text{Rate 2}}{(\text{Rate 1}/C_{pss 1}) - (\text{Rate 2}/C_{pss 2})}$$

APPENDIX D. CURVE FITTING

T.D.M.S.TM uses both Bayesian and least-squares curve fitting methods to adjust the population values of pharmacokinetic parameters (F, Vd, Cl, CF) as serum level data are obtained. The Bayesian model used was originally described by Sheiner LB et al. *Comput Biomed Res* 1972;5:441-59 and *Clin Pharmacol Ther* 1979;26:294-305 and is mathematically expressed as follows:

Formula:

$$\sum_{i=1}^N \frac{(P_i - \bar{P}_i)^2}{SD_p^2} + \sum_{j=1}^M \frac{(Cp_j - Cp_j')^2}{(SD_{Cp_j})^2}$$

where

N = the number of parameters fitted: N = 4 for outpatient oral drugs; N = 3 for inpatient oral drugs; N = 2 for inpatient intravenous and intramuscular drugs. For nonsteady-state phenytoin, N is one greater for each of these situations.

\bar{P}_i = initial (population) estimates for each pharmacokinetic parameter;

P_i = revised (fitted) estimates for each pharmacokinetic parameter;

SD_p^2 = variance of the pharmacokinetic parameter;

M = the number of serum levels obtained; M can range from 0 to 9 in T.D.M.S.TM;

Cp_j = the serum concentration predicted from initial parameter estimates;

Cp_j' = the predicted serum concentrations (based on revised parameter estimates);

$(SD_{Cp_j})^2$ = variance of the predicted serum level;

$SD_{Cp_j} = ([Cp_j' \times SD_e] + FE) \times Q^t$;

SD_e = Coefficient of variation of the assay error: Bayes: 0.1 (10%), least squares: 0.01 (1%);

FE = fixed error due to unaccounted for variability such as model misspecification; Bayes: 5% of the midpoint value of the therapeutic serum level range; least squares: 0

Q^t = time weighting multiplier;

Changing the coefficient of variation of the serum levels (SD_c) to 1% and FE to 0 during least squares fit causes population parameters to be virtually eliminated and only serum level data to be considered in arriving at the final estimate.

Q is a time weighting factor (typically 1.005 or 1.01) and t is the time in hours between the time of the most recent serum level and the time of the serum level t hours previously. The time-weighting factor applies in both the Bayes and the least-squares fitting routines. The effect of the time weighting factor is to cause earlier serum levels to have less "weight" or impact than more recent levels. More recent levels should be a better reflection of the patient's current pharmacokinetic status than older ones. The effect of this factor can be seen on the graphs where early levels sometimes seem to be further from the curve than more recent levels. Drugs whose pharmacokinetic parameters changes more dramatically with time (e.g., because of enzyme induction or disease state alterations) are time-weighted more heavily. The table below shows the effect of some representative times on the weight of the levels:

Time Weighting Factors

<u>Time of Sample</u>	<u>1.005</u>	<u>1.01</u>
Most recent	1.00	1.00
12 hours prior	0.94	0.89
1 day prior	0.88	0.79
2 days prior	0.79	0.62
3 days prior	0.70	0.49
4 days prior	0.62	0.38
5 days prior	0.55	0.30
10 days prior	0.30	0.09
20 days prior	0.09	0.01