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An Intelligent and Cost-Effective Computer Dosing System for Individualizing FK506 Therapy in Transplantation and Autoimmune Disorders

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The accuracy and precision of an intelligent dosing system (IDS) for FK506 in predicting doses to achieve target drug levels has been prospectively evaluated in transplant and autoimmune patients. For dose individualization, the knowledge base is updated with patient-specific feedback including the current dose, drug level, and the new target level. The study population of 147 patients consisted of 97 transplant patients (liver and kidney) and 50 patients with autoimmune disorders. Patients in the transplant study group were entered sequentially and followed as a cohort. Patients in the autoimmune study group were randomly assigned to one of three predefined FK506 concentration windows (low, 0.1–.3; medium, 0.4–.7; and high, 0.8–1.3 ng/mL) as part of a concentration controlled clinical trial. Predictions of steady-state plasma drug levels were made throughout the clinical course of autoimmune patients and during the first 6 weeks post-transplant in liver and kidney recipients. FK506 concentration in plasma was measured by a monoclonal antibody based ELISA assay. Accuracy was computed as the mean prediction error (mpe). Precision was computed as the root mean squared prediction error (rmspe). The accuracy of the IDS in each study group was as follows: 0.016 ng/mL (liver), −0.034 ng/mL (kidney), and −0.022 ng/mL (autoimmune). Because the 95% confidence interval included zero in each case, the IDS showed no bias. The precision of the IDS in each study group was as follows: 0.133 ng mL (liver), 0.1903 ng/mL (kidney), and 0.1188 ng/mL (autoimmune). These results indicate that the FK506 IDS is both accurate and very precise (reproducible) in transplant and autoimmune patients. The performance of the FK506 compares favorably with previously reported pharmacokinetic dosing methods such as population nomograms and adaptive control feedback methods (least-squares and Bayesian). Based on our findings, this IDS should have a number of important uses relevant to the drug development process, the prescribing physician and the individual patient. It provides an efficient method for implementing concentration controlled clinical trials. It should accelerate the physician's learning curve while at the same time help to maximize therapeutic drug efficacy and minimize toxicity with drugs exhibiting nonlinear kinetics and narrow therapeutic indices. Preliminary studies suggest that these assets result in a significant cost-benefit advantage by reducing the duration of hospitalization. Current studies are in progress to validate this and carefully measure its pharmacoeconomic impact.

FK506 is a novel and promising new immunosuppressive (IMS) agent currently under active clinical investigation for the prevention and control of organ rejection and the treatment of autoimmune disorders.[1] Preclinical studies in animal models and initial clinical experience suggested that FK506 has a narrow therapeutic index, large interpatient pharmacokinetic (PK) variability with apparent dose-dependent kinetics, and plasma level-related systemic toxicities.[2,3] Results from recent randomized and nonrandomized clinical trials further confirm, that similar to cyclosporine A (CyA), careful control and

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monitoring of plasma (blood) drug levels of FK506 are necessary to balance the opposing risks of over-immunosuppression such as drug-induced toxicity (e.g., nephrotoxicity, infection, tumor) and under-immunosuppression (e.g., graft rejection).[4,5]

Previous experience has shown that drug therapy and patient care can be improved by individualizing doses in drugs exhibiting a narrow therapeutic range, large PK variability, and a relationship between plasma drug levels and clinical pharmacodynamic (PD) responses (therapeutic and adverse).[6,7] The optimal use of current immunosuppressive drug regimens (e.g., CsA, Prednisone, Imuran) in the solid organ transplant patient requires the need to set therapeutic goals by individualizing polydrug therapy as a function of patient status, i.e., level of graft function, evidence of toxicity, rejection or graft-versus-host disease and the current plasma CsA drug level.[8,9]

Therefore, an accurate and simple-to-use dosing method that would predict doses and/or desired drug levels in individual patients and at the same time account for dynamic changes in physiologic status should improve patient care by a) reducing systemic drug-related toxicities, b) increasing the time spent in an effective nontoxic therapeutic range, and c) decreasing the length of hospitalization, all of which should result in a cost-benefit advantage. In a pilot study in solid-organ transplant recipients, we described our initial clinical experience with a novel IDS developed for FK506.[10] The present study was undertaken to a) further evaluate the performance of this FK506 IDS in a larger sequential cohort of patients undergoing allogeneic liver and kidney transplantation and b) compare its performance in a group of patients with autoimmune disorders who were randomly assigned to predefined FK506 plasma concentration windows.

