GOAL - ORIENTED, MODEL - BASED DRUG REGIMENS: SETTING INDIVIDUALIZED GOALS FOR EACH PATIENT.

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Individualized drug dosage regimens cannot be developed without first setting an individualized, specific target goal, such as a desired serum drug concentration, at a desired time after the dose (usually a peak or trough), for each patient. Serum drug concentrations have commonly been described in terms of therapeutic ranges in which most patients have a therapeutic effect and a low incidence of toxicity. It is generally held that the serum concentrations of patients should be within this therapeutic range. Clinicians look at serum concentrations to see if they are in the so-called therapeutic range, and often adjust the dose intuitively if they are not. However, they often do this without looking carefully to see if the patient is tolerating that concentration or not, or if a higher or a lower level might actually be more desirable. Often, if the level is in the "therapeutic" range, that is the end of the clinical thought process, and no further consideration is given as to whether or not a different serum level might be better for the patient. In addition, there is definitely a greater effect of the drug at the top of the therapeutic range than at the bottom, and it increases steadily throughout the range. This is should be considered in clinical decision - making.

The Therapeutic Range - Classifying the Serum Levels Qualitatively

How have therapeutic ranges usually been developed? As shown in Figure 1, therapeutic ranges of serum concentrations are usually derived from two sets of data. First, there is a quantitative relationship between the serum concentration, or area under the curve (AUC) reflecting the patient's total exposure to the drug, and the incidence of desired therapeutic effects. The beginning of the therapeutic range is usually said to occur when the incidence of therapeutic effects becomes "significant". This significance is usually not explicitly defined or quantified. At a higher serum concentration (or AUC), there is a similar relationship to a "significant" incidence of adverse or toxic effects. Serum levels are then classified as being either subtherapeutic, therapeutic, or toxic.

Figure 2 shows serum digoxin concentrations measured by Doherty [1] in the early days after such assays became available. It shows the very wide overlap in serum concentrations in patients doing well on digoxin and in those with clinical evidence of toxicity. In general, however, as shown here, most patients with toxicity had serum levels over 2.0 ng/ml. This finding has been generally confirmed by others, and has given rise to the general custom today of regarding approximately 2.0 ng/ml as the top cutoff of the therapeutic range of serum digoxin concentrations.

In our desire to classify such relationships, we have thrown away the really important data of these quantitative relationships in order simply to develop a qualitative cutoff on the bottom and the top. As a result, we have lost the ability to think of giving a gentle regimen to a patient who needs it, and a more aggressive one to another patient who needs a firmer approach - who needs to have his/her dosage "pushed". Setting the therapeutic range of serum digoxin concentrations between 0.5 and 2.0 ng/ml is a good example of how such ranges are developed by looking only at populations, not individuals, without any consideration of what is really going on with each individual patient. Therapeutic ranges are good examples of how population goals rather than truly individualized goals have been applied to drug therapy in general. Again, the bottom of such a range is not at all the same as the top in terms of either effect or toxicity.

Serum Levels versus Incidence of Toxicity - a Quantitative Approach

If one looks again at Figure 2, but now evaluates the incidence of digitalis toxicity at various serum concentrations, it happens, in that data set, to be zero when serum concentrations are from 0 to 1.0 ng/ml, 10% (4 of 39) for levels from 1.0 to 2.0, 24% (6 of 25) for levels from 2.0 to 3.0, and then 43% (6 of 14) for levels above 3.0 ng/ml. Thus, half of Doherty's patients tolerated serum levels well over 3.0 ng/ml, and presumably were able to obtain benefit from them.

As shown above, the incidence of toxic effects of the drug increases steadily with the serum level, just as does the therapeutic effect, as diagrammed in Figure 1 and shown implicitly in Figure 2. Further, as illustrated in Figure 3, Brooker and Jelliffe also showed with a probit

analysis [3] that for patients specifically in sinus rhythm, the incidence of digoxin toxicity was about 6% for a postdistributive phase serum concentration of 1.0 ng/ml, 10% for 1.5, 25% for 2.0, and 50% for 3.0 ng/ml. This increasing incidence of adverse reactions with increasing serum levels is true of almost all drugs. There is usually no sharp cutoff.

