CHAPTER V

RESULTS AND DISCUSSION

In this study, a computer software was developed to evaluate an existing gentamicin dosage regimen and to determine a new dosage regimen including prediction of the corresponding steady-state peak and trough levels by pharmacokinetic approach. The second objective is to create a file for storage or for updating patient data. After complete coding, the software must be checked for its correctness or reliability. There are 2 purposes in the testing: to test for the operation of the software and to verify the results generated by the software.

Program Testing

This software program is tested by trying it on a large number of carefully chosen data both legal and illegal. Each module was tested whether it works properly before integrating into the system or overall program. Results generated by program were checked or compared with values calculated by hand.

The first group of test cases are designed to test the common functions which the program unit was normally meant to operate. The objective is to select values that cause the execution of all flow paths through the program. One subset of normal test

cases includes the data set that fall at the very extremes or limits of a range of legal values. After the program works properly for the legal and expected data cases, the aspect of testing then moves into the area of illegal data. For all illegal cases, the program should do something meaningful and not terminate abnormally.

Overview of Operations

Operation of the software was designed to be simple by use of a self-prompting format not a prepared data file. User accesses the system with the input keyboard, the menus, and the function key without necessity to write any command on his own. Operation of the program is demonstrated in detailed process in appendix B. The overview of operations is shown below.

1. New Patient (First Consultation)

For first consultation, the user enters a unique hospital number of the patient and then is asked by the computer to provide the other demographic data, physical data, and clinical data in the first input data screen or REVIEW CHART screen. The second input screen or LABORATORY DATA screen is designed to accept laboratory and treatment data. All input are validated for legality and also for plausibility as each field is entered.

These valid input are then used to calculate individual pharmacokinetic parameters based on literature-averaged estimates of the patient's subgroup. For example, in adults, the height and sex

are used to determine ideal body weight and this weight together with other data such as sex, age, and S_{cr} are then used to estimate the patient's Cl_{cr} if data of urine collecting is not availble. Gentamicin elimination rate constant, half-life, volume of distribution, and other pharmacokinetic parameters are then determined.

An initial dosing recommendation will be made, based on either calculated or measured Cl_{cr}, or the user can enter his own dosing regimen if the patient already is receiving the drug. For the latter condition, the program will assess the patient current dosage regimen by predicting the corresponding peak and trough levels at steady-state and providing a recommendation to adjust or establish a new regimen if one of these predicted values is not in acceptable range, i.e., 4 to 10 mcg/ml for peak and 0.5 to 2 mcg/ml for trough. In the situation that measured serum concentration-time data are available, individual patient pharmacokinetic parameters used in these dosage calculations are estimated by another section of the program via the Sawchuk-Zaske method.

Determination of an appropriate dosage regimen is accomplished by three different ways in the CALCULATION MENU. The first module, "1. Assess a dosage regimen", assesses or evaluates a given or proposed dosage regimen and predicts steady-state peak and trough levels. The second module, "2. Estimate a dosage regimen", estimates the dosage regimen using input of steady-state peak and trough levels and infusion time (or period) desired for a patient. Both modules provide one output set for one input set. The third one, "3. Auto-Calculation", allows the user to specify the desired range

of steady-state peak and trough levels and vary dosing intervals and infusion times as needed. As a result, the program provides up to 30 dosage regimens that meet the requirements. User may enter any module without entering patient data again.

Regardless of which way to run, after selection of a desired dosage regimen, user goes to the next screen, CONSULTANT screen, automatically. Evaluation of the selected dosage regimen together with recommended blood sampling times for gentamicin levels and creatinine levels are displayed here.

2. Current Patient (Subsequent Consultation)

A patient already on file can be recalled from the data disk with an intact record of all input data and dosing to date including pharmacokinetic parameters as his hospital number is entered. The program internally redefines the pharmacokinetic parameters for any user-specified changes in renal function or body weight or when a set of measured serum concentration-time data are input. This feature allows automatic updating of evaluation of the current dosage regimen as patient parameters change. The user can view the effects of simulated or real changes in patient parameters with minimal effort.

Dosage Regimen and Laboratory Information

The DOSAGE REGIMEN INFORMATION screen summarizes the administered dosage regimens, the corresponding predicted steady-state peak and trough levels, and the pharmacokinetic parameters (k_e and V_d); while the LABORATORY INFORMATION screen summarizes the

renal monitors and gentamicin level monitors. The obvious advantage of this is that a patient's actual dosing regimen is tabulated, along with all dosing changes and all renal function changes.

3. Printout

One of the most important utility of the program is the printing of the consult sheets (Appendix B). The user can specify which parts are to be printed.