MATERIALS AND METHODS

The FK506 IDS used in this study is a modified artificial intelligence program designed to learn the dose-level relationships for FK506 from dosing history and corresponding drug concentrations. The knowledge base for the IDS originally derived, consisted of steady-state trough FK506 plasma levels in 142 adult heart, liver and kidney allograft recipients treated as both inpatients and outpatients at the University of Pittsburgh Presbyterian Medical Center under primary FK506 immunosuppressive therapy January 1, 1990 to December 31, 1990.[10]

To objectively assess the performance of the FK506 IDS, a cohort study was conducted at the University of Pittsburgh Medical Center. The entire study population (n = 147) consisted of a total of 50 adult liver and 47 adult kidney transplant recipients as well as 50 nontransplant patients with a variety of autoimmune disorders such as psoriasis, scleroderma, and rheumatoid arthritis. All treatment protocols were approved by the IRB of the University of Pittsburgh. Informed consent to use FK506 was obtained in all patients enrolled in these studies. Clinical studies were conducted under IND's 32463 (transplantation), 34570 (psoriasis), 36317 (multiple sclerosis) 34548 (chronic active hepatitis and IND) 34581 (primary biliary cirrhosis) monitored by the Food and Drug Administration, Rockville, Maryland. FK506 was provided by the Fujisawa Pharmaceutical Company of Japan.

Patients in the autoimmune study group were randomly assigned to one of three predefined FK506 concentration windows (0.1–0.3, 0.4–0.7, 0.8–1.3 ng/mL as part of a concentration controlled clinical trial. The FK506 IDS was used to guide all doses to prospectively achieve the target level specified in the protocol. Predictions of plasma drug levels were made throughout the clinical course of autoimmune patients and during the first 6 weeks of the post-transplant course of transplant patients including both intravenous and oral doses of FK506.

To be eligible for this cohort study, patients were required to have consecutive doses and corresponding plasma levels obtained after achieving steady-state, i.e., at least 3 days of the current dose at regular intervals (e.g. every 12 hours) and at least 48 hours after administration of a new dose at regular intervals. The time to steady-state was also consistent with the average plasma terminal half-life of approximately 8-15 hours in these patients.[11,12]

FK506 concentration in plasma was measured by a monoclonal antibody based ELISA assay as previously described.[11,12] The coefficient of variation of this assay is 17% at 1.4 ng/mL; 14.4% at 2.9 ng/mL; and 12% at 5.7 ng/mL. The effective therapeutic range for FK506 is estimated to be 0.5-2.0 ng/mL in transplant patients and is currently being defined in patients with autoimmune disorders.

RESULTS

The performance of the IDS was assessed using standard prediction error analysis.[13] The mean prediction error (mpe), computed from the average deviation between the observed and predicted target level, was used to describe accuracy or bias. The root mean squared prediction error (rmspe), computed as the standard deviation of the prediction error was used to describe precision. If the IDS were a perfect method, the mpe and the rmspe would be zero. The 95% confidence interval (CI) was calculated as the mean prediction error or the root mean squared pre-

diction error plus or minus 1.96 times the SE, i.e., mpe +/− (1.96 × SE).

Demographic characteristics of the patients in the autoimmune study group are summarized in Table I. The performance of the IDS in each of the study groups and in the three groups combined is summarized in Table II. In addition, the accuracy and precision of the IDS in all study groups is shown in Figure 1. These graphs underscore the close correlation between the observed and predicted levels. Despite the heterogeneity of the individual study groups and the marked intersubject variability in kinetics, there are no significant outliers or individuals who are difficult to predict.

