CHAPTER 3

Clinical Applications of Pharmacokinetics and Control Theory: Planning, Monitoring, and Adjusting Dosage Regimens of Aminoglycosides, Lidocaine, Digitoxin, and Digoxin

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A Representative Clinical Problem

Table 3.1 shows a typical clinical situation. A patient had received six doses of gentamicin over 3 days. At first, his serum levels were low, with an approximate peak of 3.6 μg/ml and an approximate trough of 1.8. The serum creatinine was 1.2 mg/dL. Because of this, his dose had been intuitively increased to 100 mg every 8 hr. However, his serum creatinine rose to 1.5, and the aminoglycoside levels became much higher, as shown. When these results became known, his dose was reduced to 80 mg once again. However, his serum creatinine had now risen to 2.0 and 2.1 on two separate measurements, and his “trough” gentamicin level was 4.1 μg/ml.

It is impossible for the author to look at such data and make any intelligent evaluation of it without a pharmacokinetic model. Without such a model, one cannot make any reasonable reconstruction of what serum levels were at all the other times in the past when they had not been obtained, to compare with the patient’s clinical behavior at those times. Furthermore, it is impossible to arrive at any intelligent subsequent dosage regimen to achieve clinically chosen peak and trough serum level goals. Nevertheless, that is the clinical task that must be undertaken for all such patients.

Let us now examine some of the methods of adaptive control and of creating clinically useful pharmacokinetic models that have been helpful in managing clinical problems of drug therapy, especially for unstable patients. We will then return to apply these methods to the management of this representative patient’s problem and to other clinical problems of drug therapy.

Introduction

When we give any drug to a patient, we also inevitably give him a pharmacokinetic model or system that must be controlled. An essential component of the therapeutic task is to do this part optimally.

In the first two chapters of this volume, Robinson has described the basic aspects of pharmacokinetics and pharmacokinetic models, and Schumitzky has described the general principles of adaptive control of such models, including the important new and exciting ideas of optimal stochastic control (the control of systems having factors that cannot be completely controlled and that vary in a random manner), and of optimal active closed loop control of these systems.

The present chapter will review some of the more elementary aspects of adaptive control as applied to least-squares and Maximum A-posteriori Probability (MAP) Bayesian control methods and will illustrate various ways in which these currently available control strategies have been used to date to manage therapy with the aminoglycoside antibiotics, with lidocaine, and with digitalis glycosides.

Evaluation of a Patient’s Renal Function

In order to manage a pharmacokinetic model of a drug having significant renal excretion, it is most important to have an accurate and practical appraisal of a patient’s renal function. Mere knowledge of serum creatinine or blood urea nitrogen is not enough. Measurement of creatinine clear-

R. F. Maronde (ed.), Topics in Clinical Pharmacology and Therapeutics
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ance by traditional methods has been impossible for practical purposes, owing to difficulties in obtaining reliable urine collections. A real need has existed to make a reasonable calculation of creatinine clearance without having to obtain the traditional urine specimen. This has been made possible by the development of a short computer program to make this calculation, based on a patient's age, sex, weight, and serum creatinine data, either stable or changing.

In clinical terms, use of the above computer program over the past 13 years has been of great practical value in the appraisal of renal function for patients who have needed precise adjustment of drug dosage to renal function, especially for patients whose serum creatinine levels are changing from day to day. Calculation of creatinine clearance in this way has become a component of the USC·PACK collection of computer services that are used by hospitals over a time-shared computer facility (10) to provide a quantitative clinical structure for planning, monitoring, and adjusting precise drug dosage regimens. This collection of programs is also being rewritten for the IBM Personal Computer.

Early efforts in this direction were made by Jadrny (1), by Effer (2), and by Jelliffe (3). Siersbaek-Nielsen et al. (4) then showed that creatinine production decreases by half as a person progresses from age 20 to age 80. Goldman (5) described the effect of increasing uremia to decrease creatinine production, possibly because patients with greater degrees of uremia are sicker and less active and have a decreased muscle mass as a result. A computer program for estimation of creatinine clearance, where serum creatinine may not only be stable but may also be changing from day to day, was then developed, based on those data (6), and was slightly modified by Mawer et al. (7). When serum creatinine is stable, simpler formulas may also be used (8,9).

The computer program for estimation of creatinine clearance from changing serum creatinine data (6) uses the logic, shown in equation 3.1, that the change in the total amount of creatinine in the body during a typical day ($\Delta C$) is equal to the daily production of creatinine ($P_1$) minus its daily excretion ($E$):

$$\Delta C = \text{production} - \text{excretion}. \quad (3.1)$$

$\Delta C$, the daily change in the total amount of creatinine in the body, was found to equal the apparent, volume of distribution of creatinine (approximately 40% of body weight, $W$), times the difference between two serum creatinine concentrations ($C_1$ and $C_2$, in mg/dL), divided by the number of days ($D$) between them:

$$\Delta C = 0.4 \times W \times (C_2 - C_1)/D. \quad (3.2)$$

Endogenous daily creatinine production per kilogram of body weight ($P_1$ below) was calculated based on the patient's age, using the data of Siersbaek-Nielsen et al. (4), for patients of all ages who were clinically normal, free of any overt clinical or laboratory evidence of renal disease. That figure was then adjusted for the data of Goldman (5), concerning the effect of increasing uremia to decrease the daily creatinine production, as follows. Since the average serum creatinine for Siersbaek-Nielsen's clinically normal patients was 1.1 mg/dL, the production for Goldman's data was therefore first calculated based on a serum creatinine of 1.1, to find the average production for a clinically normal patient based on Goldman's data. Next, production was similarly calculated from Goldman's data for the average of the patient's

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**Table 3.1. Data of doses given, serum levels found, and serum creatinine data from a representative patient receiving gentamicin therapy.**

<table>
<thead>
<tr>
<th>Day of therapy</th>
<th>Doses</th>
<th>Drug level</th>
<th>Serum creatinine</th>
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