Discussion

Pharmacokinetic methods that use serum drug concentrations to individualize dosing are more accurate than other methods that do not use serum drug determinations (Moore et al., 1984a; Burton et al., 1985). The Sawchuk-Zaske pharmacokinetic method (Sawchuk and Zaske, 1976; Sawchuk et al., 1977) has been thoroughly evaluated (Lesar et al., Platt et al., 1982; Zaske et al., 1982) and shown to be accurate. Hence, this method was chosen to create the software.

According to the selected method, dosage recommendation and prediction of steady-state peak and trough serum concentrations are generated for drug administration by intermittent intravenous infusions at fixed intervals only. To determine individual pharmacokinetic parameters, especially elimination-rate constant and the distribution volume, a series of measured drug concentration-time must be known. However, at the beginning of therapy or in the situation that these data are not available, literature-averaged estimates of the patient's subgroup will be used instead. Although

inaccuracy of these methods has been reported, a starting point was necessary.

The use of population-derived relationships to predict an individual's pharmacokinetic parameters will be improved if the population base that is used more closely approximates the patient under evaluation. This program provides foreign population means for initial assessment of the pharmacokinetic parameters of the Thai patient and an adaptive framework from which the specific patient parameters can be determined. As more data are accumulated, modifications in the prediction relationships by using Thai population means may enhance further the accuracy of the estimates.

A serum creatinine concentration drawn in the past 24 hours must be known for estimating of creatinine clearance, yet the elimination-rate constant; and the patient's body weight must be used to determine the distribution volume. Therefore, calculations could be done only if these two values are available. In order to provide more flexibility, the program would establish a dosage regimen for patient who has no serum creatinine measurement at that moment. However, at least body weight and age must be entered.

Since major concern of the program is for patient aged over 1 year, age is designed to be entered in year. For patient who is less than 1 year of age, input must be number in decimal format which is not good-looking. In contrast, if age is designed to be entered in month or day it is uncomfortable for most patients.

Evaluation of predicted steady-state peak and trough is done by comparison with the default values or therapeutic ranges set by the program, that is 4 to 10 mcg/ml for peak and 0.5 to less than 2

mcg/ml for trough. These values represent as a warning to clinician that the patient might be at risk. In special situations when high levels are required, clinician could prescribe a higher than recommended dose with this concern.

Together with steady-state peak and trough prediction and evaluation, the program also provide recommendation about how to adjust the dosage regimen when those evaluation does not state "both acceptable." For example, the program recommends to decrease dose or both decrease dose and prolong the dosing interval when the dosage regimen is predicted to produce high peak (more than 10 mg/L). However, this suggestion is rough for it does not specify the decrement or what amount to be decreased. User must try by himself using the module "1. Assess a dosage regimen" or "2. Estimate a dosage regimen."

The first module allows the user to propose a dosage regimen to be assessed by the program; therefore, user can fix the current dosing interval and alter only the dose to achieved the desired levels of peak and trough at steady-state. This trial might be accomplished at the first attempt or it could take time.

The second module requires desired steady-state peak and trough levels including desired infusion time as input and provides as output a recommended dosage regimen together with the corresponding predicted steady-state peak and trough levels which would be slightly different from the desired values as a result of rounding up the calculated value to the practical value. In this module of calculation, a dosing interval that conforms to 6, 8, 12, 24, 36, or 48 hours is accepted. For example, the calculated dosing

interval of 10.8 is rounded up to the nearest practical interval of 12. If user wants any other interval differed from the default values, e.g. 11 hours, this would be achieved with application of the first or the third module.

However, the "recommendation" technique above is not the only way to do and it might not promised success when follows. Modification of dosage regimen for a particular patient could be attained in several ways, including other ways not mentioned in the above technique. Hence, to assist user in this task, the third module for calculation, "3. Auto-Calculation", has been developed.

As previously mentioned, this module generates up to 30 dosage regimens for each input data set; however, these might not include "all" the acceptable ones. According to module design, only 30 dosage regimens will be shown and they are those which conform to the lower limit of the desired ranges; e.g., peak = 4, trough = 0.5, dosing interval = 6, and infusion time = 0.5. During the module testing period, this module has been provided more than 150 dosage regimens which conform to the default values for one chosen value of elimination rate constant and volume of distribution. To display all of them is not impossible, but it is not necessary. If the first 30 dosage regimens shown did not include the desired one because the corresponding steady-state peak they produced are not high enough, or due to any other reasons, the useful way to manage this is to keep the range closer or specify more definite range. Certainly, the program enables the user to do this or even change all default values as needed.

This program has limitations because of the kinetic theories and assumptions used. First, it should not be used in patients on hemodialysis or peritoneal dialysis. Secondly, in the pediatric population (age less than or equal to 18 years) the empiric dosing use adult coefficients for estimation of volume of distribution and elimination rate constant. And, as mentioned above, the method is for drug administration by intermittent intravenous infusions at fixed intervals only. Calculation of individual pharmacokinetic parameters can be accurate only if gentamicin assays are obtained and measured accurately.