



VERSION 3.15

VOLUME 2

TOUR DE PHARM

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1 INTRODUCTION

1.1 History of MW\PHARM

The idea of drug dosage calculations and simulation by means of a computer is not new. In the beginning only programs running on pocket-calculators or mainframes were available. With the rise of personal computers, scientists started developing such programs for the personal computer as well.

Within the University Centre of Pharmacy in Groningen, from 1982 onward, people from the department of pharmacology and pharmacotherapy were engaged in the development of pharmacokinetic software. Initially programs were developed for the Acorn-BBC microcomputer. These were written by Prof. Dr. D.K.F. Meijer PhD (head of the department), Mr. J.E. Boiten, MSc (at present pharmacist), and Mr. C. Neef PhD (at present hospital pharmacist) and they were mainly used for educational purposes.

With the coming of MS-DOS computers the group agreed on the fact that more practical and user-friendly software should be developed that could also be used by clinicians and hospital pharmacists. The MW\PHARM project was born. In order to deal with this task the MediWare Company was founded in 1987 with the help of the Zernike Science Park Foundation in Groningen.

Already from an early stage in the development of MW\PHARM a number of hospital pharmacists were closely involved in this project. Their co-operation resulted in a better tuning of the program for practical purposes. The co-operation between MediWare BV and the hospital pharmacists has been formalised by the founding of the Dutch MW\PHARM user group in 1988.

Currently, MW\PHARM has proven its value at the majority of the Dutch hospitals and has been declared Dutch standard by the NVZA (The Dutch Association of Hospital Pharmacists). The program is still being developed further in close collaboration with the research group of Prof. Dr. Meijer and the Dutch MW\PHARM user group in order to implement the latest developments in the field of pharmacokinetics.

1.2 Aim of MW\PHARM

Many drugs applied in a clinical environment require plasma levels to be monitored in order to avoid toxic or maintain therapeutic effects. MW\PHARM is a program especially designed to help the clinician with interpreting drug-monitoring data. In summary MW\PHARM aims to:

- Improve the quality of drug prescription
- Optimise drug information
- Reduce the number of plasma concentration measurements
- Prevent drug intoxication
- Prevent under dosing
- Decrease the number of hospitalisations
- Shorten the duration of hospitalisation

1.3 Features of MW\PHARM

MW\PHARM is an interactive program using full screen editing and screen dump procedures for user-friendly operation and rapid demonstration of drug concentration profiles. Therefore it also very suitable for teaching and training in biomedical disciplines.

- Drug database (over 180 drugs)
- Patient database (size only limited by hard disk capacity)
- Several (parallel) routes of administration
- Several kinetic models (1, 2 and 3 compartment models)
- Simultaneous linear, non-linear and extracorporeal elimination
- Automatic generation of practical dosage regimens
- Drug monitoring support (with Bayesian population feedback option)
- Monitoring of metabolite levels
- Curve fitting
- High resolution colour graphics
- Export of (fitted) plasma curves to any graphics package
- Math Coprocessor support

2 ABOUT THIS MANUAL


2.1 Using This Manual

This manual allows you to make a quick start using the MW\PHARM program. Chapter 3 explains how the basic principles of therapeutic drug monitoring are implemented in MW\PHARM. Chapter 4 contains a guided tour through the MW\PHARM program. It will explain the most common commands and procedures. Chapter 5 presents four typical TDM cases. They deal with the dosing of vancomycin in adults, dialysis patients, CAPD patients and neonates. We strongly recommend you to read these chapters in this order. For instructions concerning the installation of MW\PHARM on your computer system we refer to the volume 1 manual (Installation & Quick Reference, chapter 1).

2.2 Document Conventions

The document conventions used in this manual are very simple and clear:

Keyboard keys

Keyboard keys are symbols enclosed by a rectangle. E.g.  represents the F1 function key on your keyboard. If two keys are separated by the + sign you will have to press these keys simultaneously. In all other cases you will have to press the keys sequentially (typing). Examples are:

Press 

Press the function key F1

Press  + 

Press the Ctrl and the Insert key simultaneously.



Type   

Press the A, P and O key sequentially.

Guided tour directions

A solid rectangle with text contains instructions helping you to continue the guided tour.

Important remarks

 Remarks are preceded by the  symbol. These remarks may deal with important exceptions or other items that deserve your attention.

3 TDM BASICS

3.1 General Considerations

For a correctly executed pharmacotherapy it is essential to have knowledge about:

- ① The biological properties of drugs (pharmacology, toxicology, pharmacokinetics).
- ② The influence of the formulation on the development of the properties of the drugs present in it (biopharmaceutics).

In general a dosage regimen is determined by the following factors:

pharmacodynamic factors

- therapeutic dose
- dose-effect relation
- toxic dose
- side effects
- tolerance
- genetic
- dynamic interactions

pharmacokinetic factors

- route of admin.
- absorption
- distribution
- excretion
- enzyme induction
- genetic
- kinetic interactions
- protein binding

clinical status

- age
- weight
- urine pH
- pathology
- side-pathology

medication status

- dosage regimen
- compliance
- co-medication

Pharmacokinetics deals with the concentration curves of drugs and drug metabolites in body liquids or tissues, in time and the mathematical description of the processes, which are at the root of it. In short it comprises the study of the ADME process (absorption, distribution, metabolism, excretion).

The general objective of pharmacokinetic analysis could be summarised as follows:

- An accurate, but also clinical relevant description of the pharmacokinetic behaviour of a drug within an average patient population, or if possible, within the individual patient, for various dosage regimens of the drug, (route of administration, loading dose, maintenance dose, dosing interval, number of doses, etc.).
- A physiological interpretation of the pharmacokinetic behaviour: which processes are decisive for the absorption, distribution and excretion of the drug, and how these processes are influenced by pathological processes, environmental factors and other drugs.
- The assessment of the basic pharmacokinetic parameters (clearance and volume of distribution) for setting up and adjusting a rational dosage advice on the basis of knowledge of the therapeutic and toxic concentrations.
- An aid in the diagnosis of an unsuccessful pharmacotherapy.

From the clinical point of view pharmacokinetics is of value only then, if the data taken from it contribute to a fundamentally better pharmacotherapy. In those situations, pharmacokinetics remains just an aid of which the reliability is to a high degree dependant on the reliability of the mathematical model (pharmacokinetic parameters) that is used.

If a calculated dosage advice does not seem reasonable on the basis of experience or observation, a reconsideration is necessary:

- Are there any calculation errors ?
- Are the pharmacokinetic parameters correct ?
- Does the pharmacokinetic model reflect the actual situation ?
- Are there any possible errors in the analysis ?
- Has the sampling taken place in the right way and at the right moment ?

3.2 Program Structure

The main constituents of the MW\PHARM program are the patient and the drug database. The drug database contains two types of data. General drug data (e.g. desired plasma levels, available dosages, etc.) and pharmacokinetic population parameters. The patient database contains three types of data. General patient data (e.g. name, sex, age, weight, etc.), a medication history (list of dosing events and plasma levels), but also individual pharmacokinetic parameters which are obtained by fitting measured plasma levels to a pharmacokinetic model. The interrelationship between the patient and the drug database is depicted in figure 3.2.

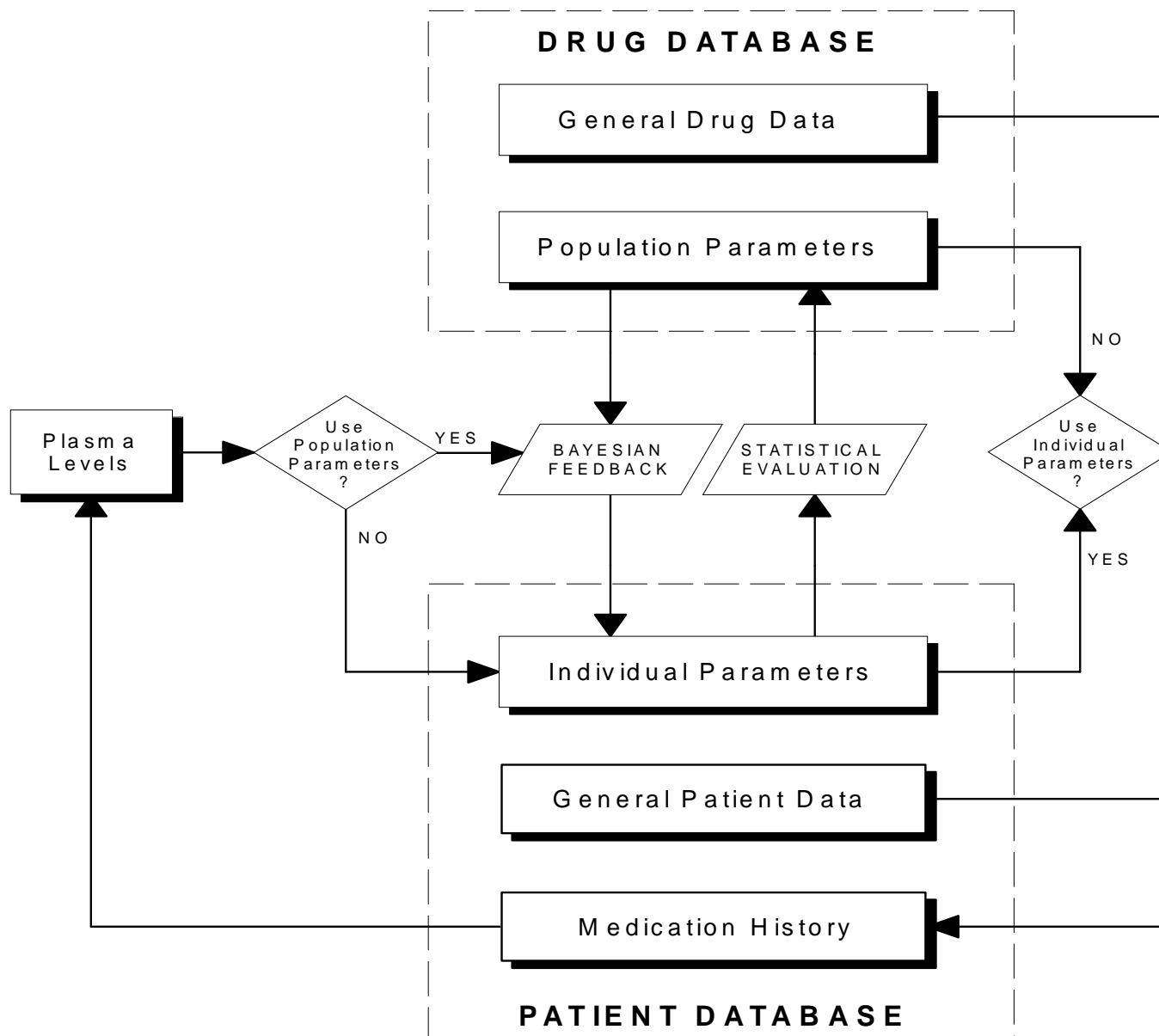


Figure 3.2. Data flow within MW\PHARM.

The clinician is mainly interested in supplying an optimal therapy to his patients. In order to do so, he will monitor the patient's plasma levels. But in this process of monitoring plasma levels and adjusting dosage regimens the clinician is also building a huge patient database containing the individual pharmacokinetic parameters of several patients. This database could then be analysed in order to establish more precise population parameters for several categories of patients.

3.3 Compartment Models

Several kinetic models are supported by MW\PHARM. These include 1, 2 and 3 compartment kinetics. Non-linear elimination kinetics (Michaelis-Menten or saturation kinetics), extra-corporeal elimination (e.g. dialysis) and several routes of administration, like intravenous injections and infusions but also oral and intramuscular administrations. All calculations can be based on total or free (not protein bound) concentrations.

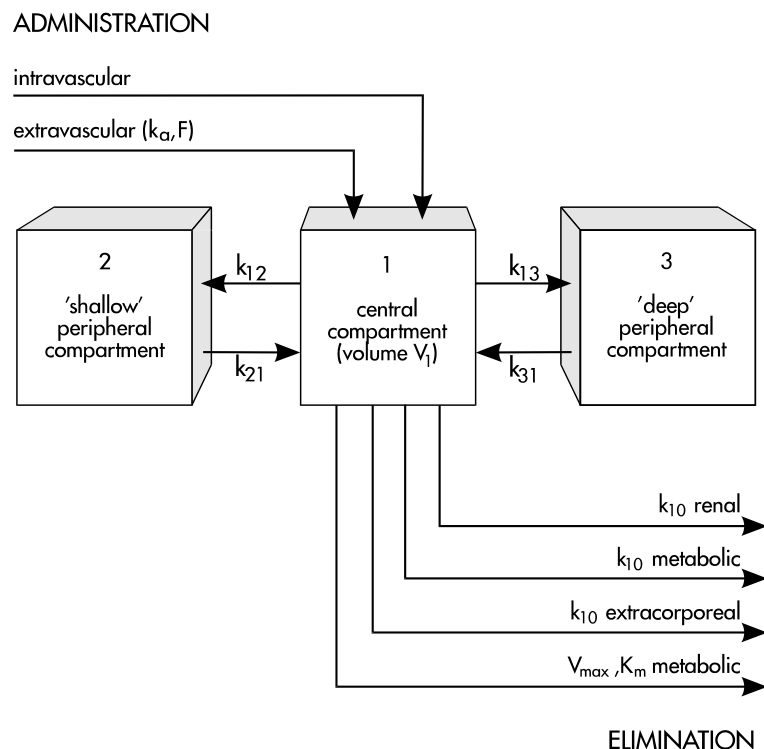


Figure 3.3. Compartment models.

3.4 Monitoring Methods

The classical method of monitoring several types of drugs is the 2-point method. Two variants of the 2-point method exist. The trough-peak method (fig. 3.4-A) and the peak-trough method (fig. 3.4-B). With the first method samples are taken just before a dose to be given and just after a given dose while with the latter method samples are taken just after a given dose and just before the next dose to be given. The main difference between the two methods is that with the peak-trough method the samples relate to the same dose while with the trough-peak method the samples relate to different doses.

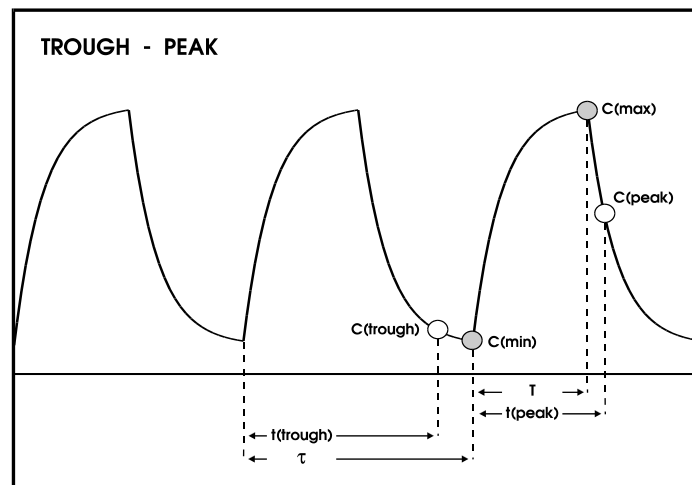


Figure 3.4-A. Trough-Peak monitoring method.

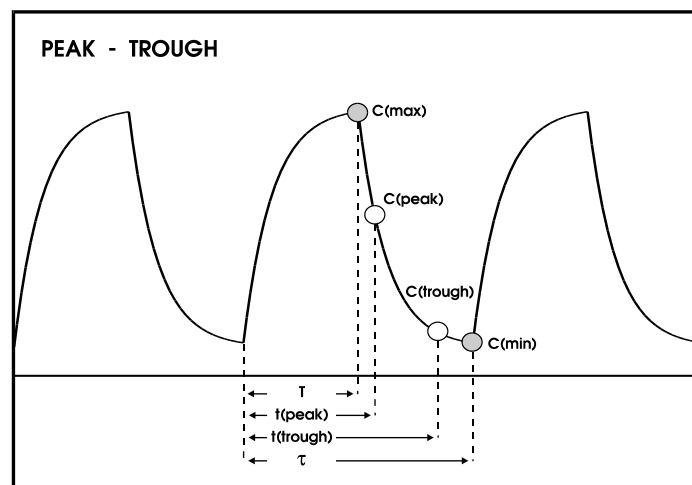


Figure 3.4-B. Peak-Trough monitoring method.

The trough-peak method is most frequently used because of the fact that sample times are relatively close together which is of course more convenient for the medical personal taking the samples. Classical calculator programs were often used to evaluate 2-point measurements. These programs often employed the steady state approximation rule in which a trough-peak measurement can be treated as a peak-trough measurement which is easier to evaluate (Sawchuk and Zaske). However in non-steady state conditions this could lead to severe errors in the calculated pharmacokinetic parameters. In non-steady state conditions the drug is still accumulating. When treating the trough-peak measurement as a peak-trough measurement the trough level is estimated too low causing an overestimation of the drug clearance. The dosage regimen based on the overestimated drug clearance may easily lead to toxic plasma levels.

