CHAPTER I

INTRODUCTION

Background and Rationale

Gentamicin is currently the most widely used aminoglycoside for the treatment of infections caused by Gram-negative bacteria. It has broad-spectrum antibacterial activity. The action of gentamicin against *Pseudomonas* is of special interest, since species of that genus resistant to other antibiotics have become an important cause of surgical infections. They almost always invade burned skin and they also cause some serious urinary tract infections. However, because of a potential risk of nephrotoxicity and ototoxicity, present systemic use of gentamicin is mainly limited to severe or life-threatening infections caused by *Pseudomonas*, *Klebsiella*, *Serratia*, *Enterobacter*, *Citrobacter*, and *Proteus* (Gennaro, 1985). Since this drug also has a narrow therapeutic index (i.e., concentrations necessary for optimal efficacy approximate those concentrations associated with a higher risk of toxicity), proper dosing is very important.

Efficacy appears to depend on optimal peak concentrations (4 to 10 mcg/ml or 5 to 12 mcg/ml) that result from proper dosage regimens (Noone et al., 1974; Barza and Lauerman, 1978; Moore, Lietman, and Smith, 1987), while toxicity appears to correlate best

with trough concentrations higher than 2 mcg/ml that occurs with improper dosage intervals (Schentag et al., 1977b). Moreover, many studies have shown that the relationship between doses of gentamicin and serum drug concentrations is poor (Winters, Litwack, and Hewitt, 1971; Barza et al., 1975; Goodman et al., 1975; Schentag et al., 1977b; Reymann et al., 1979). Thus, dosing stratagies should attempt to achieve target serum drug concentrations rather than using a "usual" or "standard" dose.

Proper dosing is complicated because there is a wide interpatient variation of pharmacokinetic parameters. Aminoglycoside pharmacokinetics are altered radically in renal disease; however, studies have indicated that the half-life of the aminoglycoside gentamicin is quite variable, even in patients with normal renal function (McHenry et al., 1971; Kaye, Levison, and Labovitz, 1974; Sawchuk and Zaske, 1976). Age, body weight, obesity, concomitant drug therapy, ascites, burns, cystic fibrosis, pregnancy, dehydration are some of the factors that can affect gentamicin dosage requirements (Siber et al., 1975; Ervin, Bullock, and Nuttall, 1976; Zaske et al., 1976, 1981; Schwartz et al., 1978; Gill and Kern, 1979; Schentag, 1980). Additionally, severity and kind of infections alter desired peak serum concentrations. These considerable data have led to individualization of drug therapy.

In order to optimize therapeutic efficacy and minimize risk of toxicity of the drug, various dosing methods have been developed. These methods include predictive algorithms or nomograms (McHenry et

al., 1971; Chan, Benner, and Hoeprich, 1972; Dettli, 1974; Tozer, 1974; Hull and Sarubbi, 1976) that do not use serum drug concentrations and pharmacokinetic (Sawchuk and Zaske, 1976; Sawchuk et al., 1977; Chow et al., 1978; Schentag, 1980) or Bayesian (Jelliffe et al., 1983; Burton, Brater, Chen et al., 1985a; Godley et al., 1986) methods that use serum drug concentrations to individualize dosage regimens. Predictive algorithms appear superior to physician intuition (i.e., standard doses) but are still subject to considerable error and should only be used as starting points in therapy. Individualization of drug dosing by use of concentrations is a better and more accurate method for achieving target serum drug concentrations than are predicitive algorithms (Platt et al., 1982; Burton, Vasko, and Brater, 1985b; Franson et al., 1988). Predictive ability between the Sawchuk-Zaske method which is the most widely used pharmacokinetic method and the Bayesian method is still controversial. Chrystyn (1988) found that the Bayesian method was more precise, while others reported no significant difference (Burton et al., 1986; Godley et al., 1986; Hurst et al., 1987). Although the methods based on measured serum drug concentrations are effective in determining dosage regimen for individual patients, routine use in clinical settings is limited by complex mathematical equations. One possible solution lies in the development of computer programs.

Clinicians have used nomograms (Sarubbi and Hull, 1978), programmable hand-held calculators (Foster and Bourne, 1977; Ng, 1980), large mainframe computers (Bennett and Scott, 1980), and

microcomputers (Kaka and Buchanan, 1983; Robinson et al., 1984) to recall pertinent pharmacokinetic variables, perform intricate mathematical calculations, design individualized dosage regimens, simulate predicted serum concentrations, and provide the prescriber with documentation for safe and effective use of gentamicin. In addition to the less accuracy as mentioned above, the limitation of nomograms is that they are designed to achieve fixed peak and trough concentrations, making it difficult to tailor the dosage according to the severity of the infection and the potential for toxicity. The programmable hand-held calculators have limited memory and storage capacity and cannot provide for storage of patient files. Therefore, in spite of their low cost, it is unlikely that use of hand-held calculators will expand further. Large mainframe computers are not convenient and generally are not available. Microcomputers overcome many of the limitations, and they are becoming sufficiently affordable to be adopted as the method of choice, pending the development of software.

In foreign countries drug dosing and monitoring services based on serum drug concentrations have been operating in many institutions since the past decade, while in Thailand we are at the beginning point. Physician awareness of gentamicin monitoring that has been increasing in recent years, associated with availability of easy and rapid serum level assays would lead to improved patient care. Microcomputer program could be a useful and convenient tool to complete the other part of services. However, to date, none is available in Thailand.

This study was aimed to develop a microcomputer program to evaluate an existing gentamicin dosage regimen and to determine a new dosage regimen and steady-state peak and trough serum levels by using an individualized pharmacokinetic approach. The program also provides for storage of patient files or for updating the file as the patient is treated.

Objective

1. To develop a microcomputer program for individualizing and monitoring of gentamicin therapy based on pharmacokinetic approach.

2. To evaluate an existing gentamicin dosage regimen and to determine a new dosage regimen and steady-state peak and trough serum levels based on individual patient parameters or measured serum levels.

3. To provide for storage of patient files or for updating the file as the patient is treated.

4. To provide the prescriber with documentation for safe and effective use of gentamicin.

Significance of the Study

1. This study will provide a microcomputer program for individualizing and monitoring of gentamicin therapy so that the patient should have the most appropriate dosage regimen which would result in optimal therapeutic efficacy and minimal risk of toxicity.

2. The microcomputer can be programmed to predict rapidly accurate guidelines for evaluating dosage regimens and best regimens for gentamicin dosing.

3. The designed software system should assist pharmacists and physicians in calculating a proper dosage regimen for individual patients. Therefore, clinicians would have more time for other clinical care.

4. The program should help physicians in making decision of gentamicin therapy, especially in high risk patients.

5. Data storage and retrieval are facilitated and might be used in determining Thai patient population pharmacokinetic parameters.

6. Inquiry or updating patient data even documentation would be convenient and rapid.