Seven "Pillars of Wisdom" for Maximally Precise Therapeutic Drug Management

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Just as T. E. Lawrence (Lawrence of Arabia) described "Seven Pillars of Wisdom" in his book, we would like to suggest seven similar pillars which we feel are important for optimal individualization of drug dosage regimens for patients.

Measurement of drug concentrations as part of Therapeutic Drug "Monitoring" (TDM) has been typically constrained to steady state sampling at a defined time, such as the end of the dosing interval (i. e., the trough concentration). The clinician or clinical pharmacist compares the result to a pre-defined "therapeutic range", which is not patient specific, and interprets the "meaning" or "significance" of values beyond that range, intuitively adjusting the dose according to perceived need.

The common custom of delaying TDM until a steady state is reached and for distribution of the drug to be complete in the body after a dose appears to have evolved, without any rigorous explanation, from a need to standardize "therapeutic ranges", and also from the now obsolete method of fitting the logarithms of the serum drug concentrations. For drugs with long half-lives in particular, this policy may result in sub- or super-therapeutic drug concentrations for days, at a significant risk to the patient. This practice may have been adequate in its time, but it is now obsolete, although it is still taught in many medical and pharmacy schools as "basic pharmacokinetics" and a cornerstone of TDM. Monitoring can begin with the very first dose.

Parametric population models and maximum aposteriori probability (MAP) Bayesian methods (1) have been available for many years, embodied in many different software packages. Using these methods, there is no need to wait for a steady state to be reached, or for distribution to be complete after a dose. A measurement can be made at any time and be useful. Indeed, D-optimal strategies (2) can now be employed to compute the optimal times to obtain serum measurements in various clinical situations. Even sparse data – even a single point – can be analyzed with this method, albeit with reduced confidence.

Population modeling was first introduced by Beal and Sheiner (3, 4). Parametric approaches (estimation of the means and covariances of the assumed normal or lognormal distributions of parameter values) have been by far the most commonly used, such as with the NONMEM software (4). However, many such parametric approaches suffer from the use of approximations in computing the likelihood of the parameter estimates, given the data. As a result, the precision of parameter estimation is less, and statistical consistency (study more subjects, the results more closely approach the true values) is not guaranteed. Indeed, the results may get worse (5). Other parametric methods (6, 7) do have exact likelihoods and are in fact statistically consistent. However, parametric approaches also suffer from the assumption that the model parameter distributions are normal, lognormal, or multimodal. Usually, there is only a single estimate for each model parameter, such as a mean, median, or mode. That single point estimator of the distribution is then used to compute the dosage regimen to hit a desired target serum concentration, for example. There is no way to evaluate in advance the precision with which any regimen will hit the target. It is simply assumed that the target will be hit exactly. Anyone in clinical practice knows that the predicted concentration for a given dose almost never matches the subsequently measured concentration with such accuracy.

Pillar No. 1.

Nonparametric (NP) population modeling approaches (8–10) have none of those weaknesses. The method was first introduced by Mallet (8). The likelihoods are exact. The methods are statistically consistent. In addition, no assumptions need to be made concerning the shape of the model parameter distributions. The theorems of Caratheodory, Lindsay, and Mallet (8, 11–12) all show that out of all the infinity of the various continuous parameter distributions that might exist, the most likely distribution "can be found" in a discrete set of points (support points), up to one such point for each subject studied. Each support point has a point estimate of each model parameter value, plus an estimate of the probability of that particular set of values. While NP methods have been criticized for a lack of confidence intervals, new approaches are addressing this issue (13).

Pillar No. 2.

Multiple Model (MM) Dosage Design. Nonparametric models lend themselves naturally to developing maximally precise drug regimens, using the method of multiple model (MM) dosage design (14–16). Here one uses the multiple support points in the NP population model and gives a candidate dosage regimen to them. Each point predicts a serum concentration profile into the future, weighted by that point's probability. At the time the target concentration is to be achieved, it is easy to calculate the weighted squared error of the failure of the regimen to hit the target, and it is then easy to find the regimen which specifically minimizes and defines that error. This results in a maximally precise dosage regimen.