☞ MW\PHARM does not employ the steady state approximation rule when evaluating trough-peak measurements. The formulas build into MW\PHARM take into account the phenomenon of drug accumulation making it possible to evaluate 2-point measurements (both trough-peak and peak-trough) at non-steady state conditions. However, in order to do this optimally it is very important to inform MW\PHARM at which dose the 2-point measurement was performed (see paragraph 4.6.2: Recalculated dosage regimen).

Another disadvantage of these classical calculator programs is that they often describe the kinetics of the drug using a 1-compartment model. The consequences of using the 1-compartment-2-point method with a drug that clearly shows 2-compartment kinetics (e.g. vancomycin) are demonstrated in figure 3.4-C.

With classical calculator programs employing the 1-compartment-2-point method it is absolutely essential that the peak level is measured after the initial distribution phase has been completed (see fig. 3.4-C.) so that only the elimination phase is characterised. However, the real maximum concentration (C_{max}) will still be underestimated under these circumstances.

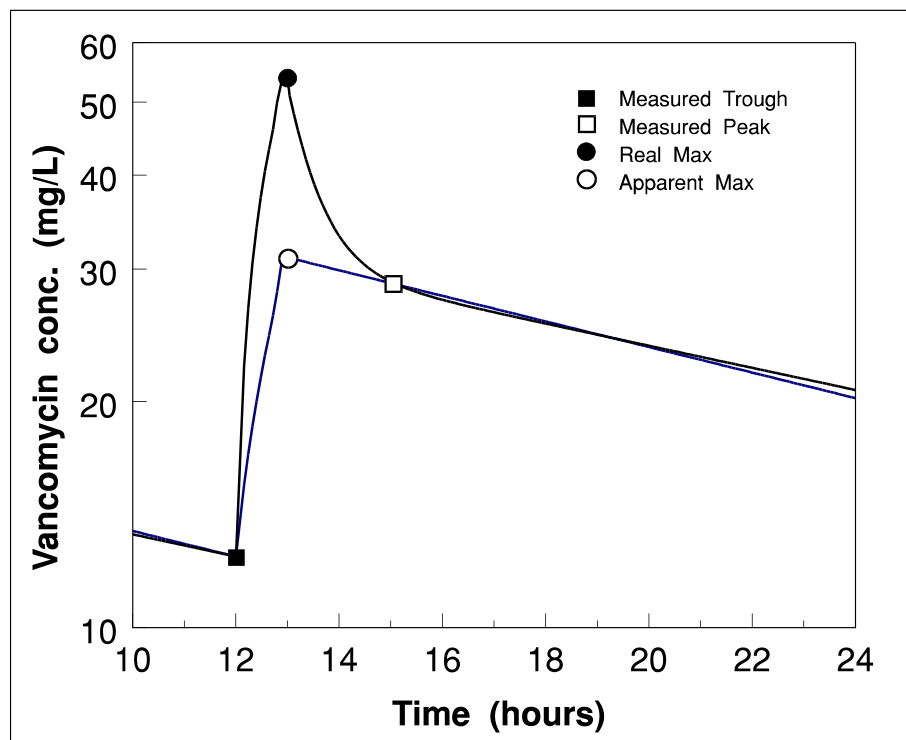


Figure 3.4-C. 2-point method with 2-compartment models.

☞ MW\PHARM is able to combine the 2-point method with both 1- and 2-compartment models. Thus the actual maximum concentration is always predicted correctly. With 2-compartment models the 2-point method can only be employed using the Bayesian population feedback method (see paragraph 3.5.)

An alternative to the 2-point method is the multi-point method in which more than 2 plasma levels are evaluated. In MW\PHARM the multi-point method is implemented by fitting the medication history of the patient. The medication history not only contains all dosing events and measured plasma levels, but also the measured creatinine levels and the weights of the patient (see paragraph 4.7, Medication History). One major advantage of the multiple-point method is that it can deal with irregular dosage regimens. It is also more accurate because more observations from the individual patient are used for determining the individual patient parameters.

3.5 Bayesian Population Feedback

The clinician evaluating the measured plasma levels always has to deal with different sources of uncertainty. First of all, there is always an error associated with the analytical method used for determining the plasma levels of a drug. Also the time points at which the samples were supposed to be taken may differ from the actual sampling times. One way of dealing with these errors is the Bayesian population feedback method. When employing the Bayesian (statistical) method not only the observations (plasma levels) of the individual patient are taken into account (a posteriori knowledge), but also the value and accuracy of the pharmacokinetic population parameters (a priori knowledge). This approach in fact simulates the normal way of thinking of an experienced clinician. Thanks to the Bayesian feedback method it is even possible to estimate individual pharmacokinetic parameters based on a single measured plasma level.

☞ The Bayesian population feedback method may be switched off in MW\PHARM (with both the 2- and multi-point method), if the number of observations (plasma levels) is equal or larger than the number of model parameters that have to be estimated. Therefore a 2-point method using a 2-compartment model (4 parameters) can only be performed if Bayesian feedback is switched on.

3.6 Exact and Practical Dosage Regimens

An Exact dosage regimen is characterised by the fact that the observed or predicted maximum and minimum plasma levels exactly match the desired maximum (C_{\max}) and minimum (C_{\min}) plasma levels. Very seldom an exact dosage regimen is also practical. E.g. a regimen subscribing 1347.5 mg every 16.31 h can hardly be called practical. MW\PHARM is able to convert exact dosage regimens into practical dosage regimens based on convenient interval times and available dosages (see fig. 3.6-A).

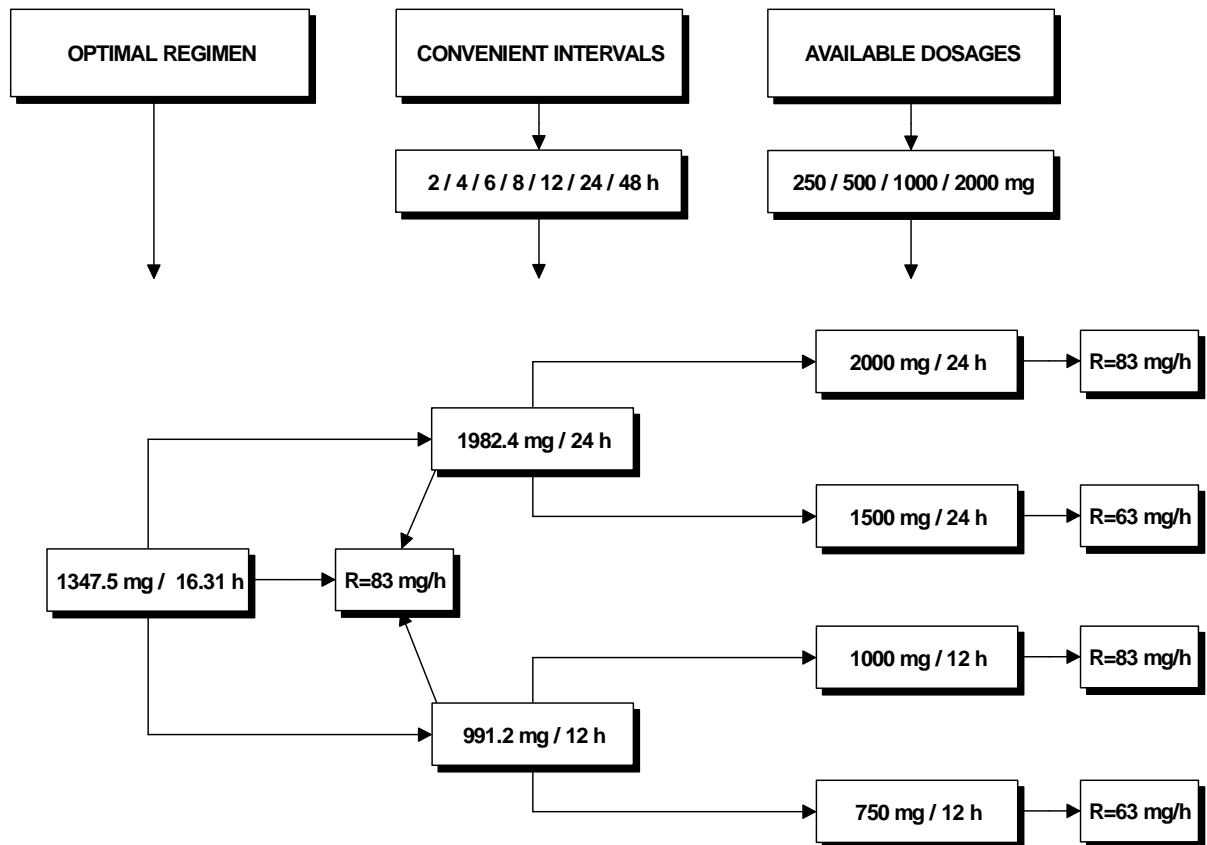


Figure 3.6-A. Generation of practical dosage regimens.

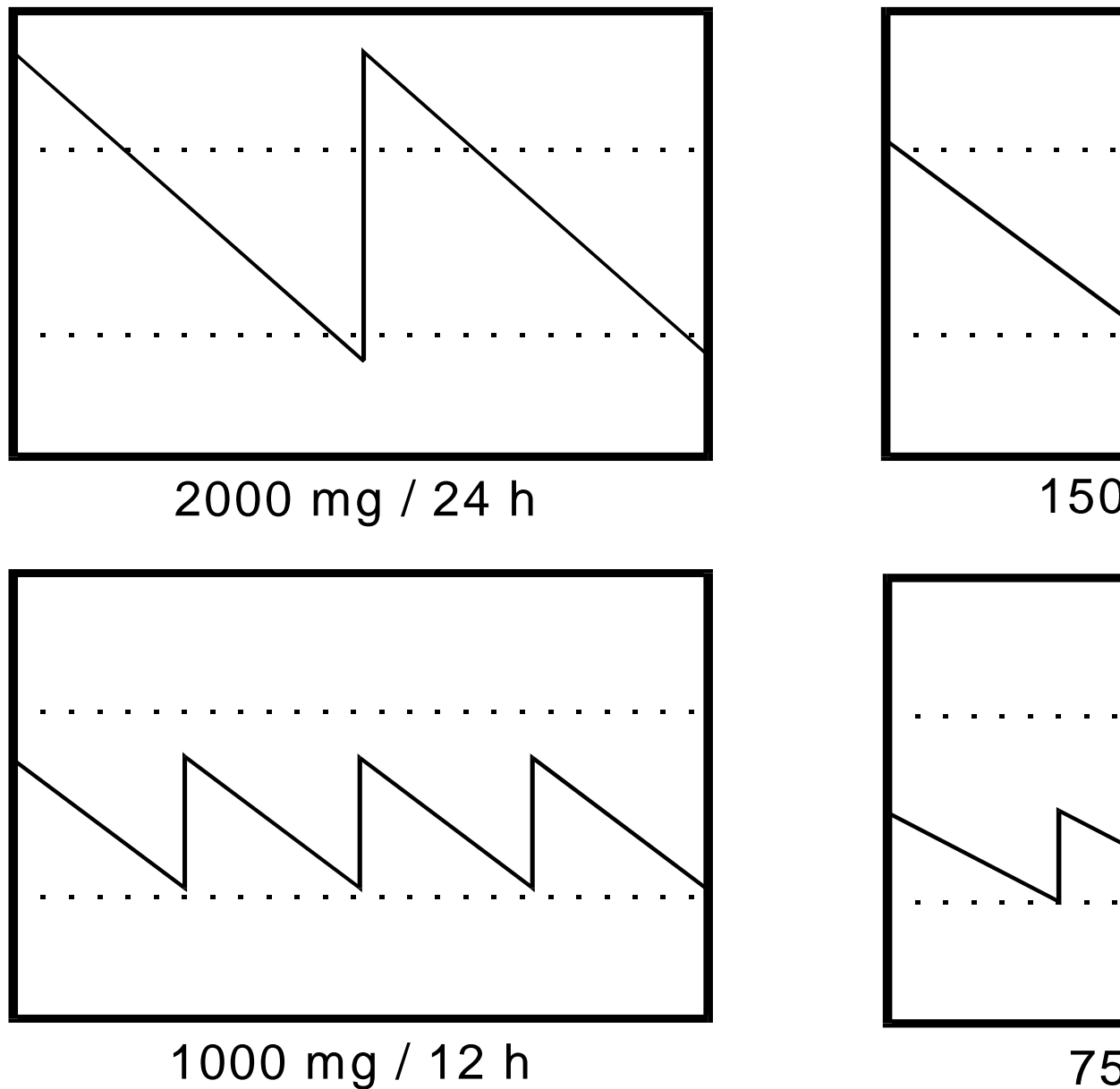


Figure 3.6-B. Plasma level profiles of different practical dosage regimens.

From figure 3.6-A. you can see that there are 4 principle practical alternatives to a single exact dosage regimen. Practical interval times are chosen so that they are convenient for the medical personal administrating the dosages. The available dosages mentioned do not represent commercially available dosages but dosages that the

hospital pharmacist is willing to prepare himself. These available dosages are listed in the drug database of MW\PHARM.

The practical dosage suggested by MW\PHARM is based on one or a combination of maximally two available dosages. So in the example of figure 3.6-A. MW\PHARM will never suggest the (better) regimen of 1750 mg / 24 h because the amount of 1750 mg must be constructed from three available dosages (1000 + 500 + 250).

As you can see from the plasma profiles in figure 3.6-B., dosage regimens with the same input rate R (mg/h) will cause the same average plasma levels. However, the difference between maximum and minimum plasma levels (amplitude) will increase with longer interval times.

☞ MW\PHARM does not sort the practical dosage regimen alternatives (e.g. based on the deviations between predicted and desired minimum and maximum plasma levels). Therefore, we strongly advice you to examine all 4 practical dosage regimen proposals before making any decision. You can base your decision on the reported trough and peak levels or by examining the different plasma profiles resulting from different practical dosage regimens.

3.7 Switching between Dosage Regimens

A given dosage regimen must be adjusted if the monitored plasma levels are either too low or too high. However, under extreme conditions (very high or very low plasma levels), the timing of such a dosage adjustment can be very critical. There exist two principal methods for optimally switching between two different dosage regimens (see fig. 3.7).

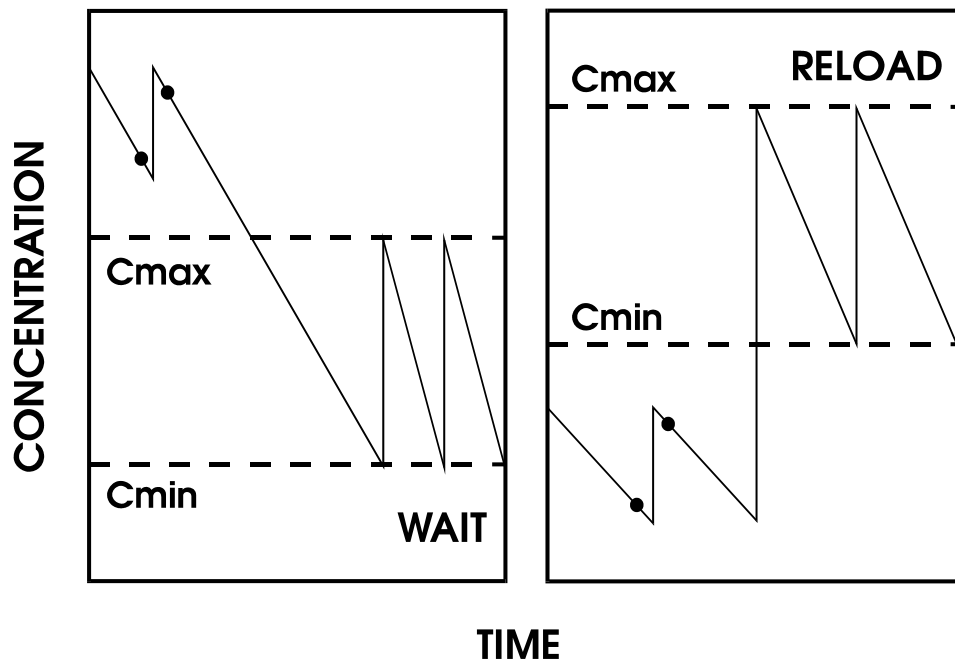


Figure 3.7. Switching between 2 dosage regimens.

MW\PHARM suggests a waiting time relative to the start of the last given dose when the measured trough level is above the desired minimum level (fig. 3.7; left panel). After the waiting time is over the new regimen (new maintenance dose and new interval time) may be applied. When the measured trough level is below the desired minimum level, a reloading dosing is suggested (fig. 3.7; right panel). The reloading dose must be given at one interval time (old regimen) after the last given dose. One interval time (new regimen) after the reloading dose the therapy may be continued using the new dosage regimen (new maintenance dose and new interval time). When the measured trough level lies within the desired minimum and maximum levels MW\PHARM will suggest to resume the adjusted therapy by using either a waiting time or a reloading dose. If you have the choice between a reloading dose or a waiting time, we suggest to use the waiting time method because it does not require any actions (except for waiting).

