Bayesian Dosing of Anesthetic Agents: Esoteric or Practical?

In this issue of Anesthesiology, Maitre and Stanski offer data demonstrating improved precision of dosing of alfentanil by use of Bayesian forecasting. The end result was better prediction of serum alfentanil concentrations that presumably should result in better control of the effects of this agent. This study represents one of a sequence of investigations by this group that have succeeded in delineating the pharmacokinetics of alfentanil, defining target concentrations to be maintained during anesthesia, and assessing use of such parameters to design infusion regimens. But what does all this mean and why is so much effort being devoted to this topic? Is it the single-minded, esoteric (perhaps misguided) goal of an isolated group of investigators, or does it have broad implications? My bias is that the latter is a distinct possibility and that future implementation of this type of technology will have considerable salutary impact on patient care in a variety of fields.

Some background information may be helpful. The medical literature is replete with data demonstrating variability among individuals in disposition of and response to virtually all drugs. Thus, a group of “normal” individuals will exhibit a broad range of pharmacokinetic values that describe each individual’s handling of a drug. This translates to the fact that the same dose of drug given to a group of supposedly similar individuals will result in a broad range of serum concentrations and responses. If one superimposes disease states, age, drug interactions, etc., the range becomes even broader.

Investigators can define categories of patients (e.g., elderly patients, patients with heart failure, etc.) and derive average pharmacokinetic values for a group of such subjects with prospectively delineated clinical characteristics. Such values are referred to as population-based. In this fashion, one can derive general notions as to the disposition of a drug in, for example, elderly versus young patients, or patients with heart failure versus normal cardiac function, etc. However, within such groups, there is considerable variability; in addition, how does one deal with patients having a combination of disorders, such as elderly patients with heart failure? After all, physicians treat individual patients, not populations. Thus, the key question is, how best to tailor therapy to individual patients?

Considerable effort has been expended in diverse fields of medicine to optimize techniques for doing so. Though a variety of methods have been promulgated, it seems that Bayesian forecasting is the most versatile. It can accommodate a variety of kinetic models; it is at least as accurate and precise as other methods, if not more so; and it can use fewer drug serum concentrations. In addition, Bayesian methods use population-based data as starting points and the variability in pharmacokinetic parameters found in such populations as weighting factors for deriving estimates in individual patients. The downside of Bayesian forecasting is that it is mathematically intimidating (to say the least), and it requires a computer for implementation.

The paper in this issue of Anesthesiology points out the state of the art of this technology. Thirty-four surgical patients were studied to determine whether Bayesian forecasting was better than population-based pharmacokinetic estimates. In other words, does this method for individualizing therapy better allow attainment of desired alfentanil serum concentrations than can be accomplished by assuming the patient behaves as if he/she were the average of the population of patients studied in the medical literature? In general, the results were consistent with similar studies of other drugs, showing the Bayesian method to be superior. The study also asked when a serum sample should be used for prediction of future alfentanil concentrations and whether multiple concentrations were better than one. One sample obtained about 1 h after the commencement of dosing was the best single value and was as good as two or three values. Thus, feedback from only one specimen obtained at 1 h substantially improved the ability to predict subsequent alfentanil concentrations. In sum, this technique better allowed dosing for the needs of the individual patient.

Does this mean we all need a magical black box that consists of a Bayesian forecaster hooked to an infusion pump, into which we input data on alfentanil (or other drug) concentrations? Not yet. Other issues should first be addressed. For example, in table 1 of Maitre and Stanski’s article, it is clear that, although Bayesian forecasting was an improvement, there were still some patients in whom predictions were poor (e.g., patients 6, 15, 16, and 22). In some patients, the population-based estimate was about as good as the Bayesian forecast from one of the

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Address reprint requests to Dr. Brater: Clinical Pharmacology Section, Wishard Memorial Hospital, 1001 West Tenth Street, WOP 316, Indianapolis, Indiana 46202.

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samples and better than the other Bayesian estimate (e.g., patients 11, 20, 21, 26, 31, and 32). In these patients, use of the wrong Bayesian forecast would have resulted in a worse outcome. Lastly, in some patients (25 and 29), the Bayesian forecast was always worse. On average, then, Bayesian forecasting was superior, but clearly it was not the best for all patients. How can one predict, a priori, the best method for individual patients? Since our goal is optimal treatment of individual patients, we must direct future studies to defining how we can prospectively identify patients who don’t follow the average. Further questions will then need to be pursued. For example, in such patients, does input of multiple concentrations help?

Such patients demonstrate that one ingredient outside the magical black box will always be key; namely, the clinician’s judgment. Though I believe that the future will ratify the approaches being explored in this paper, I know of no method sufficiently accurate and universal that it can serve as a substitute for clinical judgment. Instead, such techniques should be viewed as an amplification of clinical judgment. As a consequence, though I enthusiastically endorse the directions pursued in this study, I am adamant that they should be implemented only by those skilled in their use who have appropriate concern about their limitations.

In addition to directing future studies to assure adequate performance of Bayesian forecasting in all patients, prospective assessment of therapeutic impact is crucial. Is patient care improved? It is conceivable that better attainment of a desired drug concentration does not result in improved patient outcome. Though I doubt this to be the case, variability in patient response to a defined drug concentration could dilute the benefit of such technology. We cannot accept its benefits de facto without documentation. I am confident that appropriate studies will demonstrate clear benefits to patients in a cost-effective manner. I can then envision a system of quick and accurate on-site drug assay, with input into a Bayesian forecaster, coupled manually or automatically to an infusion pump. If a good clinician is concomitantly monitoring clinical endpoints of response, we will indeed have a better mousetrap. If not, we have an esoteric toy.

D. CRAIG BRATER, M.D.
Professor of Medicine and Pharmacology
Director of Clinical Pharmacology
Indiana University School of Medicine
Indianapolis, Indiana 46202

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