TABLE I

Summary of Demographic Data

Protocol	Age	Sex	Race	Treatment Group
AIED	36	Male	White	High
ALS	57	Male	White	None
CAH-A	57	Female	White	High
CAH-A	33	Female	White	Low
CAH-A	28	Female	White	Low
CAH-A	32	Female	Other	None
CAH-A	34	Male	White	High
CAH-A	37	Female	White	Low
Diabetes	41	Male	White	High
IBD	31	Female	White	Low
IBD	48	Male	White	High
IBD	32	Female	White	None
IBD	31	Male	White	High
IBD	23	Female	White	High
MS	40	Female	White	Medium
MS	41	Male	White	Low
MS	56	Male	White	Medium
MS	52	Male	White	Medium
MS	46	Female	White	Medium
MS	37	Male	White	High
MS	57	Female	White	Low
MS	48	Female	White	Low
MS	28	Female	White	High
MS	39	Male	White	Medium
MS	41	Male	White	High
MS	33	Female	White	Medium
MS	51	Female	White	Low
MS	56	Female	White	Low
MS	42	Female	White	High
MS	37	Male	White	High
Nephrotic	5	Male	White	Low
Nephrotic	47	Male	White	Low
Nephrotic	10	Male	White	High
Nephrotic	13	Male	White	Low
Nephrotic	14	Male	White	Low
PBC	48	Female	White	Low
PBC	65	Female	White	Low
PBC	49	Female	White	Low
PBC	51	Female	White	Low
PSC	32	Male	White	High
PSC	53	Female	White	Low
PSC	27	Male	White	High
PSC	39	Female	White	Low
PSC	41	Male	White	Low
Psoriasis	52	Female	Black	High
Psoriasis	39	Male	White	Low
Pyoderma	56	Male	White	Low
Scleritis	24	Female	White	Low
Sprue	39	Female	White	Low
Vasculitis	71	Male	White	None

AIED = autoimmune inner ear disease; ALS = amyotrophic lateral sclerosis; CAH-A = autoimmune chronic active hepatitis; IBD = inflammatory bowel disease; MS = multiple sclerosis; Nephrotic = nephrotic syndrome; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; Low = 0.1–0.3 ng/mL; Medium = 0.4–0.7 ng/mL; High = 0.8–1.3 ng/mL; None = based on individual patient response.

TABLE II

Summary of Mean Prediction Error Analysis

Patient Group	mpe	Standard Deviation of Prediction Error	95% Confidence Limits
All groups	−0.013	0.149	0.029--0.055
Kidney transplant	−0.034	0.190	0.020--0.008
Liver transplant	0.016	0.133	0.053--0.021
Autoimmune diseases	−0.022	0.119	0.011--0.055

The accuracy (mpe) of the IDS ranged from 0.016 (liver) to 0.034 (kidney) ng/mL. The accuracy of the combined study groups was 0.013 ng/mL. Because the 95% confidence interval in all groups includes zero, the IDS shows no bias in predicting FK506 levels in transplant and autoimmune patients. The precision (rmspe) of the IDS ranged from 0.1188 (autoimmune) to 0.1903 (kidney). The rmspe in the combined group was 0.1499 ng/mL.

To further put the performance of this IDS into perspective, a scattergram that depicts the observed relationship between a given dose and the corresponding FK506 plasma level at steady-state for the combined study population is shown in Figure 2. The FK506 dose-level response profile is variable and does not appear to be simply linear over the dose range of 0.5–60 mg/day. Because FK506 did not exhibit dose proportionality with standard graphical methods,[14] we explored the linearity versus nonlinearity of FK506 by using a novel three-dimensional graphical method recently described.[15]

To help visualize and quantitate the apparent dose-level relationship, we graphed three variables (current dose, new dose, and the associated percent change in FK506 level). The relationship between these parameters is shown in Figure 3. While there is relative linearity in the low dose range (>10 mg/day), there is a rapid and disproportionate increase at higher total daily doses indicative of nonlinear pharmacokinetic behavior.

The disproportionate increase in the surface area between a nonlinear plane and a linear plane can be