Waiting times and reloading doses are only required under extreme conditions (very high or very low plasma levels). Under normal circumstances (small deviation of the expected optimal levels) you may ignore this suggestion of MW\PHARM.

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4 TOUR DE PHARM

4.1 Starting MW\PHARM

For instructions concerning the installation of MW\PHARM on your computer system we refer to the volume 1 manual (Installation & Quick Reference, chapter 1).

Type **A P O** at the DOS prompt to start MW\PHARM.
The opening screen (fig. 4.1) should now appear.

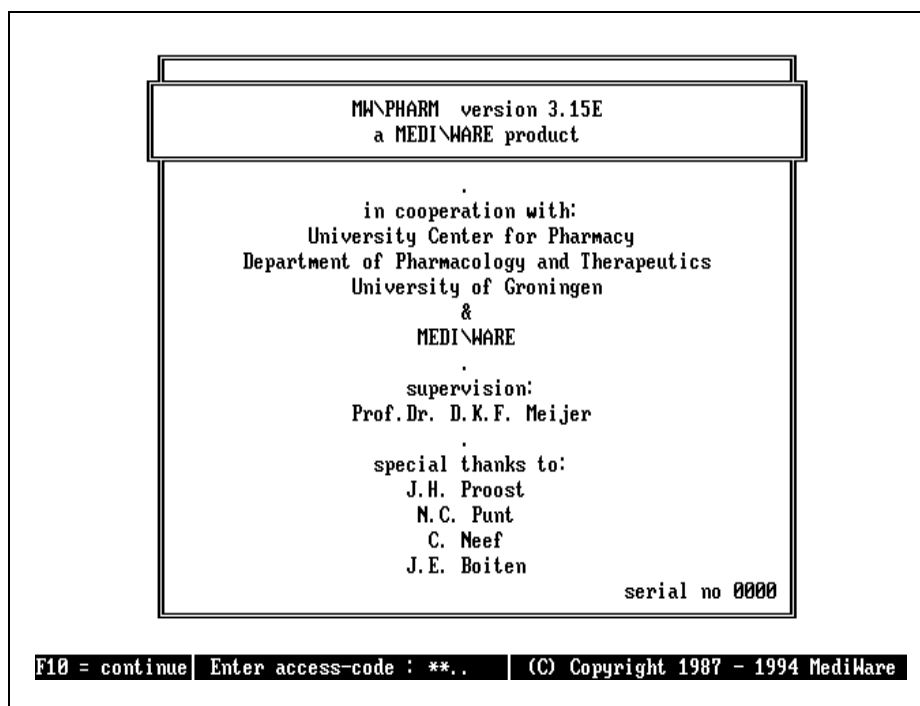


Figure 4.1. MW\PHARM opening screen.



Make sure that the numlock light on your keyboard is switched off before you continue.

On start-up MW\PHARM asks for an access-code. If you do not enter the correct access code you can only store data of patients whose names start with the letters TEST (e.g. Test 1). The default access code is set to 4444.

Type to continue to the main menu.

4.2 Main Menu

Figure 4.2-A shows the main menu of the MW\PHARM program. You can make a menu choice by pressing to .

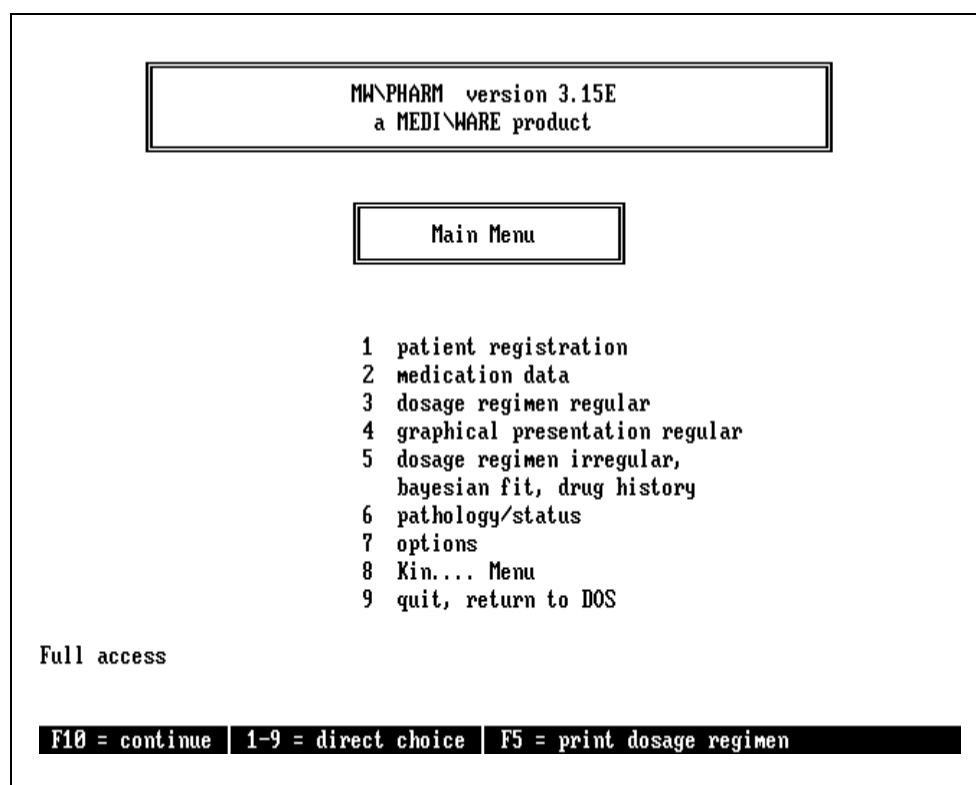


Figure 4.2-A. The main menu screen.

The highlighted bar at the bottom of screen displays the most important commands available for the current menu screen.

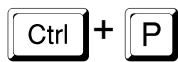
The following commands are valid in almost every MW\PHARM (sub)menu.



Go to the next (sub) menu in sequence.



Go back to the main menu.



Print the current screen.

Press followed by in order to go to the calculation options screen (fig. 4.2-B).

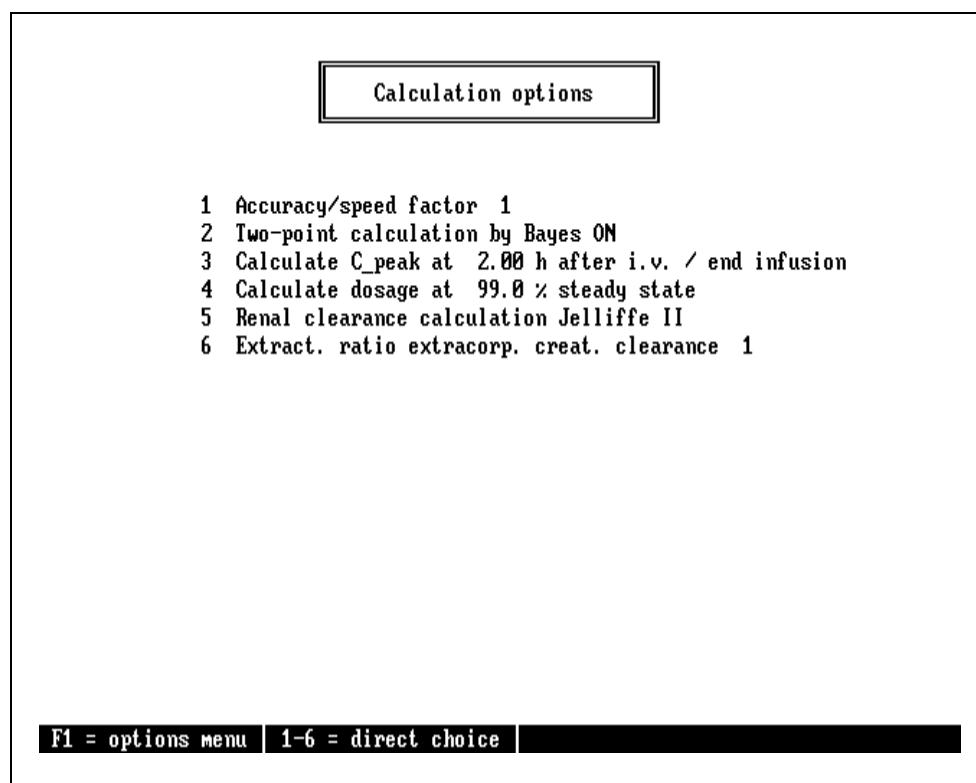


Figure 4.2-B. The calculation options menu.

We will use vancomycin as an example drug in this tour. One of many possible parameter settings in the MW\PHARM program is the time at which a peak sample is taken when using the 2-point method.

The default setting is 0.5 hours after stopping the administration of drug. In MW\PHARM this value is also correct for vancomycin. However, in the past vancomycin samples were always taken 2 hours after stopping the i.v. infusion because at that time the distribution phase was completed (see paragraph 3.4 for a discussion on this subject). In order to obtain peak and trough values most users can relate to, we will change the default sampling time to 2 hours.

Press **[3]** in order to change the C_{peak} sampling time. Thereafter press **[2]** followed by **[Enter]**.



In this tour we also want to demonstrate the 2-point method in combination with the Bayesian feedback principle. By default the Bayes method for 2-point recalculations is disabled. Therefore we will enable it.

Press **[2]** to switch on the Bayes method for 2-point recalculations. Press **[F1]** twice in order to return to the main menu.

The **[F10]** key leads you directly from sub menu to sub menu in a pre-defined logical sequence without the need of returning to the main menu again.

Press **[F10]** or **[1]** to go to the patient registration menu.

4.3 Patient Registration

In the patient registration menu (fig. 4.3-A) you can register a new patient to the patient database of MW\PHARM. The only data fields that have to be filled in (using  and ) are the patient number, name and date of birth.

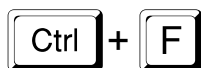
PATIENT REGISTRATION

patient number	:	1
name and initials	:	MW
date of birth	:	06-01-1940
address	:	
postcode/zipcode	:	
city	:	
family doctor	:	
requesting physician	:	
ward	:	
room number	:	
age	:	55 years
last medication	:	

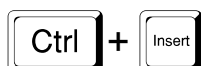
F10 F1 ↑↓ ^f=find ^t=next ^-=previous ^Del=erase ^Ins=save ^s=st. pat. BS

Figure 4.3-A. Patient registration screen.

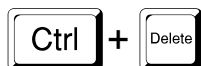
The following commands are important:



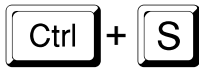
Open the browse window. The search criterion can be based on the patient number, name or date of birth dependent on the location of the text cursor.



Save patient data (including pathology, medication history and individual pharmacokinetic parameters).





Delete patient data. Patient data are removed from the database on disk but remain present in memory.





Recall standard patient (male, 55 years old, weight 70 kg, height 175 cm and a serum creatinine of 70 M).





Note that in the computer screens the  key is represented by the ^ sign (^ = ).



From the entered date of birth and the computer system date, the age of the patient is calculated. It is therefore very important that the computer date is set correctly.

When you enter the patient registration screen for the first time MW\PHARM presents you a standard patient. At any later stage you are able to recall this standard patient by pressing  +  clearing the data of the current patient. The main advantage of having a standard patient is that you don't have to enter any data that in your opinion are not important for a dosage regimen calculation. It might also be that you simply do not have all patient data available. In both cases the standard patient can save you a lot of work.

If you want to save patient data press  + . If the patient was already present in the database you will be given 3 options:



Exit, do not save patient data.





Overwrite patient data (update).



Add patient data.

Option 2 allows you to add an existing patient to the database who is receiving a second drug.

Press  +  to open the browse window (fig. 4.3-B).

In the browse window you can browse through the patient database using the , , , ,  and  keys. You can select the

highlighted patient by pressing **Enter**. Press **Esc** to leave the browse window without selecting a patient.

Press **Esc** to leave the browse window. Then press **F10** to continue to the pathology sub menu screen.

PATIENT REGISTRATION

patient number : 1
name and initials : MW
date of birth : 06-01-1948
address :
postcode/zipcode :

city :
family doctor :
requesting physician :

0 EXAMPLE 1	Adult	19-07-1939	vancomycin (adult)	5
0 EXAMPLE 2	Dialysis	19-07-1939	vancomycin (dialysis)	2
0 EXAMPLE 3	CAPD	19-07-1939	vancomycin (capd)	4
0 EXAMPLE 4	Neonate	14-07-1994	vancomycin (neonate)	1
0 HISTORY	Tour De Pharm	19-07-1939	vancomycin (adult)	5
102	TEST-D	01-01-1951	phenytoin	24
1234	TEST-E	01-01-1935	gentamicin	8
31	TEST-B	01-01-1958	theophylline	4
51	TEST-A	01-01-1958	flecainide	27
65	TEST-C	12-09-1948	cyclosporine	21

F1 F10 Enter = select patient Esc = exit ↓, ↑, PgDn, PgUp, Home, End

Figure 4.3-B. Patient browse window.

4.4 Pathology

In the pathology screen (fig. 4.4-A) you can enter more specific patient data like weight, height and sex (press **1**, **2** or **3**). You can also enter the status of the patient (press **5**). When you enter new values for weight, height and sex, the BSA (Body Surface Area) and LBM (Lean Body Mass) parameters are updated immediately. The currently used renal function (creatinine clearance) is listed under 4. Press **4** if you want to specify the kidney function of the patient.

Press **4** in order to continue to the kidney function screen (fig. 4.4-B.).

PATHOLOGY/STATUS DATA INFLUENCING PHARMACOKINETICS

1	weight	:	70.0 kg				
2	height	:	175 cm	}	→	BSA = 1.85 m ²	LBM = 70.0 kg
3	sex	:	M				
<div style="display: flex; justify-content: space-between;"> <div>4 renal function :</div> <div>CLcr = 89.5 ml/min/1.73m² 95.6 ml/min</div> </div>							
<div style="display: flex; justify-content: space-between;"> <div>5 pathology :</div> <div style="background-color: black; width: 200px; height: 1.2em;"></div> </div>							

F10 = continue
F1 = main menu
1-5 = change

Figure 4.4-A. Pathology screen.

In the medication data screen you can access all data present in the drug database. There are in fact 2 medication data screens. One contains general drug data like the available dosages, desired maximum and minimum concentrations, unit of dose, unit of concentration, etc. The second one contains the pharmacokinetic population parameters.

You can use the same key commands for browsing through the drug database as for the patient database (patient registration screen). Also the keys for saving and deleting drug records from the drug database are the same.

Type **V****A**. Then press **Ctrl**+**F** in order to activate the browse window. Highlight "**vancomycin (adult)**" using the **↑**, **↓** keys.

☞ Note that of vancomycin (and many other drugs) several variants are listed, each defining a different patient population

Press **Enter** to load the "**vancomycin (adult)**" drug data. The medication screen should now resemble fig. 4.5-A.

In this manual we will not discuss the meaning of every listed parameter. The only parameter fields which are probably of interest to you, are the available dosages, the infusion duration (duration) and the desired maximum (C_{\max}) and minimum (C_{\min}) concentrations. You can navigate through the screen using the **↓**, **↑**, **←** and **→** keys in order to edit the different fields.


Name of drug	:	vancomycin (adult)	06-01-95
Unit of dose	:	mg	Unit of concentration : mg/l
Available dosages	:	250 500 1000	
Adequately described with		2	compartment(s)
Calculation CL or kel	:	$CL = CL_m * BSA/1.85 + fr * CL_{cr}$	
Administrations:		<input type="checkbox"/> I.M. <input type="checkbox"/> I.V. <input type="checkbox"/> ORAL <input type="checkbox"/> INFUS. <input checked="" type="checkbox"/> INFUS. (r)	duration 1 h
Cmax:	60	mg/l	Cmin: 0 mg/l Cav: 25 mg/l Ctox: 75 mg/l
Dose calculations based on		Cmax - Cmin	
Concentration scale limit	:	72	mg/l
Calculations based on		total	concentration
Active metabolite	:		

patient	
CL	4.51 l/h
V1	14.70 l
V	55.93 l
t _{1/2} 1	0.38 h
t _{1/2} 2	8.59 h
fe	0.9535

F10=continue F1 ↑↓+ PgDn ^f=find ^+=+1 ^-= -1 ^Del=erase ^Ins=save Esc BS

Figure 4.5-A. Medication data screen (1) containing general drug data.

Note that for vancomycin the infusion duration is set to 1 hour, which is now generally recommended. If you are using different infusion duration times you will have to change this value accordingly.

Press  in order to go to the second medication screen (fig. 4.5-B).

