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Evaluation of a Novel "Intelligent" Dosing System for Optimizing FK 506 Therapy

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THE available clinical evidence suggests that careful control of plasma drug levels of FK 506 and therapeutic monitoring are important to balance the opposing risks of drug toxicity and graft rejection.[1,2] An accurate and simple dosing algorithm that could be applied at bedside would facilitate standardization of patient management. Therefore, a computerized dosing algorithm for FK 506 and prednisone was developed. This "intelligent" dosing system (IDS) assumes no previous computer experience and operates on any IBM or IBM-compatible microcomputer system.

The advantages of an accurate and simple automated drug dosing program include minimizing the learning curve for the physician prescribing the drug, particularly for drugs with large pharmacokinetic variability and a narrow therapeutic index. It should also improve patient care by reducing toxicity and decreasing the length of hospital stay experienced by patients, both of which should result in a cost-benefit advantage.

The computerized dosing algorithm for FK 506 can best be described as an "expert system" utilizing stochastic open loop control theory.[3] Expert systems are computer programs that use a body of knowledge and specific rules to solve problems that are usually solved by human experts. In essence, an expert system uses what is called a "knowledge base" to solve problems. A knowledge base is a large body of information about a particular subject that is based on experience.[3] The expert system developed for FK 506 dosing is a prediction system that uses data about a patient's current state to predict the patient's future state based on a large body of empirical clinical experience with the drug in the patient of interest. Since individualization of FK 506 dosing is important, specific parameters of patient status have been incorporated into the decision matrix. In such a system, a "learned response" is predicted based on previously obtained empiric experience. In this study, a dosing algorithm for FK 506 is described. In addition, the results of a prospective study designed to validate the accuracy and precision of the prediction capabilities of the program are reported.

ALGORITHM

The appropriate dosage of FK 506 and prednisone to be utilized for a given allograft recipient is a function of the patient's status, ie, level of graft function and whether or not any evidence of toxicity or rejection is present and the current plasma drug level.[1,2] For example, if a given patient is demonstrating signs of drug toxicity, eg, either nephrotoxicity or hepatic dysfunction, and has no evidence for rejection, then a reduction in either the FK 506 dosage, the prednisone dosage, or both is indicated. On the other hand, if a patient has no evidence for drug toxicity and manifests signs of graft rejection, an increase in either the FK 506 dosage or the prednisone dosage or both may be in order, depending on the current FK 506 plasma level (see Fig 1). The specific decision-making ability of the system is provided by a knowledge base containing facts and rules which have been determined empirically, which the system uses to define the best course of action.

To determine FK 506 dosage required to achieve the desired target plasma level, an artificial intelligence dosing system (IDS) that would predict drug dosages and levels was developed. This IDS was programmed with hundreds of dosing histories, ie, previous dose, previous level, current dose, and current level. The system was then used as a model to develop an equation that relates the current FK 506 dose and level with the desired dose and level. To use the dosing algorithm, the physician enters the patient's current FK 506 dose (total milligrams per day), the patient's current plasma level (nanograms per milliliter), and the target plasma level (nanograms per milliliter). The IDS calculates the FK 506 dose required to achieve the target level. The IDS can also be used to predict the next FK 506

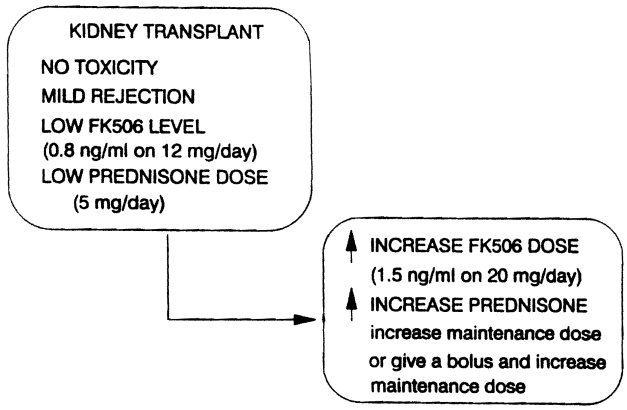

Fig 1. Dosing example.

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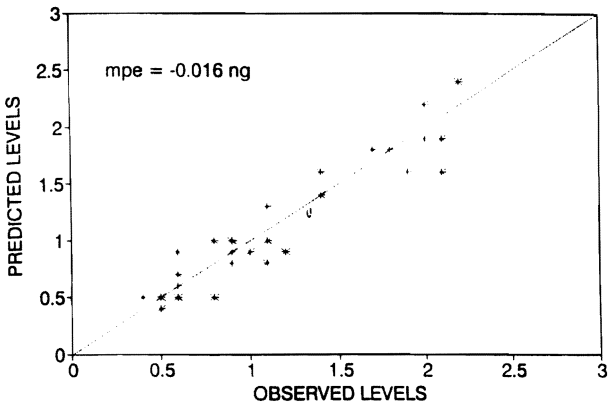

Fig 2. Observed versus predicted plasma levels.