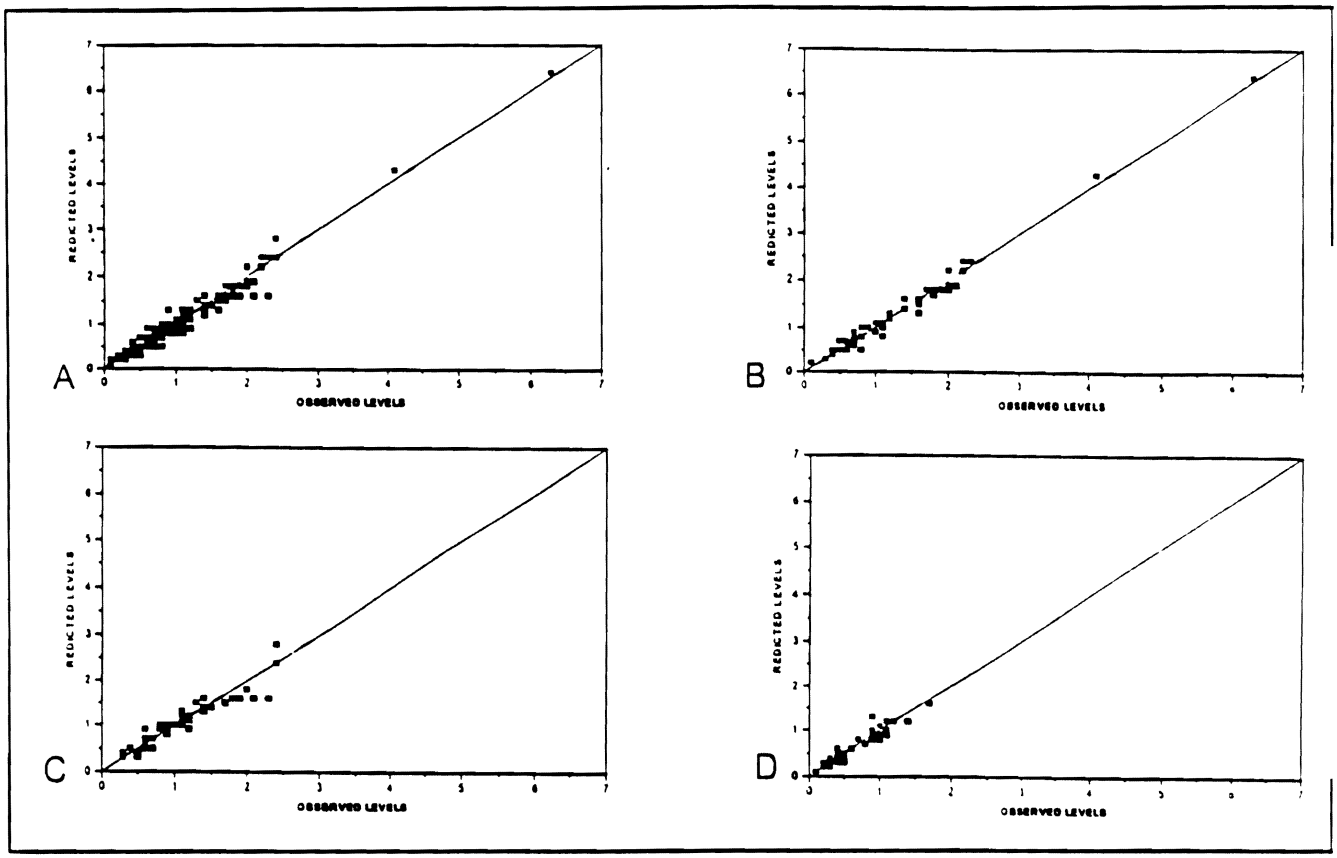

Figure 1. Scattergrams of predicted versus observed FK506 levels are shown for each study group in the combined group. These graphs show the close correlation between the observed and predicted FK506 plasma levels in each study group. The study groups are as follows: a. Kidney, liver, and autoimmune disease patients; b. Kidney transplant recipients; c. Liver transplant recipients; d. Patients with autoimmune diseases.

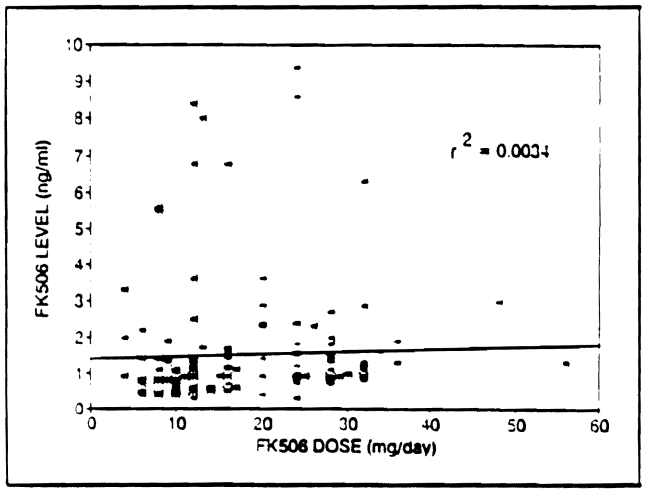

Figure 2. Scattergram of the observed relationship between FK506 dose over a wide range (0.5–60 mg/day) and the corresponding FK506 plasma level at steady-state in the combined study population. The marked intersubject variability and the lack of a simple linear relationship (r^2 = 0034) between FK506 dose and achieved steady-state plasma level is evident.

seen in Figure 4. In this model, the degree of nonlinearity is calculated as the nonlinear surface area divided by the linear surface area. The surface area of the nonlinear plane of fit was 1.88 times greater than a linear plane over the normal dosing range (0–50 mg/day). This deviation from linearity especially at doses above 10 mg/day helps to explain why FK506 doses should not be used alone to guide therapy without measuring drug levels as well.