4.6 Dosage Regimen Calculation

4.6.1 Initial dosage regimen

Press **F10**. The dosage regimen screen will appear (fig. 4.6-A.).

vancomycin (adult)		MW		08-01-1940			
Infusion (repeated)		Selected	Exact	Practical			
Loading dose	mg	1536.4	1536.4	1500	1500	1500	2000
Maint. dose	mg	1347.5	1347.5	750	1000	1500	2000
Infusion time	h	1.00	1.00	1.00	1.00	1.00	1.00
Dosing interval	h	16.31	16.31	12	12	24	24
Total duration	h	49	49	48	48	48	48
Number of doses		3	3	4	4	2	2
C _{max} ss	mg/l	60.00	60.00	36.15	48.20	62.35	83.14
C _{min} ss	mg/l	8.00	8.00	7.44	9.92	4.09	5.46
C _{av} ss	mg/l	18.30	18.30	13.85	18.46	13.85	18.46
Steady state	%	99	99	101	100	98	98
C _{peak}	mg/l	23.98	23.98	16.05	21.05	22.77	30.36
C _{trough}	mg/l	7.64	7.64	7.70	9.82	3.50	4.67
T _{peak}	h	3.00	3.00	3.00	3.00	3.00	3.00
T _{trough}	h	0.00	0.00	0.00	0.00	0.00	0.00

F10=continue F1=main menu F3=adapt F4=copy F5=print F6=recalc. F7=roa ↓

Figure 4.6-A. Initial dosage regimen of vancomycin (standard patient).

The dosage regimen screen can be in 2 different modes. The first one is the **dosing mode** (fig. 4.6-A) and the second one is the **recalculation mode** (fig. 4.7-A). The default mode of the dosage regimen screen is the dosing mode and we will deal with this mode first.

The dosage regimen screen (fig. 4.6-A) displays 6 input parameters (the dosage regimen) and 8 output parameters (4 steady state and 4 current state parameters) for 6 different dosage regimens (1 selected, 1 exact and 4 practical regimens).

Dosage regimen input parameters.

The first row consists of the six parameters defining a regular dosage regimen:

- Loading dose : The first given dose
- Maintenance dose : Subsequent given doses
- Infusion time : Duration of administration (infusions only)
- Dosing interval : Time between subsequent administrations
- Total duration : Time required to reach steady state
- Number of doses : Number of doses required to reach steady state

Steady state output parameters.

The second row contains the results of the dosage regimen input parameters in terms of predicted steady state concentrations.

- C_{max_ss} : Predicted maximum steady state concentration
- C_{min_ss} : Predicted minimum steady state concentration
- C_{av_ss} : Predicted average steady state concentration
- Steady State % : Predicted percentage steady state level

☞ The “number of doses” or “total duration” parameters have by definition no influence on the C_{max_ss}, C_{min_ss} and C_{av_ss} parameters (only on the percentage steady state).

Current state output parameters.

The third and last row contains the results of the dosage regimen input parameters in terms of predicted concentrations at the given sampling times of the **last given dose** (current state) which is identified by the “number of doses” parameter.

- C_{peak} : Predicted concentration at time T_{peak}
- C_{trough} : Predicted concentration at time T_{trough}
- T_{peak} : Time of sampling C_{peak}
- T_{trough} : Time of sampling C_{trough}








☞ In case of extravascular administrations the value of T_{peak} does not refer to a pre-set sampling time but to the time of actual maximum concentration.




Dosage regimens

The following dosage regimen data of 1 route of administration are shown on screen:

- **Selected** The by the user selected or entered dosage regimen. Simulated plasma profiles and printed dosage advises always relate this regimen.
- **Exact** The pre-set calculated dosage regimen that exactly matches the imposed C_{\max} and C_{\min} target criteria listed in the medication data screen.
- **Practical** Four pre-set practical dosage regimens generated from the available dosages listed in the medication data screen and convenient interval times.


The following keys are important:

	<i>Go to the simulation graphics screen</i>
	<i>Navigate cursor to different input fields</i>
	<i>Adapt dose to interval or vice versa</i>
	<i>Select exact or one of four practical dosage regimens</i>
	<i>Print current dosage advice</i>
	<i>Initiate & complete 2-point recalculation</i>
	<i>Select next available route of administration</i>

You can reach the different input parameter fields by pressing the  and  keys. In the moment you enter a new value for one of the input parameters all output parameters are erased. If you press  when the cursor is located at the last input parameter field (number of doses) the cursor will jump back again to the first input parameter field (loading dose).




This event also triggers the updating of the output parameters displayed in the lower section of the screen. Thus if you want to study the effect of changes you made to the dosage regimen

move the cursor to the top row again by repeatedly pressing the  key.

Changing input parameter does not only affect output parameters but also other input parameters. The following rules apply here:

Changed parameter	Updated parameter
dosing interval	total duration = number of doses x dosing interval
number of doses	total duration = number of doses x dosing interval
total duration	number of doses = total duration / dosing interval

When you enter the dosage regimen screen for the first time the selected dosage regimen will be a copy of the exact dosage regimen.

Press  to simulate the plasma profile of the current dosage regimen (currently an exact regimen).

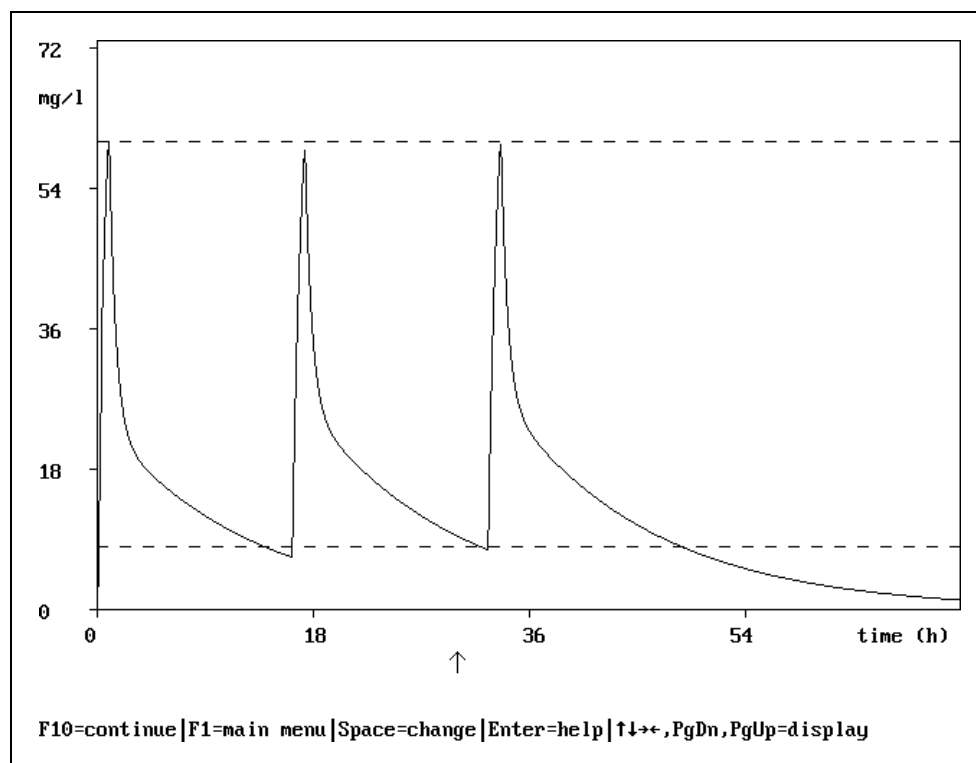



Figure 4.6-B. Plasma profile of an exact dosage regimen.


MW\PHARM does a good job in calculating the exact dosage regimen as can be seen from the plasma level profile of fig. 4.6-B. However a regimen of 1347.5 mg vancomycin every 16.31 hours is not very practical. Thus our next task is to devise a practical dosage regimen.



Press  to return to the dosage regimen screen.

If you want to study the differences between the exact and the practical regimens, examine the expected peak and trough levels in the lower section of the screen. The following table summarises all regimens displayed in the dosage regimen screen of fig. 4.6-A.

Initial exact and practical dosage regimens

Type	Loading dose (mg)	Mainten. dose (mg)	Interval (h)	Peak (mg/L)	Trough (mg/L)
<i>E</i>	1536	1348	16	24.0	7.6
P1	1500	750	12	16.1	7.7
P2	1500	1000	12	21.1	9.8
P3	1500	1500	24	22.3	3.5
P4	2000	2000	24	30.4	4.7

The initially calculated exact dosage regimen is very seldom also a practical dosage regimen. You can copy the practical dosage regimens into the selected regimen by repeatedly pressing .

Press  twice so that practical regimen P2 (which seems most appropriate) is the currently selected regimen. Then press  in order to simulate the plasma profile of this practical dosage regimen (fig. 4.6-C.).

When you compare figure 4.6-B with figure 4.6-C you will see that selecting a practical dosage regimen almost always results in a less optimal plasma profile. It is the task of the user to select a practical dosage regimen which most closely resembles the profile of the exact dosage regimen.

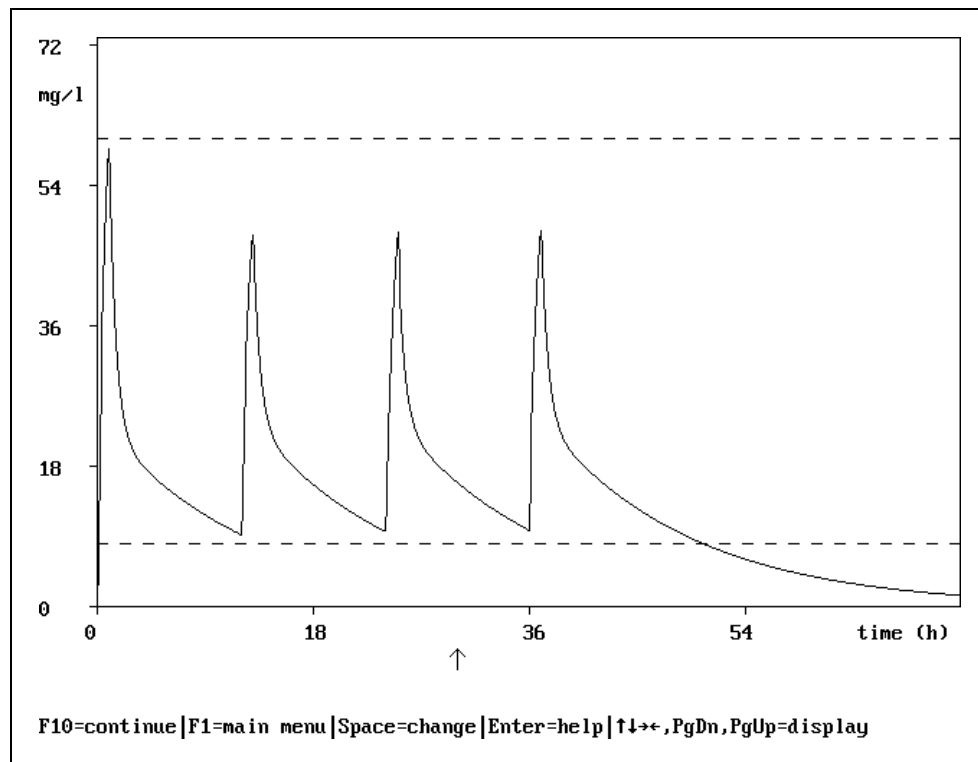


Figure 4.6-C. Plasma profile of a practical dosage regimen.

You can base your decision on the reported trough and peak levels or by examining the different plasma profiles resulting from different practical dosage regimens.

Press to return to the dosage regimen screen. If you have a printer connected press in order to print the current dosage advice (make sure the printer is on-line).

4.6.2 Recalculated dosage regimen

In paragraph 4.6.1 we calculated an initial dosage regimen for the standard patient based on basic patient data (age, weight, sex, etc.) and the pharmacokinetic population parameters of vanco-mycin. Without further information this is the best we can do at this stage. However, there is always a change that the patient in question deviates from the 'normal' population of patients with respect to his or her individual vancomycin pharmacokinetics. At this point TDM becomes important. The only way to determine if a patient shows deviant pharmacokinetics is to measure the actual plasma levels in this patient.

MW\PHARM has 2 methods available for processing measured plasma levels (see paragraph 3.4). First, a 2-point method in which a trough and a peak level is measured and evaluated. Second, a multi-point method which is implemented by fitting the medication history of the patient (see paragraph 4.7). In this paragraph we will deal with the 2-point method. One advantage of the 2-point method over the multi-point method is that the measured plasma data can directly be entered into the dosage regimen screen. You will have to switch the dosing regimen screen from dosing mode to recalculation mode by pressing **F6** in order to enter measured plasma levels.

Press **F6** to switch the dosage regimen screen from dosing mode to recalculation mode.

In the moment you press **F6** the exact and practical dosage regimens are hidden and the heading of selected regimen column changes from "Selected" into "Recalc.". Also the steady state output parameters are temporarily hidden. You can reach the different regimen fields by repeatedly pressing **↓** or **↑**.

vancomycin (adult)		MW		08-01-1940			
Infusion (repeated)		Recalc.					
Loading dose	mg	1500.0					
Maint. dose	mg	1000.0					
Infusion time	h	1.00					
Dosing interval	h	12.00					
Total duration	h	48					
Number of doses		3					
C_peak	mg/l	40.00					
C_trough	mg/l	25.00					
T_peak	h	3.00					
T_trough	h	0.00					
F6=calculate parameters time in h (decimal) ↓							

Figure 4.6-D. Dosage regimen screen in recalculation mode.

☞ Note that when the dosage regimen screen is in recalculation mode, you can also reach the fields in the lower section of the screen.

At this stage you can change the displayed values for loading dose, maintenance dose and dosage interval because the actual given regimen might deviate from the earlier advised regimen.

☞ Note that when the dosage regimen screen is in recalculation mode, the field "number of doses" requires you to enter the dose number at which the trough and peak level were actually measured.

In the lower section of the screen you can enter the measured peak and trough values together with the times the samples were taken. All times are expressed relative to the time when the last dose was given. See paragraph 3.4 (fig. 3.4-A/B) for the exact definition of these fields.










MW\PHARM can process both trough-peak and peak-trough measurements. Let's assume at the 3rd dose we measured a peak level of 40 mg/L at 2 hours after stopping the infusion (infusion duration of 1 hour) and a trough level of 25 mg/L at 0.5 hours before the next administration (dosing interval of 12 h). Dependent on whether the trough was measured before the peak (trough-peak method) or vice versa (peak-trough method) the following values should be entered:


Output Parameter	Trough-Peak Method	Peak-Trough Method
C _{peak} (mg/L)	40	40
C _{trough} (mg/L)	25	25
T _{peak} (h)	3 [#]	3 [#]
T _{trough} (h)	-0.5	11.5

[#]Under calc. options listed sampling time (2 h) + inf. duration (1 h)

☞ Thus with the more usual trough-peak method, T_{trough} times are entered as negative values.

For our guided tour we will assume that the aforementioned data were obtained from a trough-peak measurement. Furthermore, we will assume that the trough level was measured just before the next dose was given. This means it is set to zero which is also the default value for this parameter.

Bring the cursor to the **number of doses** field by repeatedly pressing the  key. Then press . Press  to move the cursor to the **C_{peak}** field and type . Press  once again in order to navigate the cursor to the **C_{trough}** field and type   (see fig. 4.6-D).

Now activate the recalculation process by pressing . The screen displayed in figure 4.6-E will appear.

Bayesian fit					ss = 3.439890E+00
		measured	population	initial ->	fit
C_peak	:	40.0000		->	39.4681
C_trough	:	25.0000		->	23.4652
CLm	:		0.2100	0.2100 ->	0.2078
fr	:		0.7500	0.7500 ->	0.3083
V1	:		0.2100	0.2100 ->	0.2033
k12	:		1.1200	1.1200 ->	1.0744
k21	:		0.4800	0.4800 ->	0.5041
(press any key to continue)					

Figure 4.6-E. 2-point Bayesian fit progress screen.

In the 2-point Bayesian fit screen (fig. 4.6-E) the progress of the Bayesian fit is displayed. A detailed explanation of this screen is beyond the scope of this manual. You will hear a beep sound when the fit has been completed.

- ☞ The fitting process will stop automatically when the fitted parameter values stop changing with every iteration. If this does not happen press the **F1** key to stop the fit manually.