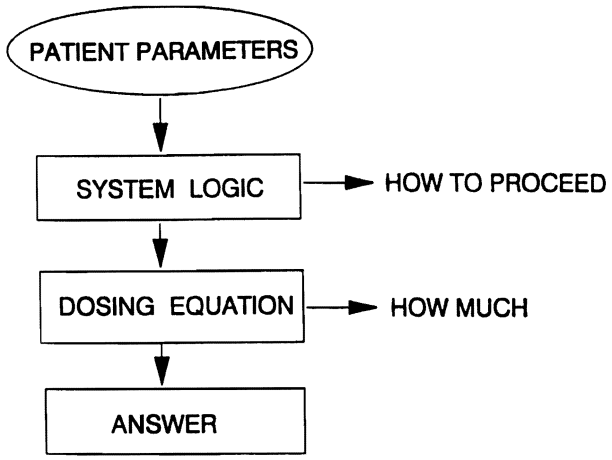

Fig 3. IDS algorithm.

level given the patients current FK 506 dose, current FK 506 level, and the new FK 506 dose.

RESULTS

To validate the IDS, a prospective study was conducted at the University of Pittsburgh Health Center. The patient population studied consisted of 32 adult liver (n = 17) and kidney (n = 15) transplant patients. Predictions of patient plasma blood levels were made throughout their clinical course which included the use of both IV (postoperative) and oral (maintenance) dosing with FK 506.

The mean prediction error (mpe), calculated as the mean difference between the observed and the predicted target values, was used to describe the model's accuracy. If the model was perfect, the mpe would be zero. The accuracy of the model was calculated to be 0.016 ng/mL. The root mean squared prediction error (rmspe), calculated as the standard deviation of the prediction errors, was used to describe the precision of the model. The root mean squared prediction error was calculated to be 0.189 ng/mL. The 95% confidence interval for the mean prediction error was calculated to be between 0.084 and 0.052, which brackets our calculated accuracy (including zero). This means that the model is 95% accurate in describing the relationship between FK 506 dosage and FK 506 plasma level, and that there are no biases in the dosing predictions. The accuracy of this IDS is illustrated in Fig 2, which shows the close correlation between the observed and predicted FK 506 plasma levels.

The "intelligent" portion of the program, the part that decides what action should be taken, was modeled after the clinical judgment of knowledgeable physicians practicing at the University of Pittsburgh Health Center who have had considerable clinical experience using FK 506 in transplant patients.

DISCUSSION

The use of artificial intelligence (AI) is a novel approach to understand and describe what has been observed in a complex biological situation based on specific knowledge and inference techniques.[3] By using standard AI methods and tools, it has been possible to define and model pharmacokinetic (PK) events and important PK-pharmacodynamic (PD) relationships, which are essential for clinical dosing decisions with FK 506 in transplant patients. As a result, this IDS can be used clinically to provide accurate predictions of clinical events associated with transplantation. For example, it is possible to predict the effect a specific change in FK 506 dose has on either toxicity or rejection. Because the model developed is a multiparameter system, more complex models can be built that describe such PK-PD relationships in a multivariate fashion. For example, a model could be constructed to identify the patient factors or covariates commonly involved in cases of rejection and/or toxicity. Furthermore, the current dose, new dose, and percent change in FK 506 level can be plotted to generate a three-dimensional graph or kinetic profile of the drug. This method allows for the direct comparison of the kinetic profiles of various drugs such that clinically important properties, ie, "linearity" and "dose proportionality" can be visualized (manuscript in preparation).

Importantly, the IDS developed is very user friendly. It has been routinely used by transplant physicians without previous computer training or experience. To run the program the physician is asked to make choices from menus to answer questions about a patient's condition. The only keyboard input required is to enter the values (current FK 506 doses and levels, etc) which are used to do the dose calculations. The critical components of the IDS algorithm are shown in Fig 3. This IDS makes predictions based on the patient's previous dosing experience, and has been shown to accurately predict appropriate alterations in FK 506 and prednisone dosages. The flexibility of the model is such that it could be modified to account for additional parameters, such as a third immunosuppressive agent.

The experience with this IDS suggest that a user-friendly, PC-based dosing system can efficiently individualize and optimize FK 506 therapy, and should simplify the physician learning curve relative to the use of FK 506, while maximizing patient care and providing an effective means for conducting concentration-controlled clinical trials with FK 506.

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