Prior to 1970, when serum digoxin assays become widely available, it was generally felt that digoxin was a useful and effective drug in the therapy of atrial arrhythmias and congestive heart failure. The usual adult maintenance dose was 0.5 mg/day. Toxicity was not uncommon. Since the general acceptance of 0.5 to 2.0 as the limits of the therapeutic range, however, physicians have generally been unwilling to have their patients have levels over 2.0 ng/ml. Toxicity is now less common. There is now practically an entire generation of cardiologists trained in this view, and it is generally their experience (and seemingly correctly so for them) that digoxin is not a very effective drug, as they have limited themselves to looking at the serum level instead of the patient, and have not been trained to carefully titrate the patient clinically to determine the concentration which is actually optimal for that patient, looking for maximal effect or early toxicity. In addition, most physicians today are reluctant to prescribe more than 0.25 mg as a daily dose today, regardless of the patient's weight, renal function, or apparent need for the drug. Thus the tendency of physicians to be afraid of toxicity and to be influenced by an arbitrary serum cutoff point of 2.0 ng/ml has led to a tendency to look at the serum concentrations (or at standard doses) more than at the patient himself, who is actually the real assay system.

Individualizing the Goal - and thus the Regimen - a Specific Approach

On the other hand, it is also generally realized that the dosage of digoxin, or of any other drug with a narrow therapeutic range, should somehow be individualized. One might begin this process by considering each patient as an individual, with his/her own individual need for the drug. Rather than use a sharp cutoff or a general range, examine what is present in the data shown in Figures 2 and 3 about the relationship between serum concentration and the incidence of toxicity. The past incidence becomes the estimated risk when applied to the future. Consider clinically what you feel to be the upper acceptable risk of toxicity which it appears justified to accept in order to obtain the expected benefit of the drug in a specific individual patient,

according to his/her need for the drug. If the need is small, so is the upper acceptable risk. One can then set a low therapeutic goal such as a trough serum digoxin level of 0.5 ng/ml for a patient in sinus rhythm, for example. This would lead to a very gentle regimen, adjusted to the patient's body weight and renal function, to best achieve that desired goal.

On the other hand, if previous therapy has not sufficed and a significant or urgent need exists, then a higher goal may justifiably be selected, accepting a greater risk of toxicity, such as 1.5 or 2.0 ng/ml, or even higher if clinically required. In each case, one monitors both the patient's serum levels and clinical response in order properly to evaluate each patient's individual sensitivity to the drug. This is especially important when the principal clinical effect of the drug correlates better with computed concentrations in the peripheral, nonserum, compartment of a pharmacokinetic model of a drug than with the serum level itself. In such a case, measurement of serum levels still remains the key to making an individualized, patient-specific, pharmacokinetic model. The computed concentrations in the peripheral compartment cannot be found without measurement of the serum levels. This crucial point is examined more closely in another paper in this issue. It is only by selecting spedific individualized target goals for each patient that one can be gentle with a drug when that is needed, or more firm or aggressive when that is required. In contrast, when we simply accept a general "therapeutic range", we discard the ability to be gentle, firm, or aggressive with a drug when it is required.

One usually wishes to give the patient as much drug as possible, to obtain the maximum possible benefit from it. Instead of choosing a wide, population-based therapeutic range, one can choose an explicit serum concentration peak, trough, average, or profile as a therapeutic goal, based on each patient's individual need for the drug. If the patient's need is small, one would select a low therapeutic goal associated with a low incidence of adverse reactions. This will result in a gentle dosage regimen. If the patient's need is greater and/or if a previous dosage regimen has not brought about the desired clinical response, one can choose a higher serum concentration as the therapeutic goal, accept a greater risk of adverse reactions, and develop an appropriately higher dosage regimen to achieve that goal. This approach, even before the advent of serum assays, permitted significant reduction of digitalis toxicity from 36% to 12% and to 4% with dosage regimens individualized to each patient's age, sex, weight, and renal function, to

achieve individualized target total body concentration goals [4]. One is always keeping the risk of adverse reactions only to what is justified by that patient's need for the drug. For example, instead of using a general therapeutic range for digoxin, one can consider the data above that the risk of toxicity in patients with sinus rhythm, and select a trough serum goal of 1.0 ng/ml if one wishes to be gentle, with a risk of about 6%, 1.5 ng/ml for more firmness and a risk of about 10%, and 2.0 or greater for an aggressive approach to the patient, with a risk of about 25%.