After the fit has been completed press any key (e.g. **Enter**) to return to the dosage regimen screen.

individual data		MM		08-01-1940			
vancomycin (adult)							
Infusion (repeated)		Selected	Exact	Practical			
Loading dose	mg	1500.0	1366.2	1250	1250	1500	2000
Maint. dose	mg	1000.0	1191.5	750	1000	1500	2000
Infusion time	h	1.00	1.00	1.00	1.00	1.00	1.00
Dosing interval	h	12.00	33.32	24	24	48	48
Total duration	h	36	100	96	96	96	96
Number of doses		3	3	4	4	2	2
C _{max} ss	mg/l	73.82	60.00	41.40	55.20	70.42	93.89
C _{min} ss	mg/l	31.18	8.00	8.82	11.76	4.73	6.31
C _{av} ss	mg/l	42.15	18.09	15.81	21.07	15.81	21.07
Steady state	%	85	99	100	99	98	98
C _{peak}	mg/l	39.47	29.18	21.91	28.85	31.77	42.36
C _{trough}	mg/l	23.47	7.72	8.88	11.43	4.10	5.46
T _{peak}	h	3.00	3.00	3.00	3.00	3.00	3.00
T _{trough}	h	0.00	0.00	0.00	0.00	0.00	0.00
t _{1/2} (h)		8.59 → 16.58	U1 (l)	14.70 → 14.23	CL (l/h)	4.51 → 1.98	
ADVICE: Waiting time after the last dose (give maintenance dose) : 40.66 h							
OR: Reloading dose after the last dose (after 1 interval) : 762.62 mg							
F10=continue F1=main menu F3=adapt F4=copy F5=print F6=recalc. F7=roa ↓							

Figure 4.6-F. Dosage regimen screen after recalculation.

Figure 4.6-F. displays the dosage regimen screen after a recalculation. The screen is now in the dosing mode again. Just above the command bar (at the bottom of the screen) the old and the recalculated pharmacokinetic parameters are displayed. The exact and practical dosage regimens are based on these new parameters. The selected dosage regimen still contains the actual given (old) dosage regimen.

Also displayed at the bottom of the screen (just above the pharmacokinetic parameters) is an advice concerning the switching between the old and new dosage regimen. The interpretation of this advice (waiting time or reloading dose) is discussed in paragraph 3.7). For now just remember the suggested waiting time of 40 h. We will demonstrate the implementation of this advice in paragraph 4.7 (medication history).

Press **F10** to simulate the actual given regimen in combination with the recalculated pharmacokinetic parameters. The plasma level profile displayed in figure 4.6-G. will appear.

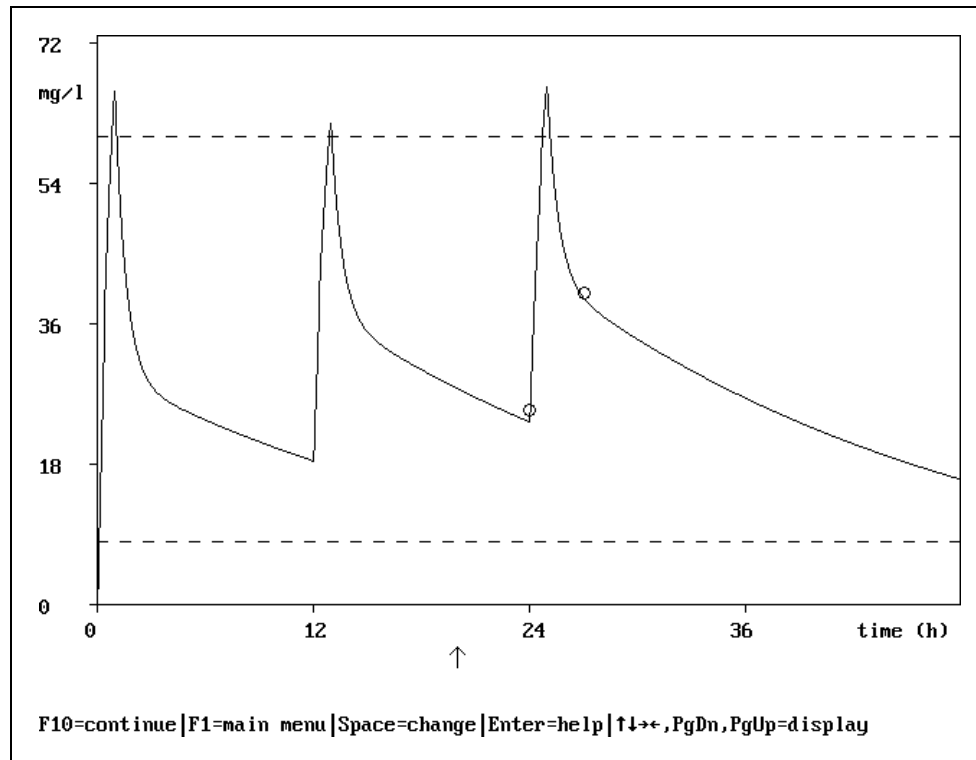


Figure 4.6-G. Actual observed plasma profile after TDM.

As can be seen from figure 4.6-G. the plasma levels observed in this patient were much higher than we expected. Therefore the dosage regimen for this patient must be adjusted.

Press **F1** to return the dosage regimen screen and closely examine the new exact and practical regimens.

When you followed the guided tour instructions you will have seen the following exact and practical dosage regimens (see fig. 4.6-F):

Recalculated exact and practical dosage regimens

Type	Loading dose (mg)	Mainten. dose (mg)	Interval (h)	Peak (mg/L)	Trough (mg/L)
<i>E'</i>	1366	1192	33	29.2	7.7
P1'	1250	750	24	21.9	8.9
P2'	1250	1000	24	28.9	11.4
P3'	1500	1500	48	31.8	4.1
P4'	2000	2000	48	42.4	5.5

☞ After a recalculation also a new value for the loading dose is listed. This loading dose is only valid if you wait for a very long period before starting with the newly calculated regimen. Otherwise you may ignore this loading dose.

Repeatedly press **F4** until practical regimen P2' (which seems most appropriate) is the currently selected regimen. Then press **F10** in order to simulate the plasma profile of this practical dosage regimen.

If you now examine the simulated plasma levels you will see a profile similar to that of figure 4.6-C. The levels are completely situated within the therapeutic range again.

Press **F1** to return to the main menu. Next press **2** to take a another look at the medication data screen.

If you now examine the medication data screen you can see the label **"individual data"** in the upper right corner of the screen. This means that the listed pharmacokinetic parameters are not popula-

tion parameters anymore but individual parameters. The next time you load this patient from the patient database also the pharmacokinetic population parameters are replaced by the individual patient parameters (if available).

☞ Individual pharmacokinetic parameters are stored in the patient database and not in the drug database

☞ Go to the patient registration screen if you want to save the patient data (including the individual pharmacokinetic parameters). See paragraph 4.3 for instructions.

Summary

We can summarise the guided tour until now as follows. We calculated an initial vancomycin dosage regimen for a patient resembling the standard patient in MW\PHARM. This regimen amounted to a loading dose of 1500 mg followed by 1000 mg every 12 h. We expected the trough and peak levels to be 9.1 and 21.1 mg/L respectively. After an actual measurement (TDM) these levels turned out to be 25 and 40 mg/L respectively, which is of course much too high. After processing these values we calculated an adjusted dosage regimen which amounted to 1000 mg every 24 h (we ignored the suggested loading dose). MW\PHARM also suggested that we should wait 40 h relative to the start of the last given (old) dose before starting with the new regimen.

4.7 Medication History

4.7.1 Creating a medication history

Press **F1** to return to the main menu again. Press **F10** in order to go to the patient registration screen. Press **Ctrl** + **F** to open the patient browse window. Select (highlight) the patient with number **"0 HISTORY"** and name **"Tour de Pharm"** using the **↓** and **↑** keys. Confirm this selection by pressing the **Enter** key. Press now **F1** to return to the main menu. Then press **5** to enter the medication history screen (fig. 4.7-A).

date	time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY	HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[μM]	[ml/min]
01-01-94	08:00	1500	iv	1		1		70	70	
01-01-94	20:00	1000	iv	2	12	1				
02-01-94	08:00						25			
02-01-94	11:00						40			
04-01-94	03:00									

All SD values present: weighting on
 Bayes ('b'): ON Conc. at t=0 ('c') 0 Algorithm ('a'): Marquardt
F10=continue F1 ↑↓↔, PgUp, PgDn Del Ins ^→ p=date +=+1 --=1 F4=reg. d F6=recalc. d









Figure 4.7-A. Medication history screen of patient "Tour de Pharm".

Figure 4.7-A displays the initial medication history screen of patient "Tour de Pharm". This screen contains a list of dosing events combined with several types of measurements (e.g. concentration,

weight and creatinine levels). The screen is composed of 10 vertical columns.

Medication history parameters

- **Date Time** Date and time at which a dose was given or a measurement was performed (dd-mm-yy hh:mm).
- **Dose** Total given dose. With infusions the total given dose equals the infusion rate (mg/h) times the infusion duration (h).
- **Roa** Route of administration:
iv = intravascular, im = intramuscular and po = oral.
- **No** Number of given doses.
- **Interv.** Interval time between doses (only required if No>1).
- **T(inf)** Infusion duration. If this field contains no data or is set to zero an intravascular administration (iv) is interpreted as a bolus injection.
- **Conc.** Measured drug concentration.
- **Weight** Measured patient weight.
- **Creat** Measured serum creatinine level.
- **Q(EC)** Estimated extracorporeal clearance (see paragraph 5.3).

You can navigate through the medication history screen using the , , , ,  and  keys. You can change the default input direction (automatic cursor movement direction) by pressing  + . The default input direction is indicated by an arrow in the bottom right corner of the screen (just above the command bar).

Other important keys for editing the medication history are:



Delete/Insert current line



Enter {current date}



Enter {last date} / {last date +1} / {last date -1}




Insert initial regular dosage regimen



Insert recalculated regular dosage regimen

We will now take a closer look at the medication history displayed in figure 4.7-A. On the 1st of January 1994 (01-01-94) at 8 a.m. (08:00), a single dose (loading dose) of vancomycin (1500 mg) was administered using a one hour infusion. 12 hours later (01-01-94 20:00) a regular regimen was started consisting of 1000 mg every 12 hours. A total of 2 doses were given (no=2). The above described dosage regimen is in fact the same as the initial dosage regimen we calculated in the previous example (see paragraph 4.6.1). The plasma levels we used in the previous example are also listed in this medication history. On 02-01-94 at 08:00 a trough level was measured of 25 mg/L. On 02-01-94 at 11:00 a peak level was measured of 40 mg/L. The last date listed in the medication history (04-01-94 03:00) is optional. It marks the last date and time we want to see in the simulated plasma profile. The time in this last date entry may seem somewhat odd (3 a.m.) but we placed it in this medication history for reasons we will explain later.

 For the sake of clarity, the sampled concentrations in this example medication history correspond to the 2-point method we used earlier. However, the user is free to enter any number of plasma values at any time point in the medication history.

4.7.2 Fitting a medication history


Press  to simulate the medication history of this patient.

Figure 4.7-B displays the simulated plasma profile of the current medication history. The plasma curve is based on population pharmacokinetic parameters because it is not processed (fitted) yet. From the 2 measured concentrations (open circles) we can already conclude that this patient has deviant vancomycin pharmacokinetics causing plasma levels which are too high. Now we must calculate the individual pharmacokinetic parameters of this patient.

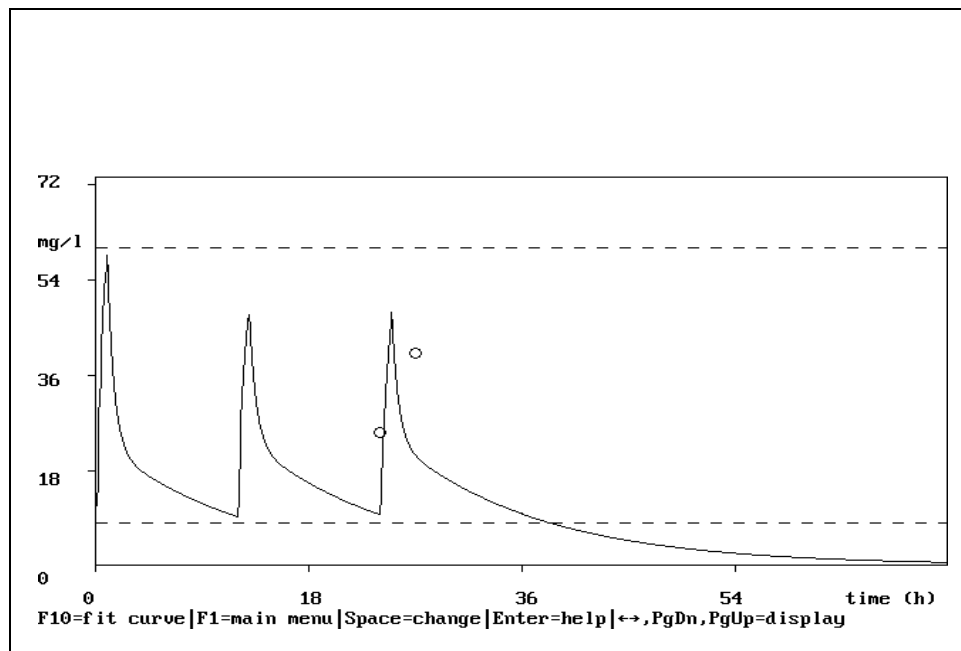


Figure 4.7-B. Simulated medication history.

Press **F10** to start the fitting process (parameter recalculation).

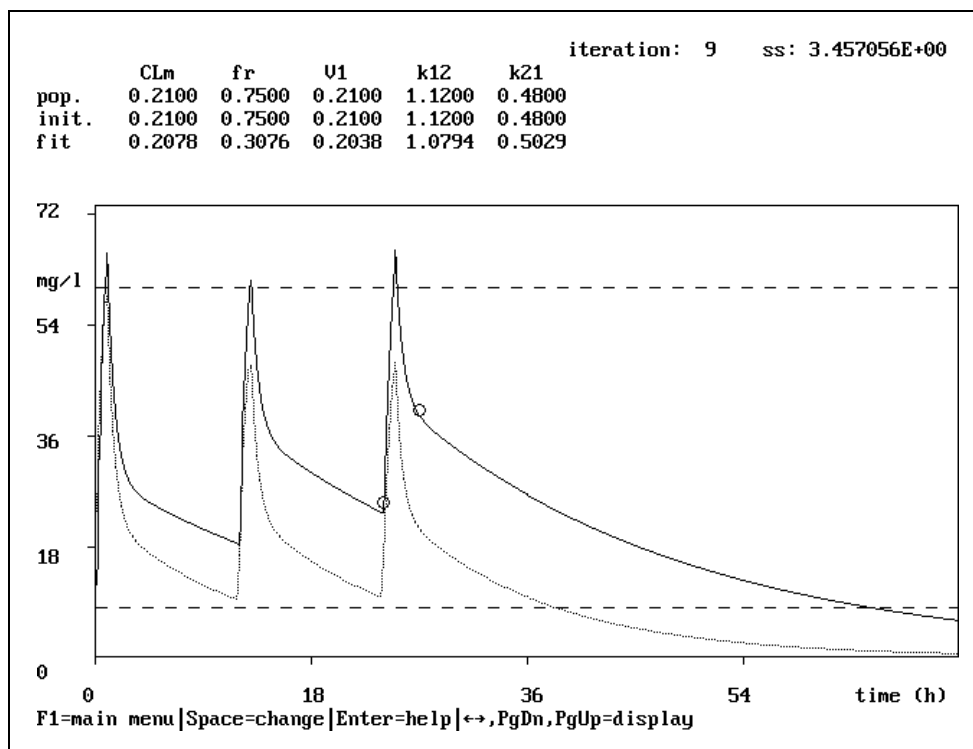



Figure 4.7-C. Fitted medication history.

Figure 4.7-C displays the fitted medication history of patient “Tour de Pharm”. The newly calculated (fitted) parameter values are displayed above the plasma curve (fit). At this point we have determined the individual pharmacokinetic parameters of this patient. Now we have to adjust the dosage regimen so that the plasma levels will return to the therapeutic window again.

4.7.3 Dosage recalculation based on medication history

In this paragraph we will demonstrate the procedure for inserting an adjusted dosage regimen (based on the parameters obtained from the previous fit) into the current medication history. The new adjusted dosage regimen is composed in the (regular) dosage regimen screen.

Press **F1** to return to the main menu. Then press **3** to enter the dosage regimen screen. Press **F4** twice so that 2nd practical regimen (1000 mg every 24 h) is the currently selected regimen. Now disable the suggested loading dose by pressing **0**.

 A loading dose is only given at the start of a therapy. When you are in the middle of an existing therapy you may ignore it. However, if under these circumstances you want to insert a dosage regimen into the medication history screen (using **F4**), you must set the loading dose value in the dosage regimen screen explicitly to zero, unless you are using the "reload" strategy for switching between 2 different dosage regimens. In that case you could enter the suggested reloading dose value in the loading dose field.