Pillar No. 3.

Select a specific target goal, not a range. One could easily use multiple model dosage design to develop a regimen which maximizes the probability that the predicted concentrations will be within some desired therapeutic window. However, this ignores the fact that things

are not the same at the bottom as at the top of such a window, and that there is therefore no "window of neutrality". Further, some predictions will be below (usually ineffective), and some above (usually toxic), the window. Also ignored is the fact that some individual patients will benefit most from concentrations that are outside a pre-specified range. From a decision theoretical point of view, the consequences and therefore the utilities of such outcomes are quite different. There is no data to provide either utility, and so making a decision concerning the course of action (the regimen) having the greatest expected value is not possible.

Instead of this, one can use clinical judgment to ask how badly the patient needs the drug in question. If only a gentle approach appears justified, one can select a low target value appropriate to the patient's need, while minimizing the risk of toxicity, and develop a gentle regimen to hit that target most precisely. If the patient is in a more dangerous situation, where it appears appropriate to accept a greater risk of toxicity to obtain the desired benefit of the drug, then one can select a higher target. In any case, one does not wish the patient to run any greater risk of toxicity than is felt to be warranted. On the other hand, one wants to get the maximum possible benefit from the drug. The risks of being a small bit above or below the target are hardly different. This provides the rationale for selecting a specific target, and then for hitting it most precisely.

Pillar No. 4.

Eliminate censoring of low drug concentrations. The current practice of censoring laboratory reports below an arbitrary "limit of quantification" wastes valuable samples obtained from patients and delays appropriate dose adjustments. This problem arises when the percent coefficient of variation is used as a measure of precision, rather than the standard deviation, so that "precision", by definition, degrades to infinitely poor as measured concentrations approach zero. This is simply false, as even a blank sample measured in replicate has a finite standard deviation from zero. The medical community has been ignorant, perhaps willfully so, that all laboratory results are imprecise to some degree, such that repeated testing of the same sample will always return results with a defined variance. Several policies have been proposed to deal with the problem of censored data (17). None has been as successful as the actual measurement itself. Ultimately, we believe medical care can be improved if TDM and other clinical laboratory data are reported as a value with a standard deviation calculated from calibration curves. This would abolish the practice of data censoring; it would provide clinicians with a means to assign a level of confidence to any single result; and it will permit pharmacokinetic modeling software to appropriately weight the data by the reciprocal of the assay variance (standard deviation squared) for each measurement (18–20). This is easily done, and should be incorporated into standard laboratory practice.

Pillar No. 5.

Evaluate renal function as it changes from day to day and dose to dose, not just as if it were in a stable steady state. Current methods of estimating glomerular filtration rate or creatinine clearance based only on a single sample of serum creatinine (21–22) assume that the patient is in a stable steady state. This will not work for patients who are acutely ill and very unstable in intensive care settings. Instead, it is preferable to use a method based on a pair of serum creatinine measurements, which can also take into account the rate of rise or fall of serum creatinine during a stated time period. Such methods (23–27) are much better able to track drug behavior in unstable patients.

Pillar No. 6.

Use improved Bayesian feedback to make individualized patient drug models. There are now four Bayesian methods for developing individualized models of drug behavior in patients.

a) *Conventional maximum aposteriori probability (MAP) Bayesian analysis.* This was introduced by Sheiner (1), and has been the most widely used procedure. However, only a point estimate rather than a complete distribution is obtained, and no easy way to visualize its errors is available. Dosage regimens based on this approach have no way to estimate in advance, and to minimize, the error with which stated target goals are achieved.

b) *Multiple Model (MM) Bayesian analysis.* Here the multiple support points in a nonparametric population model are used. The locations (values) of the support points in parameter space do not change. Instead, those combinations of parameter values that predict the patient's measured data well become much more probable. Those that predict them poorly (most of them) become much less probable. In this way, the MM Bayesian posterior joint parameter density is obtained. Dosage regimens based on this will be maximally precise (14–16).