Patients with atrial fibrillation often require more digoxin than those with sinus rhythm, as their needs are different. This fact is not considered at all in the usual statement of the population therapeutic range. Chamberlain [2] showed that patients with atrial fibrillation who have no intrinsic disease of the atrioventricular node actually require serum levels of about 2.0 ng/ml for really good control of their ventricular rate. In that report, in patients who previously had resting ventricular rates of at least 120/min before digoxin, the mean serum digoxin concentration was approximately 1.0 ng/ml for those who subsequently had ventricular rates above 100/min, 1.5 for those with rates of 81 to 100, and 2.0 ng/ml for those with resting ventricular rates of 61 to 80/min. This work shows that patients with atrial fibrillation require the modest AV block for proper control of ventricular rate, and patients with sinus rhythm do not, and that this fact is not reflected in the usual overall stated therapeutic range of 0.5 to 2.0 ng/ml.

In patients with atrial fibrillation, one can titrate the patient with digoxin (or, as I prefer, digitoxin) and look for 1) good control of ventricular rate, often not achieved until serum digoxin levels are 2.0 ng/ml or somewhat more, 2) conversion to sinus rhythm, or 3) appearance of clinical toxicity. If titration is carried out in gentle increments, one need not be afraid of serum levels over 2.0 ng/ml, and toxicity, when it occurs, is usually not life-threatening, simply because the titration was done in gentle small increments. One then can choose a somewhat lower target goal and develop a regimen, individualized to that patient, to achieve that specific goal. This is how one determines a patient's clinical sensitivity to the drug. Often patients with atrial fibrillation are left with ventricular rates that are not optimally controlled, as physicians are afraid to have a serum level at the top of the so called "therapeutic range", even though it may be clinically very useful to do so, simply because of their fear of the patient having such a level. The power of such so-called therapeutic ranges as published in books is immense. It greatly inhibits individual

thinking and dosing. Further, if the serum level is said to be "therapeutic", then that is too often thought to be all that is needed, and no further consideration is given to the patients actual clinical need for the drug.

One must always look at the patient. The patient, not the serum level, is the final assay system for the drug. Only by looking at each individual patient can we evaluate their widely varying sensitivities to the serum concentrations we achieve in them, as illustrated by Figures 2 and 3. Only by looking at each patient, and by evaluating that person's individual clinical sensitivity to the serum level, can we set the target goal properly. Only by looking at each patient later on can we tell if we selected the correct goal, or if it needs to be adjusted up or down.

After such an individualized goal is chosen, it needs to be achieved as precisely as possible. One does not want the patient to run any greater risk of toxicity than is justified by the need, nor does one want the patient to have anything less than the maximum possible benefit within the constraints of the risk of toxicity. That is the reason for trying to achieve a chosen target goal with the greatest possible precision.

After the regimen is given, serum levels need to be measured and an individualized, patient-specific pharmacokinetic model should be made. Without the model, with only the raw serum level, one cannot perceive the important exchanges that occur between serum and nonserum compartments of the drug, and we lack the precision given by the combination of the assay and the model to evaluate properly the patient's sensitivity to the drug.