Press **F1** to return to the main menu. Press **5** to enter the medication history screen again. Move the cursor to the last date field (04-01-94 03:00) by repeatedly pressing the **↓** key. When the cursor is located on this date press **F4** to insert the previously selected practical dosage regimen (fig. 4.7-D). Thereafter press **F10** to simulate the medication history (fig. 4.7-E).

date	time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY	HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[μM]	[ml/min]
01-01-94	08:00	1500	iv	1		1		70	70	
01-01-94	20:00	1000	iv	2	12	1				
02-01-94	08:00						25			
02-01-94	11:00						40			
04-01-94	03:00	1000	iv	4	24	1		70	70	
08-01-94	03:00									

All SD values present: weighting on →
 Bayes ('b'): ON Conc. at t=0 ('c') 0 Algorithm ('a'): Marquardt
 F10=continue F1 ↑↓↔, PgUp, PgDn Del Ins ^ p=date t=+1 --1 F4=reg.d F6=recalc.d

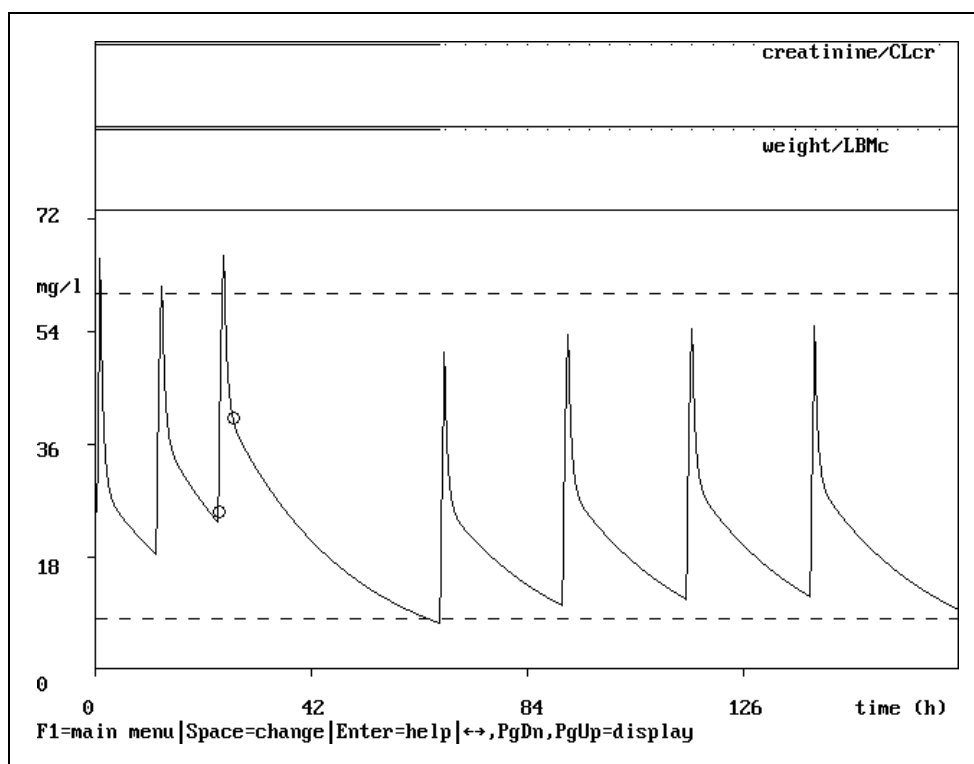


Fig 4.7-E. Simulated medication history demonstrating a dosage regimen adjustment.

From figure 4.7-E you can see that the date and time we had chosen for resuming the therapy with the newly calculated dosage regimen was not chosen at random. This time point in fact was calculated from the suggested waiting time after the 2-point recalculation in the previous example of paragraph 4.6.2. In this example MW\PHARM suggested that we should wait for a period of 40 h relative to start of the last given dose before resuming therapy with the new dosage regimen. Thus figure 4.7-E very nicely demonstrates the waiting time principle for switching between two different dosage regimens. Based on the suggested waiting time, the therapy should be resumed on 04-01-94 at 03:00. However, usually no dosages are administered in the middle of the night. Therefore it seems more convenient to wait for an additional 5 hours (45 h in total) so that the therapy may be resumed at 08:00 the next morning.



Go to the patient registration screen if you want to save the patient data (including the individual pharmacokinetic parameters). See paragraph 4.3 for instructions.

4.8 KinFit

4.8.1 Introduction

KinFit is a very easy to use yet extremely powerful MW\PHARM module for fitting and analysing single dose administrations. The module offers two analysis methods:

- HPSTRIP : Automated curve stripping
- KINFIT : Non-linear curve fitting

Both methods are based on a least squares method. KINFIT employs the very robust Simplex method for minimising the weighted sum of squares (SS) fitting criterion whereas HPSTRIP uses a linear regression method.

One of the main problems with non-linear curve fitting programs are the first estimates that have to be entered by the user. Most programs get stuck (sometimes even crash) if the first estimates are far away from the final estimates.

☞ KINFIT solved the first estimates problem by presenting the user default first estimates that were automatically taken (behind the scenes) from the HPSTRIP module.

Press **F1** to go to the main menu. Then press **F10** to go to the patient registration screen. Press **Ctrl+S** to recall the standard patient. Then press **F10** twice to go to the medication data screen. Type **V A**. Then press **Ctrl+F** in order to activate the browse window. Highlight the entry "**vancomycin (adult)**" using the **↑**, **↓** keys. Press **Enter Enter F1** to return to the main menu again. Then press **8** to go to the kin menu. Then press **1** in order to go to the KinFit menu (fig. 4.8-A).

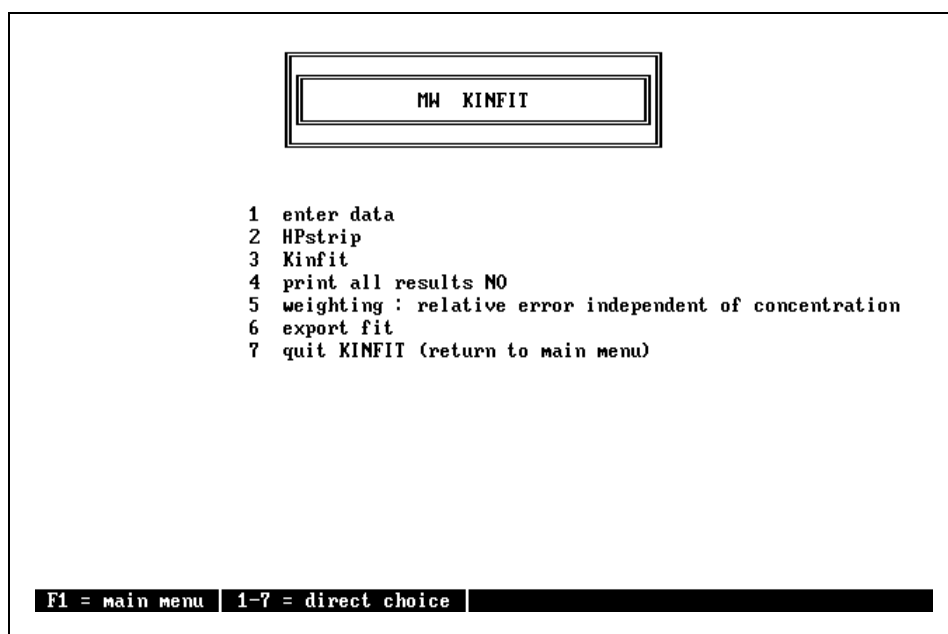


Figure 4.8-A. The KinFit menu.

4.8.2 Data input

Press **1** in order to go to the data input screen (fig. 4.8-B). Press **F6** and then type **VANCO** followed by **Enter** to load a demonstration data set (fig. 4.8-B).

time	conc.	time	conc.	time	conc.	time	conc.	
[h]	[mg/l]	[h]	[mg/l]	[h]	[mg/l]	[h]	[mg/l]	↓
.25	15							
.5	25							
.75	34							
1	40							
1.25	28							
1.5	24							
1.75	20							
2	17							
2.5	15							
3	14							
4	11							
6	9							
8	8							
10	7							
12	6							

↑↓←→ Del= delete xy Ins= insert xy F6= load F7= save F8= erase F1= ready

Figure 4.8-B. KinFit data input screen

The data set listed in figure 4.8-B is obtained from a single dose vancomycine study administered using a 1 hour infusion. Both pre and post infusion data are present.

4.8.3 Curve stripping

Although the stripping procedure is automatically invoked by the non-linear fit procedure for automatically generating first estimates, the curve stripping procedure can be called manually for obtaining a first impression of the data set.

Press **[F1]** to return to the KinFit menu. Press **[2]** to go to the HPSTRIP menu. Press **[2]** to select the infusion type of administration. Specify an infusion duration of 1 h by typing **[1]** followed by **[Enter]**. The screen displayed in figure 4.8-C will be visible.

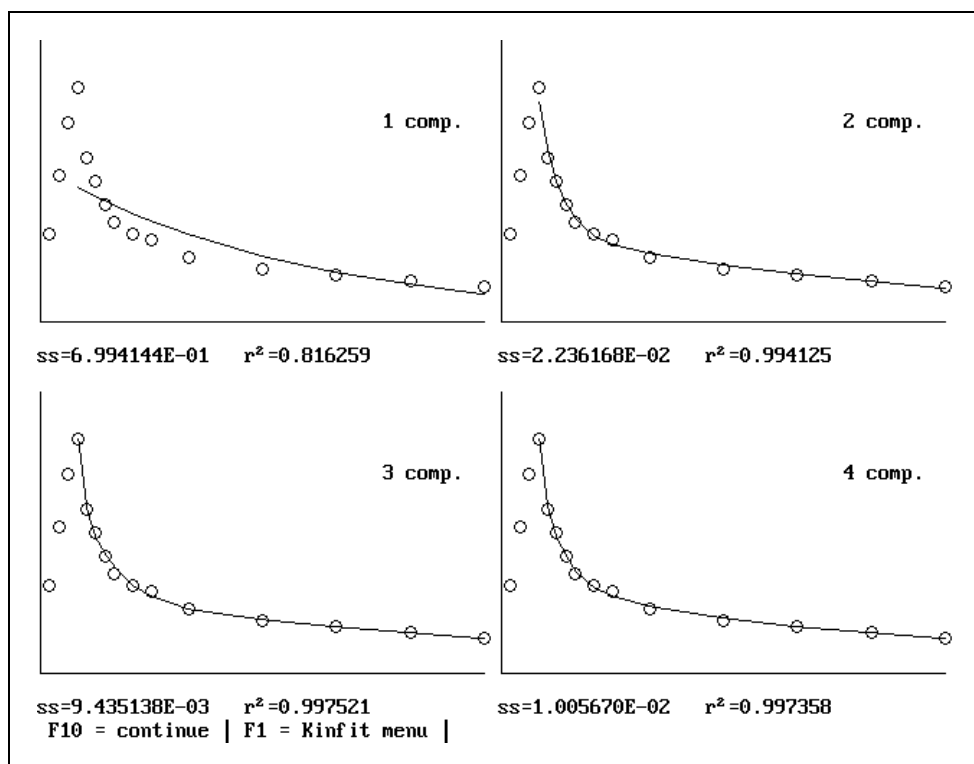


Figure 4.8-C. Graphical representation of curve stripping.

HPSTRIP performed a curve stripping procedure on the data set for a polyexponential equation containing 1, 2, 3 and 4 exponents (fig. 4.8-C). It looks as if 2 exponents would suffice to describe the data set accurately (2-compartment system).

4.8.4 Curve Fitting

The curve fitting procedure is typically used for a more detailed data analysis. In general curve fitting outperforms curve stripping.

Press **F1** to go to the KinFit menu again. Now press **3** to go to the KINFIT menu. The correct model should already be selected (infusion with an duration of 1 h). Press **F10** to continue. Take over the automatically generated first estimates by pressing 2 times **Enter** (fig. 4.8-D).

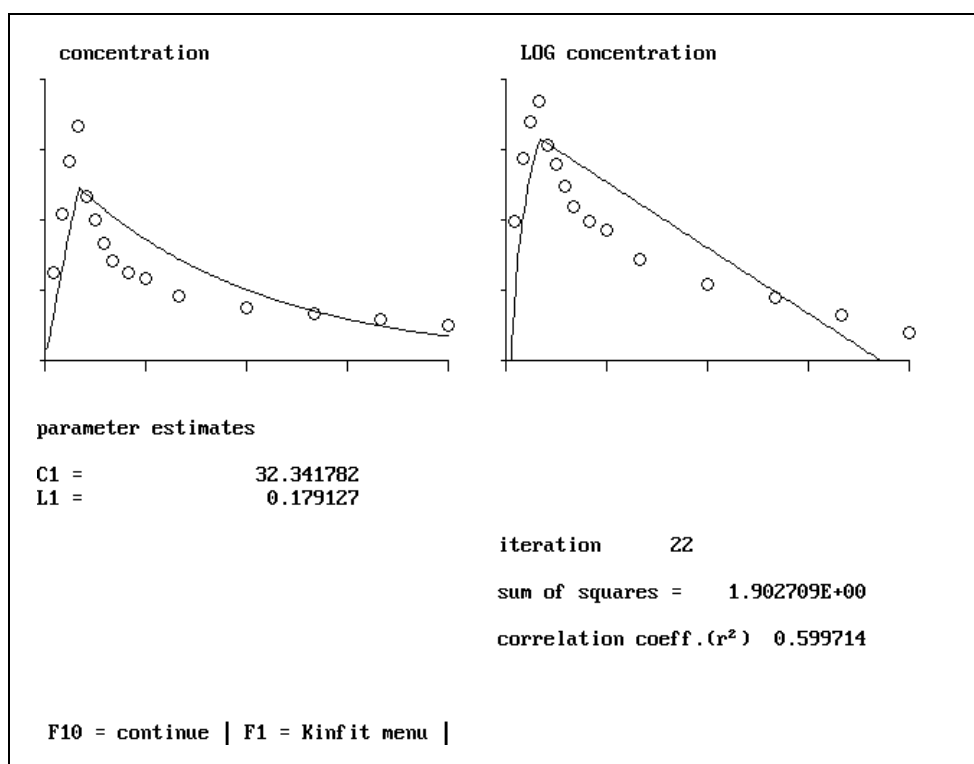


Figure 4.8-D. Curve fitting using a 1-compartment model.

Figure 4.8-D clearly demonstrates that the given data set cannot be described by a 1-compartment model. The curve stripping procedure performed earlier confirms this conclusion. Let's try a 2-compartment model now.

Press **F1** to go to the KinFit menu again. Now press **3** to go to the KINFIT menu. Press **2** in order to select a 2-compartment model. Press **F10** to continue. Take over the automatically generated first estimates by pressing 4 times **Enter**. Figure 4.8-E suggests a much better fit. Press **F10** twice in order to go to the statistics screen (fig. 4.8-F).

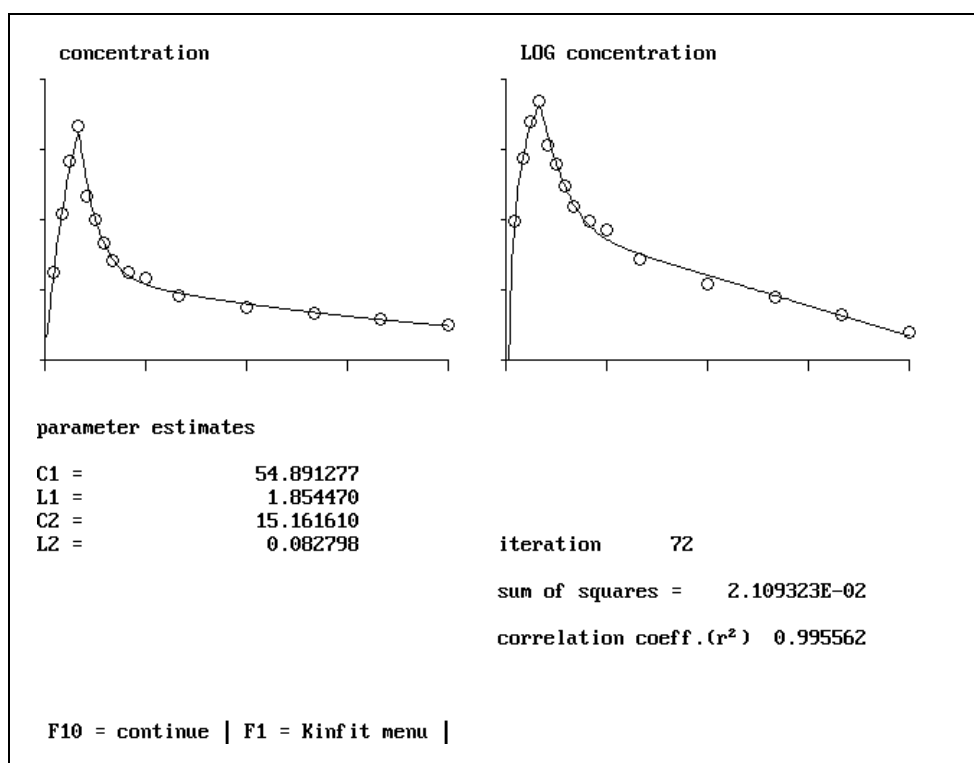


Figure 4.8-E. Curve fitting using a 2-compartment model.