c) *Hybrid Bayesian analysis.* A patient's individual Bayesian posterior model may be poorly represented if it is in an area of the population model where there are few support points. In addition, a very unusual patient may be outside the stated parameter ranges of the population model. Poor or very bad fits may result. Because of this, a hybrid procedure has been developed. This begins with a MAP Bayesian estimate. Other support points are then added in that area, thus augmenting the population model and making sure that the patient will be well represented by them. Finally, an MM Bayesian analysis is done on this augmented population model. This has the advantages of greater precision and safety of Bayesian analysis (28).

d) *Interacting Multiple Model (IMM) Bayesian analysis.* Some patients are so unstable that their model parameter values change significantly during the period of data analysis. The great majority of fitting procedures assume that the parameter values are fixed and unchanging during the period of the data analysis. However, some very unstable patients will have significant changes in their clinical state, and in their model parameter values, during this time. The method of interacting multiple model (IMM) sequential Bayesian analysis has been developed to deal with this problem. It is used in the aerospace community to track (and hit) hostile targets taking evasive action. This approach (29) has now been used to track drug behavior in unstable patients, and tracks it better than either the MAP or MM Bayesian approaches (30).

Pillar No. 7.

Use linked pharmacokinetic-pharmacodynamic models. For example, rather than use empirical correlations between serum concentrations and bacterial kill such as peak/MIC or AUC/MIC, which usually do not state how often the peak is to be achieved, one can use Hill models of bacterial growth and their kill by antibiotics, which much better quantify such relationships. These models can be presented with serum concentration profiles over time, and the number of possibly viable organisms (or viral load) can be computed. Such models are begin-

ning to be incorporated into clinical software for individualizing drug therapy (31–33). Libraries of such models of relationships between organisms of varying sensitivity to various antibiotics can be developed, and should be quite useful. Similarly, diffusion of drug into porous spherical objects such as bacterial vegetations is also beginning to be computed (33–37).

Outcomes with goal-oriented, model based, individualized drug regimens

Many of the pillars (tools) are available in several software packages (14, 38–40). They are important for understanding drug behavior in populations of patients, and for optimizing the care of each individual patient by developing the most precise dosage regimens currently available (14–16). For digitalis glycosides, in the past, with older software, therapeutic efficacy was preserved while toxicity was significantly reduced (41). For lidocaine, better arrhythmia control was achieved with no increase in toxicity (42). For aminoglycoside antibiotics, survival improved, toxicity was less, hospital stay was reduced by 6 days, and hospital costs were reduced (43). For busulfan in children receiving bone marrow transplants, survival improved and veno-occlusive disease was reduced (44). For cyclosporine in similar children, severe graft versus host disease (GVHD) was greatly reduced, and an average net cost savings of approximately 70,000 Euros was achieved for each episode of severe GVHD prevented (45). The new MM software [ref] does better than other and older types (14–16). In addition, it has been useful in optimizing dosage individualization in adults and children with HIV (46).

Conclusions

Precise therapy with dangerous drugs requires a formal structure and specific quantitative tools. It cannot be done well by simply by looking up the literature, by getting an impression from the raw serum level data, or by using clinical judgment. Use of these tools has improved outcome, and reduced costs in many instances.

These tools also need to be taught to medical and pharmacy students. The failure of the greater medical and clinical pharmacology communities to accept and to use them may well be the reason why clinical pharmacology and clinical pharmacy have so greatly declined as a specialty outside of the pharmaceutical industry. These methods, many of which have been around for decades, have not yet been incorporated into medical school curricula and practice. We continue to train physicians who have no knowledge of the techniques of optimal drug therapy with potentially dangerous drugs. A change badly needs to be made.

Good software is the key to optimally individualized therapy for each patient. Most hospitals have perceived only the added cost of monitoring and analysis. They have not perceived the shortening of hospital stay and the significant reduction of overall hospital costs achieved by reducing complications associated with suboptimal drug therapy. Hospital and health administrators and the FDA should consider these aspects of health care. Use of the "Seven Pillars" described here should help to provide maximal, and maximally precise, use of the information contained in whatever data is present about the patient and in the population data from which s/he appears to come.

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