These concepts have been discussed here for digoxin, but they are general ones, applicable to all drugs. Setting an explicit target goal, adjusted to the need, and using a pharmacokinetic / dynamic model of the drug to develop a dosage regimen to achieve it with optimal precision, provide both the conceptual structure and the practical tools to obtain truly optimal individualized drug therapy. These approaches have been applied to therapy with aminoglycoside antibiotics, vancomycin, lidocaine, theophylline, antiviral agents, a variety of anesthetic agents, psychiatric drugs, and anticancer agents, some of which will be discussed in other papers in this issue. If one has doubt about selecting a goal, one might select a gentle goal as one being near the bottom of

the therapeutic range, a modest one as being at about the middle of it, and a more aggressive one as being at about the top of the therapeutic range. One can then select still higher goals as needed, and as determined by the patient's sensitivity and clinical response to the drug, and his/her serum concentrations, and the behavior of his/her fitted model.

References

1.   Doherty J: Clinical Pharmacology of Digoxin. An Access audio tape and slide presentation of the America, College of Cardiology Postgraduate Education Program, 1972. Redrawn and reproduced with permission.

2.   Chamberlain D: Plasma Digoxin Concentrations as a Guide to Therapeutic Requirements; in Biological Effects of Drugs in Relation to their Plasma Concentrations, ed. by Davies D and Prichard B, University Park Press, pp 135-143, 1973.

3.   Brooker G and Jelliffe R: Serum Cardiac Glycoside Assay based on Displacement of 3H-Ouabain from Na-K ATPase. Circulation, 45: 20-36, 1972.

4.   Jelliffe R, Buell J, and Kalaba R: Reduction of Digitalis Toxicity by Computer-Assisted Glycoside Dosage Regimens. Ann. Int. Med. 77: 891-906, 1972.
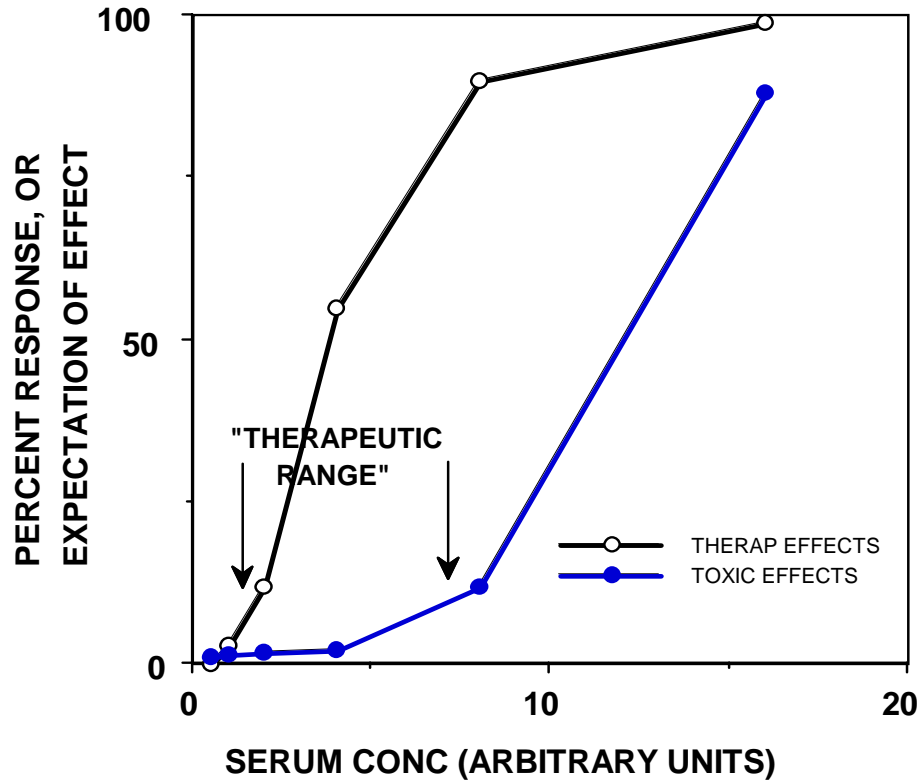
Figures and Legends