STATISTICS			
Number of data points	N	=	15
Number of parameters	P	=	4
Degrees of freedom	df	=	11
Sum of Squares	ss	=	2.109323E-02
Root Mean Square error	RMS	=	4.379003E-02 (4.38%)
Correlation coefficient	r ²	=	0.995562
RUNS TEST			
Number of runs	=	9	
Run profile	=	+--+--+---++ (p)=0.05)	
EXTRA PARAMETER SIGNIFICANCE			
	ss	df	r ²
Previous fit	1.902709E+00	13	0.599714
Current fit	2.109323E-02	11	0.995562
F = 490.6261	p = 0.0000	(p<0.001)	
F10 = continue F1 = Kinfit menu			

Figure 4.8-F. Statistics report screen.

Figure 4.8-F shows a statistical analysis of the last fit (2-compartment model). Besides the calculation of the usual statistical parameters, also two statistical tests are performed. First, a so called runs test which checks if the distribution of data points around the curve (above or below) is random. Second, a F-test that compares the current fit (2-compartment model) with the previous fit (1-compartment model). In our example the 2-compartment model describes the data set significantly better than the 1-compartment model.

Press **F10** in order to go to the parameter report screen. Specify a dose of 1000 mg by typing **1000** followed by **Enter** (fig. 4.8-G).


Figure 4.8-G displays an overview of the fitted model parameters. Which parameters are listed here is model dependent.


Dose	[mg]	: 1000.0
Area Under the Curve (AUC)	[h.mg/l]	: 212.7
AUC polyexponential (t= 12)		: 142.0
AUC trapezoidal rule (t= 12)		: 141.4
Clearance (CL)	[l/h]	: 4.701
Volume of distribution comp.1	[l]	: 14.27
Volume of distr. steady state	[l]	: 49.23
Volume of distribution	[l]	: 56.78
Half-life phase 1	[h]	: 0.3738
Half-life phase 2	[h]	: 8.372
Rate constant k10	[1/h]	: 0.3293
Rate constant k12	[1/h]	: 1.142
Rate constant k21	[1/h]	: 0.4662
Mean Residence Time (MRT)	[h]	: 10.47

F10 = continue	F1 = Kinfit menu
----------------	------------------

Figure 4.8-G. Overview of fitted parameters.

Press **F10** to continue. You will be asked if you want to transfer the fitted parameters to the main program. Confirm this by pressing **Y**. Then you will be prompted for an **fe** value (fraction excreted unchanged). Enter 0.95 by typing **. 9 5** followed by **Enter**.


 You will only be prompted for a transfer of pharmacokinetic parameters from KinFit to the main program if you already selected a drug in the main program.

Press **F1** to go the KinFit menu. Press **7** to return to the main menu. Press **2** to enter the medication data screen. Press  to investigate the pharmacokinetic parameters.

If you now examine the medication data screen you can see the label **"individual data"** in the upper right corner of the screen. This means that the listed (highlighted) pharmacokinetic parameters are not population parameters anymore but individual parameters.

4.9 KinBes

Although the MW\PHARM KinFit module is able to estimate the first order rate constant for absorption (k_a), it cannot determine bioavailability (F). The KinBes program (fig. 4.9-A) was especially designed for the advanced determination of bioavailability and rate of drug absorption using various methods. Some of these methods are listed in figure 4.9-B.

 KinBes is an independent program module that must be purchased separately.

```

      MAIN MENU

Data file in memory : DEMO.DAT

Free memory       : 237304 bytes

<1> Data input (enter or change)
<2> Simulation Menu
<3> Load data from disk
<4> Save data to disk
<5> Print Menu
<6> Calculation Menu
<7> Mean values Menu
<8> Statistics Menu
<9> Installation (graphics card, screen colors, printer)
<0> Quit KINBES

Enter your choice, or <H> for Help :
```

Figure 4.9-A. KinBes main menu


```

      CALCULATION  MENU

Subject    no 1 (number = 8) : A
Dosage form no 2 (number = 2) : product X

Route of reference administration : oral, duration 0
Integration algorithm : standard procedure

<G> Graph of concentration - time
<T> Table of data (time, concentration, cum.input)
<C> Table and graph of cumulative input
<R> Erase cumulative input
<A> Algorithm for integration and interpolation
<M> Moment analysis, AUC ratio, Wagner-Nelson method, multiple-dose projection
<L> Loo-Riegelman method
<D> Deconvolution method
<O> Optimization of input using WLS Reconvolution method
<S> Smoothing of input
<K> Calculation of input rate constant k1 or k0

Enter your choice, or <H> for Help:

<F1>,<F2> : previous, next subject      Shift < > : batch processing
<F3>,<F4> : previous, next dosage form  <ESC>      : return to Main Menu
    
```

Figure 4.9-B. KinBes calculation menu.

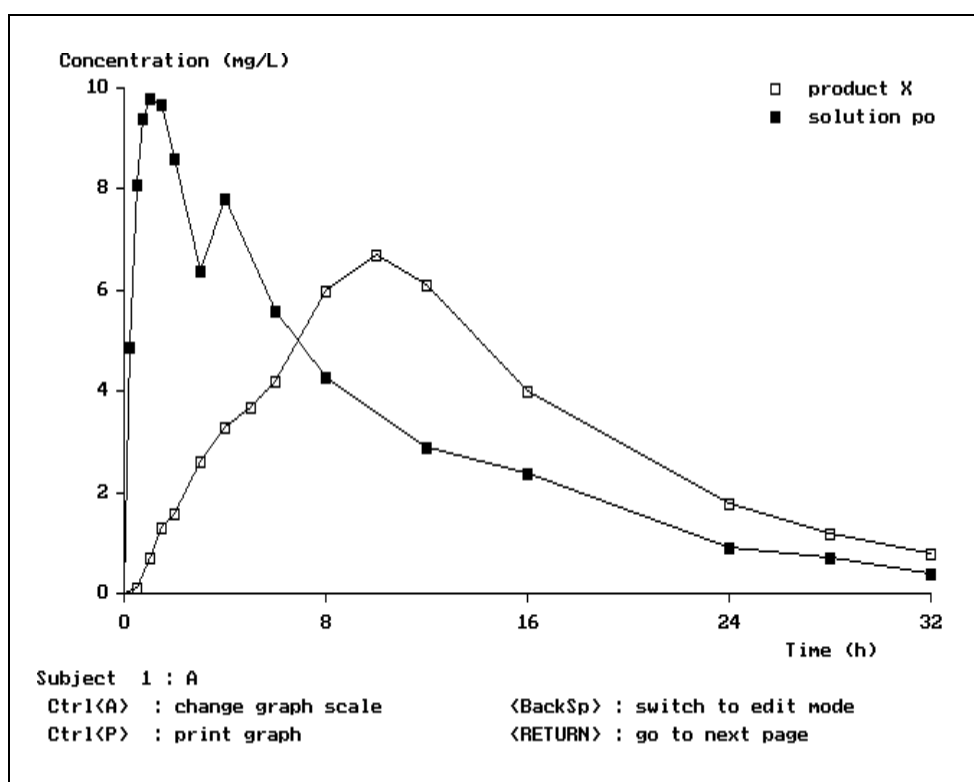
















Figure 4.9-C. Plasma levels of drug (product x) and a reference (solution po).


Figure 4.9-C nicely illustrates the application of KinBes. It shows the plasma levels of a subject receiving a slow release theo-phylline tablet (300 mg) in relation to the levels generated by a reference solution of theophylline. In total 8 subjects were involved in the study based on a cross-over design using long enough wash-out periods between both administrations. KinBes is able to conduct a complete analysis of this study (including statistics).





5 EXAMPLES

5.1 Adult Patients

In chapter 4 we already presented an example of an adult patient. In this chapter we will use another adult patient to demonstrate some features of MW\PHARM which are not discussed yet.

Press  to go to the main menu. Then press  to enter the patient registration screen. Press  +  to open the patient browse window. Select (highlight) the patient number "**0 EXAMPLE 1**" using the  and  keys. Press  to confirm the selection. Press  to return to the main menu. Next press  to enter the medication data screen. Press  to simulate the current medication history. Then press  again to fit the current medication history. Press  to go back to the medication history screen. Press  again to simulate the plasma profile again. The old curve will be removed from the graph. Now press  to display a list of available options (fig. 5.1-A).

The number of available options in MW\PHARM graphics screen is too large to fit all on the command bar. You can obtain a list of available graphics options by pressing the  key (fig. 5.1-A).

Create and move a readout cursor by repeatedly pressing  (coarse right movement) or  (fine right movement). Press  or  to move the cursor in the opposite direction. Time and plasma values at the location of the cursor are visible in a window in the upper right corner of the screen (fig. 5.1-B).

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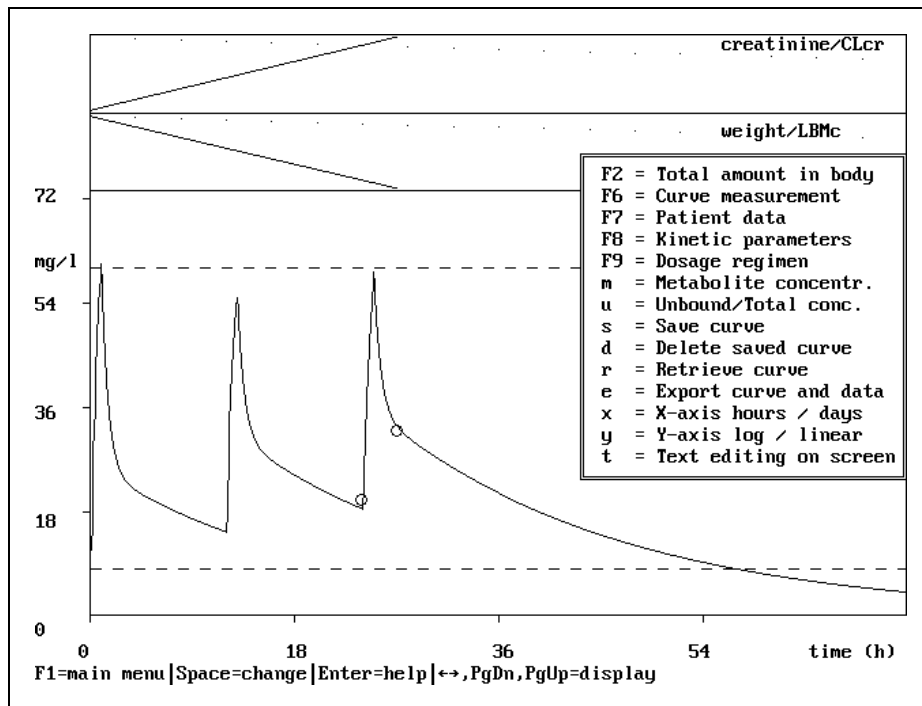


Figure 5.1-A. Options in MWPHARM graphics screens .

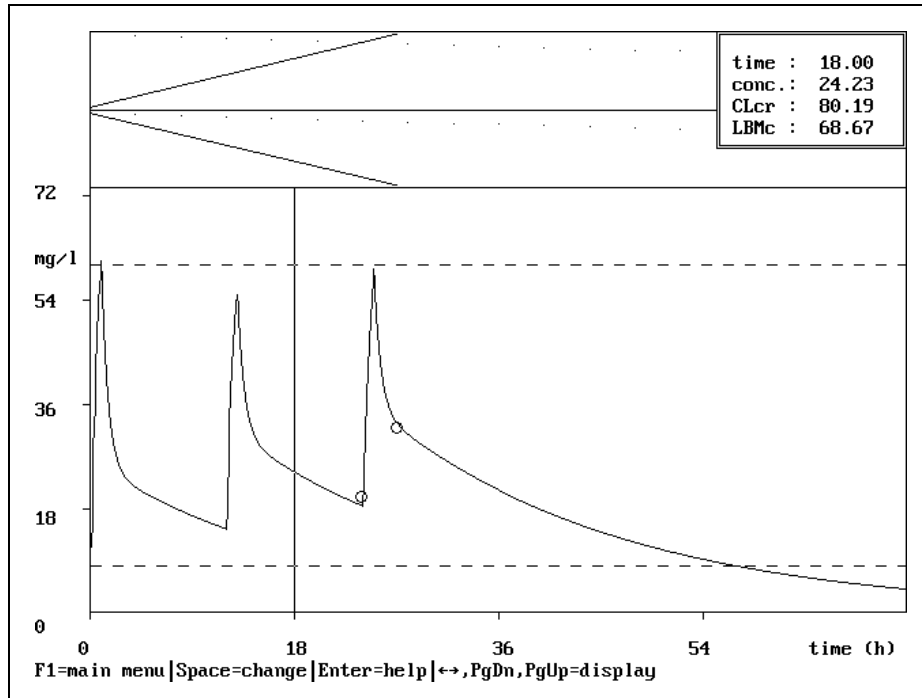


Figure 5.1-B. Readout cursor for inspection of plasma levels.

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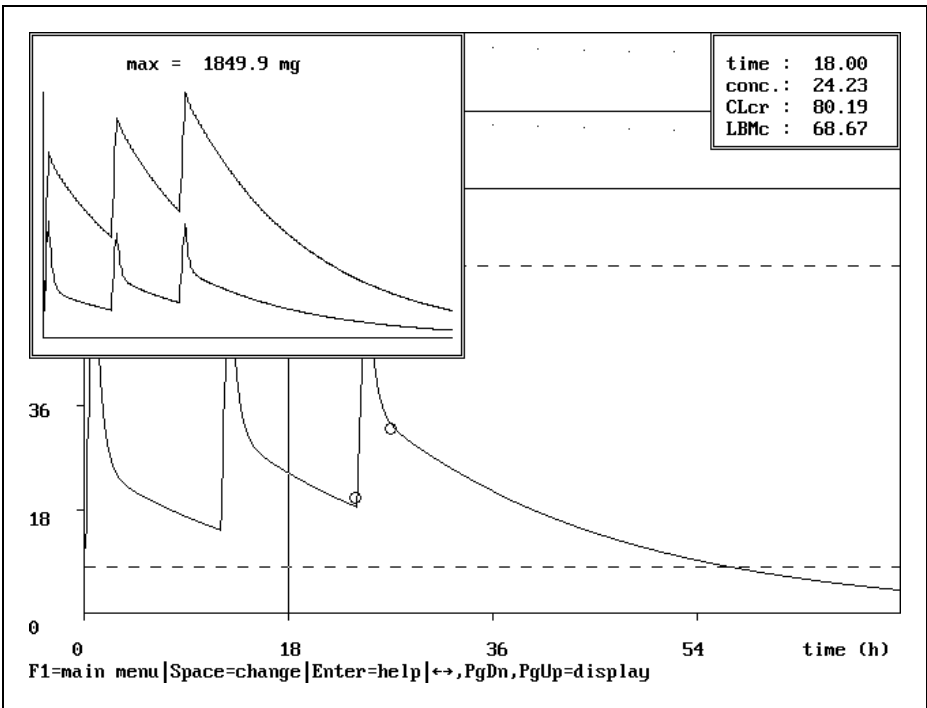


Figure 5.1-C. Pop-up window containing total amount data.

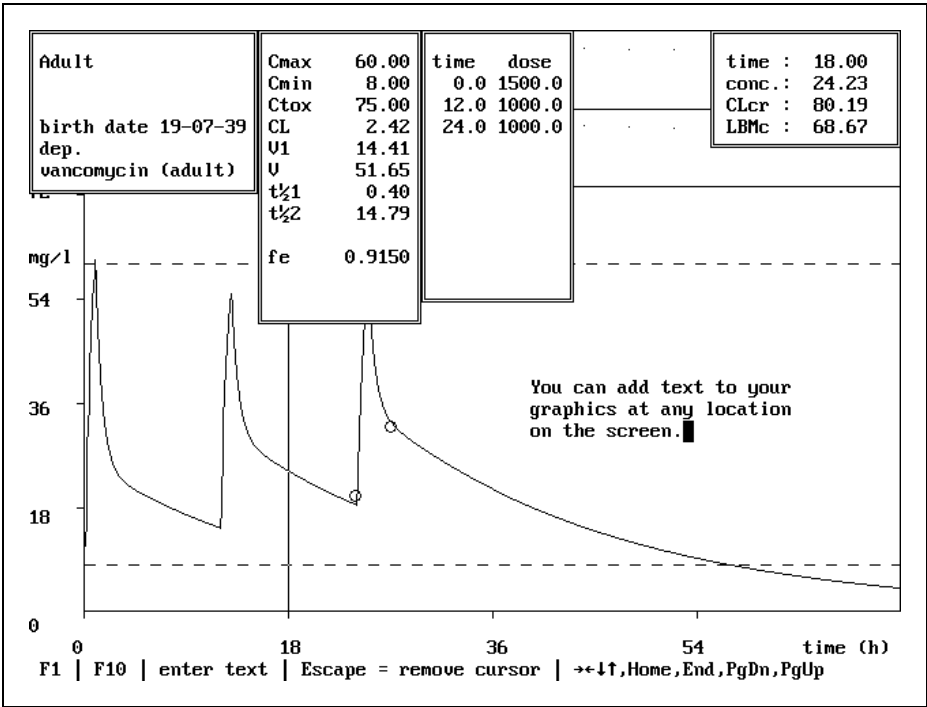


Figure 5.1-D. Additional pop-up information windows.