Figure 1. *General relationships usually found between serum drug concentrations and the incidence of therapeutic and toxic effects. The eye is drawn to the bends in the curves, and the therapeutic range is classified in relation to these bends. This procedure discards the important quantitative relationship of the incidence of toxicity versus serum concentration.*
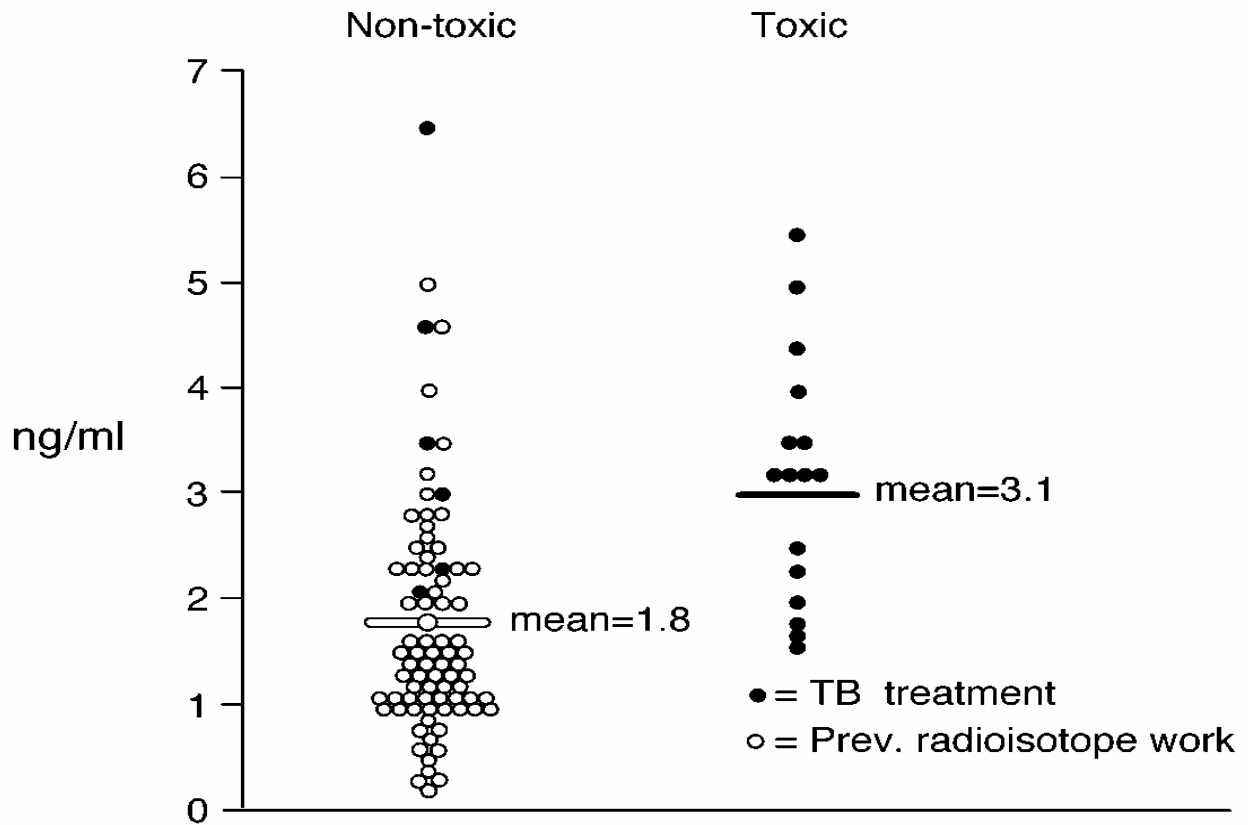
SERUM DIGOXIN LEVELS

Figure 2 - *Serum digoxin concentrations in patients without (left) and with (right) digoxin toxicity, found by Doherty [1], redrawn with permission. Note the great overlap between therapeutic and toxic concentrations, and the fact that approximately half the patients with serum levels of 3.0 ng/ml or more tolerated that level and were not toxic. Also note that the incidence of toxicity is very low for levels up to 1.0 ng/ml, moderate (though significant) for levels of 1.0 to 2.0, and still only about 50% for levels of 3.0 ng/ml or greater.*
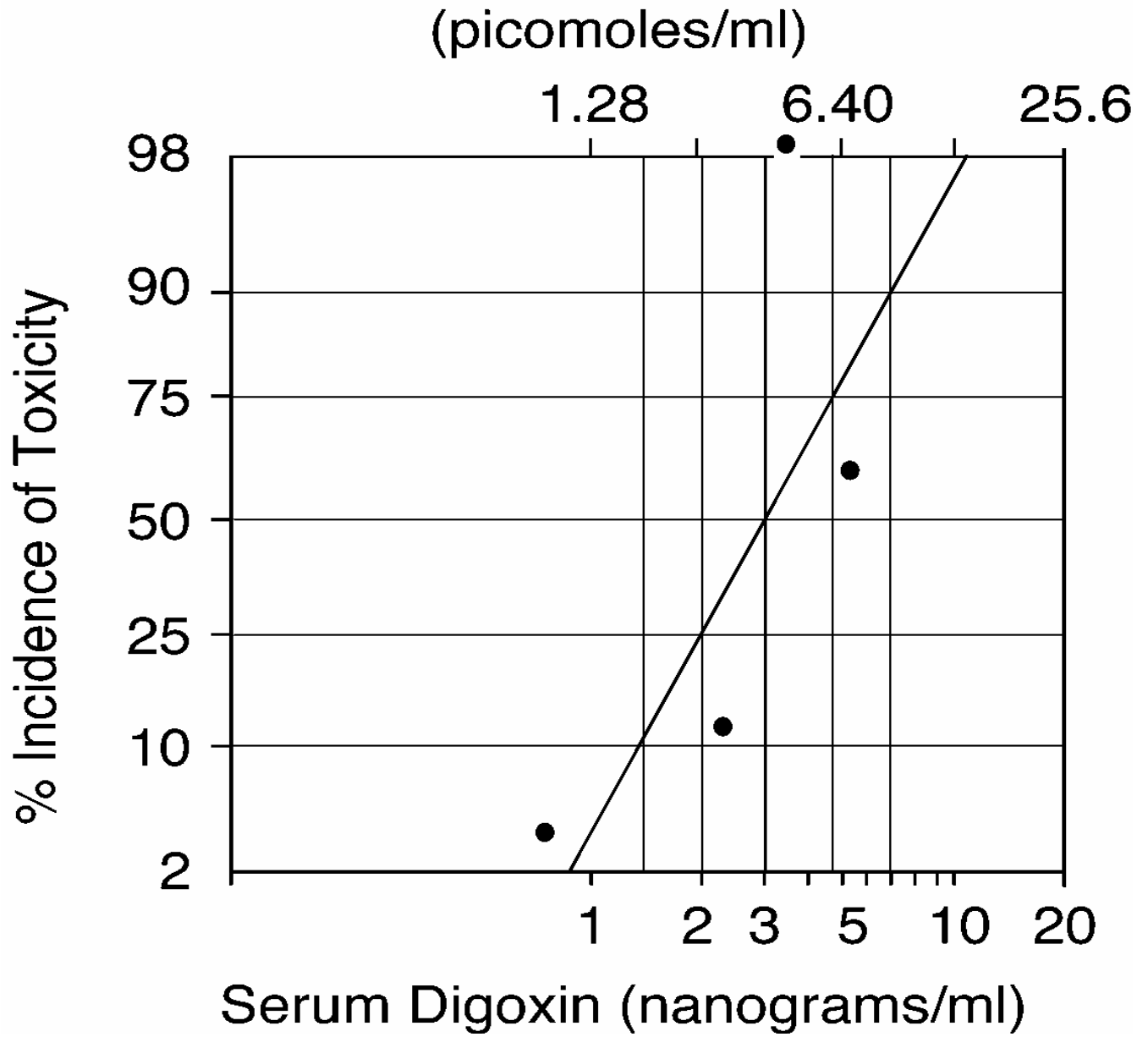
Figure 3. Relationship between serum digoxin concentrations and incidence of toxicity [3].