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Press **F2** to view a graph displaying the total amount of vancomycin (fig. 5.1-C).

Figure 5.1-C displays a pop-up window (upper left corner of the screen), containing two curves. The lower curves represents the total amount of vancomycin present in the central compartment. The upper curve represents the total amount of vancomycin present in the whole body (sum of all amounts present in all compartments). This graph can be very useful for examining the total amount of vancomycin that has accumulated in the body.

☞ With 1-compartment systems only one curve will be visible in the pop-up window displaying the total amount in the body.

Press **F7** (show patient data), **F8** (show kinetic data) and **F9** (show dosing data). Press **T** (**S** in Dutch language mode). A text cursor will appear. Move the text cursor using the **↑**, **↓**, **←** and **→** keys to some location on the screen. You can now type in some explanatory text (fig. 5.1-D). Press **Esc** when you are finished typing.

5.2 Dialysis Patients

Press **F1** to go to the main menu. Then press **F10** to enter the patient registration screen. Press **Ctrl+F** to open the patient browse window. Select (highlight) the patient number "**0 EXAMPLE 2**" using the **↓** and **↑** keys. Press **Enter** to confirm the selection. Press **F1** to return to the main menu. Next press **5** to enter the medication data screen (fig. 5.2-A).

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Figure 5.2-A displays the medication history of a dialysis patient. As can be seen from the medication history the chosen dosing interval is extremely long (192 h). This situation is typical for these category of patients. Note the high creatinine value (875 mol/L) indicating an extremely bad kidney function.

date	time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY	HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[μM]	[ml/min]
01-01-94	08:00	1000	iv	1		1		70	875	
09-01-94	08:00	500	iv	5	192	1				
One or more SD values missing: weighting relative →										
Bayes ('b'): ON Conc. at t=0 ('c') 0 Algorithm ('a'): Marquardt										
F10=continue F1 ↑↓→←, PgUp, PgDn Del Ins ^→ p=date +=+1 --=1 F4=reg.d F6=recalc.d										

Figure 5.2-A. Medication history of a dialysis patient.

☞ The renal function used in the medication history is completely determined by the specified creatinine levels in the medication history. This means that values entered in the kidney function menu have no effect whatsoever. If you have no creatinine levels available but the creatinine clearance is known, you can experiment in the kidney function menu to find out which creatinine value yields the desired (estimated) creatinine clearance; or you can set the creatinine clearance in the kidneyfunction screen manually, in which case the creatinine levels in the medication history are ignored. A creatinine value of 875 mol/L results in a creatinine clearance of 5 ml/min/1.73m² (Jelliffe II).

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Note that no value is specified for the extracorporeal clearance. This means that removal of vancomycin by the dialysis process itself is not taken into account.

- ☞ Newer types of high permeability filters may cause removal of significant amounts of vancomycin. In this case an appropriate value for $Q(EC)$ must be entered together with a correct value for the vancomycin EC-extraction ratio in the medication data screen (see paragraph 4.5).

Press **F10** to simulate the current medication history (fig. 5.2-B). Move the readout cursor using the **Page Up** and **→** keys to the point where the plasma curve crosses the dashed horizontal line ($C_{min}=8$ mg/L).

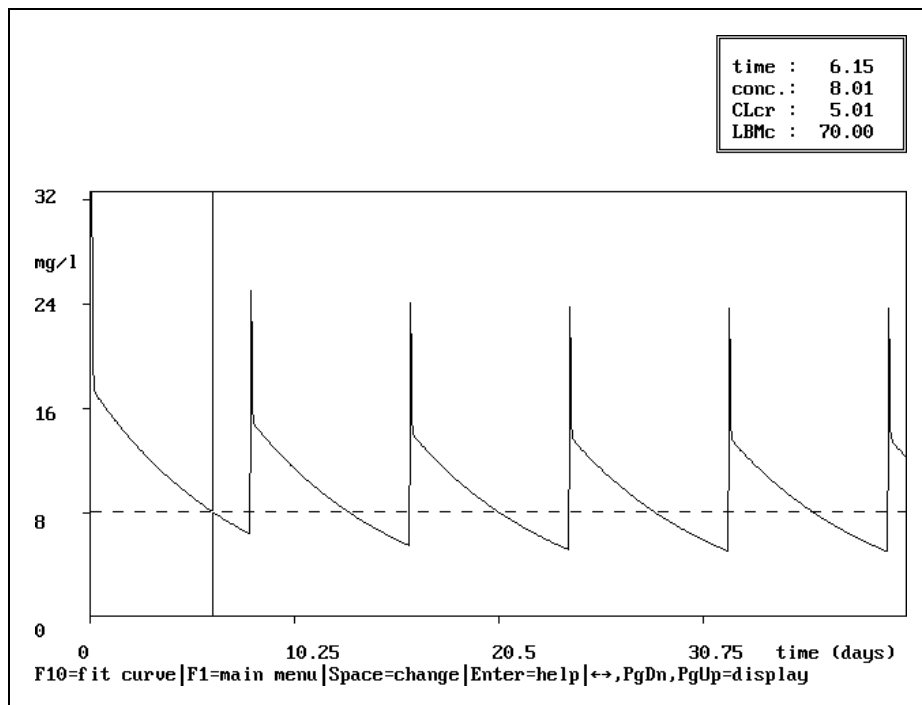


Figure 5.2-B. Vancomycin plasma profile of a dialysis patient.

Figure 5.2-B shows the simulated plasma profile of the current medication history. Using the readout cursor we can determine that

after the initial loading dose of 1000 mg it takes almost 6 days before plasma levels are below 8 mg/L again.

Press **F1** to go to the main menu. Then press **F10** to enter the patient registration screen. Press **Ctrl**+**F** to open the patient browse window. Select (highlight) the patient number **"0 EXAMPLE 3"** using the **↑** and **↓** keys. Press **Enter** to confirm the selection. Press **F1** to return to the main menu. Next press **5** to enter the medication data screen (fig. 5.3-A).

One or more SD values missing: weighting relative →
 Bayes ('b'): ON Conc. at t=0 ('c') 0 Algorithm ('a'): Marquardt
 F10=continue F1 ↑↓←, PgUp, PgDn Del Ins ^ p=date t=+1 --1 F4=reg. d F6=recalc. d

Figure 5.3-A. Medication history of a CAPD patient.

The (prophylactic) intraperitoneal administration of vancomycin to CAPD patients has the following drug input characteristics:

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- The drug absorption from the peritoneum to the blood is a first order process which is typical for extravascular administrations.
- The drug absorption is stopped abruptly (by removal of the peritoneal dialysis fluid) which is typical for infusions.

MW\PHARM has no route of administration available combining the characteristics described above. However, there is very good alternative. It is generally known that after a dwell period of 6 hours, 50% of the vancomycin dose is absorbed into the blood. We can simulate this process using an infusion (zero order input) with a duration equal to one dwell period (6 hours). The dose value specified in the medication history screen must then be 50% of the actual given dose.

☞ Simulation of intraperitoneal vancomycin administration to CAPD patients using the infusion approximation method, requires you to specify a dose value equal to one half of the actual given dose.

The infusion approximation method has been verified using the PhEdsim Professional program (MediWare B.V.). PhEdsim Professional for Windows is a advanced program used in pharmaco-kinetic research and education, enabling the user the construct any type of model using any type of equations..

We will now examine the medication history of fig. 5.3-A more closely. Note that all doses are infused in 6 hours (infusion duration) every 6 hours (dosing interval). First a loading dose is given of 500 mg followed by maintenance dosages of 25 mg. This means that the actual given dosages amounted to 1000 and 50 mg respectively! Furthermore, it was assumed that the peritoneal clearance amounted to 1.5 ml/min. Therefore this value has been entered in the Q(EC) column. The columns interv. and T(inf) are used to indicate the time periods of an active extracorporeal clearance (analogous to repeated infusions). In this example the extracorporeal clearance (peritoneal clearance) is active for a period of 24 hours (T(inf)) every 24 hours (interv.). As a result the EC- clearance is continuously active.

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Press **F10** to simulate the current medication history. Press **S** (**B** in Dutch language mode) followed by **1** in order to save the current curve in slot number 1. Next press **□** to return to the medication history screen.

Repeatedly press **↓** until the cursor is located on the 2nd row. Now repeatedly press **→** until the cursor is located on the 2nd column. The cursor should now be located on the dose field containing a dose of 500 mg. Change the dose to 25 mg by typing **25**. Press **F10** to simulate the new medication history. Get the previously stored curve by pressing **R** (**T** in Dutch or **Z** in German language mode) followed by **1** (fig. 5.3 B).

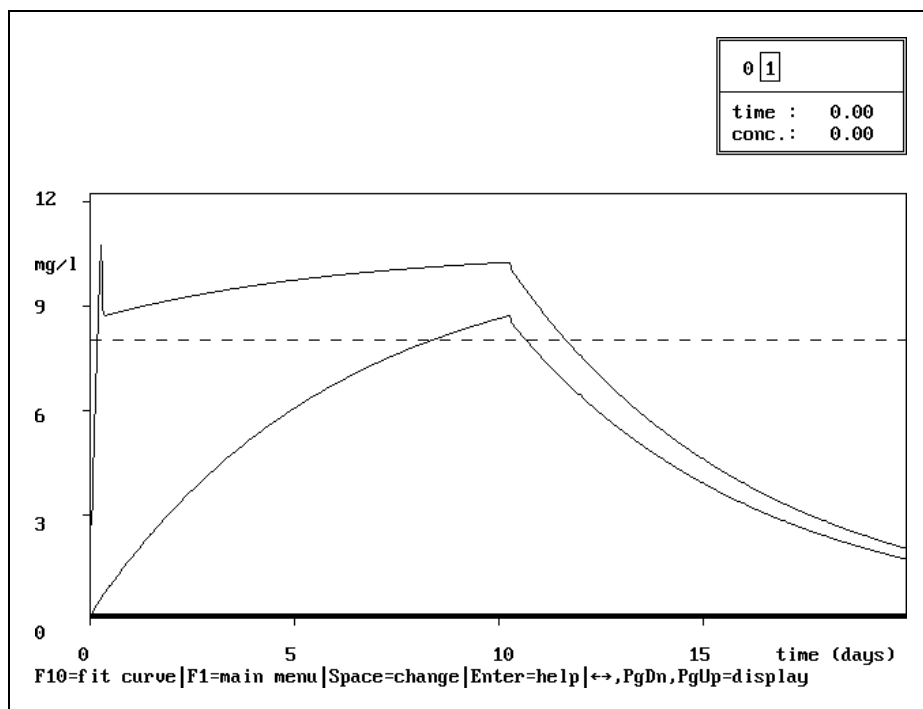


Figure 5.3-B. Intraperitoneal administration of vanco-mycin with and without a loading dose.

Figure 5.3-B very nicely demonstrates the effect giving a loading dose with peritoneal administrations. With a loading dose (upper curve) levels above 8 mg/l are reached within 6 hours. To reach the same plasma levels without a loading dose (lower curve) takes more than 6 days.

5.4 Neonate Patients

Press **F1** to go to the main menu. Then press **F10** to enter the patient registration screen. Press **Ctrl+F** to open the patient browse window. Select (highlight) the patient number **"0 EXAMPLE 4"** using the **↑** and **↓** keys. Press **Enter** to confirm the selection.

Examine the patient's age in the patient registration screen. When we created this example the child was 5 days old. However, as in real life, the patients in the database get older every day. So in this very moment the child might be a lot older.

Repeatedly press **↓** until the cursor is located on the date of birth field. Now enter a valid date of birth so that the child is approximately 5 days old again. Thereafter press **F10** to continue to the pathology screen. Press **4** to enter the kidney function screen.

If you examine the kidney function screen you will notice that Schwartz formula for the kidney function calculation is the only method available. This is caused by the fact that the current patient is younger than 18 years. The minimum age at which this formula is still valid is 0.5 years. However, our current patient is only 5 days old. This means that we have no reliable calculation method available for the determination of the kidney function of neonates. In order to avoid problems with incorrect kidney functions we have assumed the vancomycin clearance in neonates to be 100% non-renal. As a consequence different entries in kidney function screen will have no effect on the calculated vancomycin clearance.

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- ☞ In order to avoid problems with unreliable kidney functions in neonates the clearance in these patients is assumed to be 100% non-renal.

The only consequence of this approach is that we cannot take into account measured serum creatinine values when establishing an initial dose for a neonate.

- ☞ MediWare will implement a neonate kidney function formula describing the relationship between creatinine levels and the creatinine clearance as soon as reliable data on this subject become available. Also required are reliable data on the relationship between the creatinine clearance and the vanco-mycin clearance in neonates.

Press **F1** to return to the main menu. Next press **5** in order to enter the medication history screen of this patient (fig. 5.4-A).

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date	time	dose	roa	no	interv.	T(inf)	conc.	weight	creat	Q(EC)
DD-MM-YY	HH:MM	[mg]	i/e		[h]	[h]	[mg/l]	[kg]	[μM]	[ml/min]
19-07-94	08:00	30	iv	5	24	1		1.5	70	
One or more SD values missing: weighting relative →										
Bayes ('b'): ON Conc. at t=0 ('c') 0 Algorithm ('a'): Marquardt										
F10=continue F1 ↑↓→←, PgUp, PgDn Del Ins ^→ p=date +=+1 --=-1 F4=reg.d F6=recalc.d										

Figure 5.4-A. Medication history of a neonate patient.

The current patient received a dose of 30 mg vancomycin every 24 hours (see medication history screen of fig. 5.4-A). The weight of the patient is 1.5 kg. In other words, this patient received a dose of 20 mg/kg/24 hours. This dose is generally recommended for neonates younger than 7 days (postnatal age) weighing 800 to 1500 gram. Also listed in the medication history of this patient is a creatinine level of 70 mol/L. As explained earlier this entry has no meaning with neonate patients.

Press **F10** in order to simulate the current medication history (fig. 5.4-B).

EXAMPLES

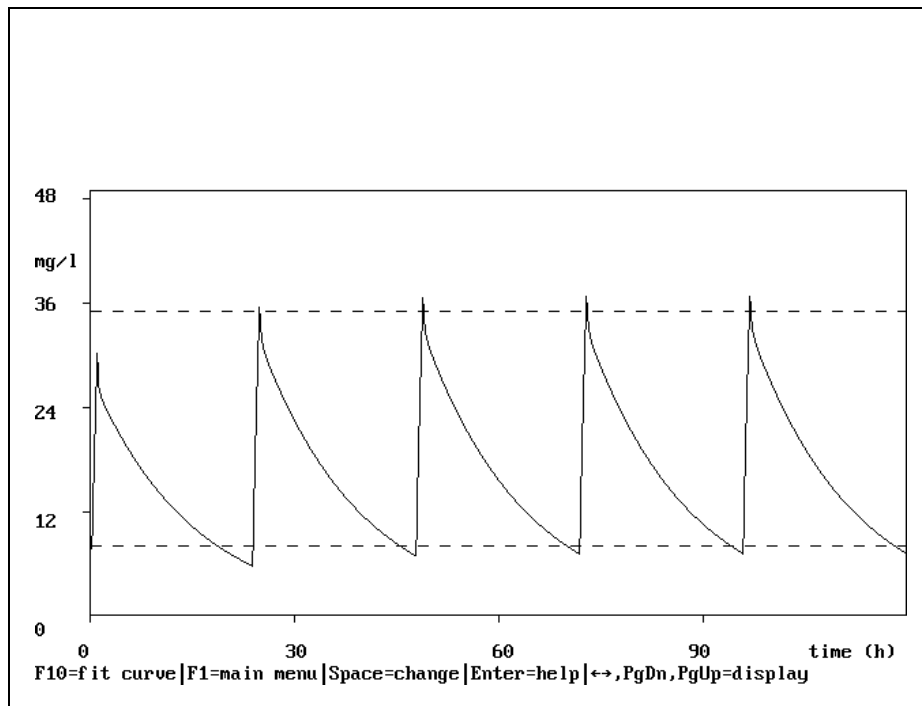


Figure 5.4-B. Vancomycin profile in a neonate patient.

Figure 5.4-B displays the plasma profile of the medication history of the current neonate patient. The applied dosage regimen caused a very satisfactory plasma profile. Note that no loading dose was given in this patient.

With this last patient our “tour de pharm” has been completed. More in depth background information can be found in the volume 3 (Methods).