DISCUSSION

We have prospectively evaluated the accuracy the precision of an IDS for FK506 in predicting doses to achieve target drug levels in transplant (liver, kidney) and autoimmune patients. This IDS uses a knowledge-based derived from steady-state trough drug levels in transplant patients to learn (predict) the expected dose-level relationship for FK506. For dose individualization, the knowledge base is then updated with patient specific feedback, i.e., current dose and drug level and the new target level.

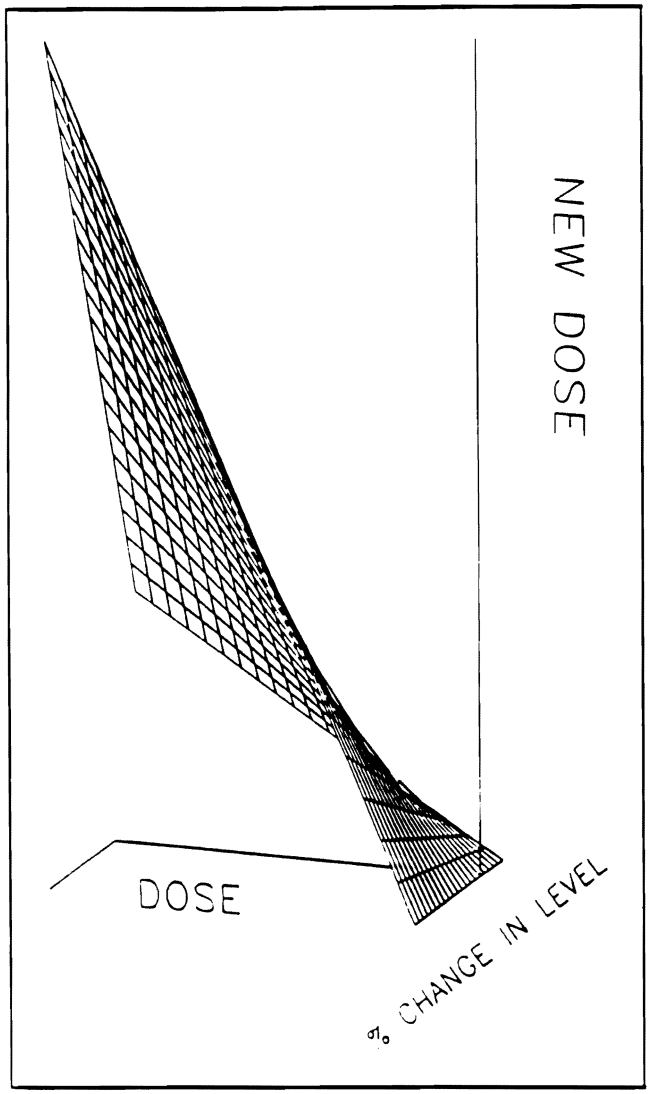

Figure 3. A three-dimensional surface plot of the relationship between current dose, new dose and the percent change in FK506 level is depicted. The surface area of the nonlinear plane observed was calculated using Design CAD 3D, a software package which uses surface integrals to make the surface area calculation.

We observed excellent predictive performance across all three groups studied. The accuracy (mpe) of the IDS was determined to be −0.013 ng/mL in the combined study group. Since the 95% CI includes zero, the IDS is without bias. The precision (rmspe) was determined to be 0.1499 ng/mL in the combined study groups which represents less than 10% of the span of the effective therapeutic range (0.5–2.0 ng/mL) and less than the coefficient of variation of the FK506 assay. Thus the IDS is both accurate and reproducible in transplant and autoimmune patients. The performance of the IDS in autoimmune patients, a category of patients excluded from the original knowledge base, i.e., transplant patients, is strong evidence of the broad applicability of artificial intelligence to the field of adaptive control dosing methods.[16–18]

The performance of the FK506 IDS in autoimmune patients compares favorably with previously reported PK guided methods such as population based nomograms and Bayesian prediction methods using feedback control. Because feedback methods (nonlinear least-squares and Bayesian estimation) are usually more precise than population nomograms, our results were compared with feedback methods. For example, the following performance results have been reported for digoxin: RMSE = 0.35, 0.36 and 0.30 ng/mL; lidocaine: RMSE = 0.7, 0.55 and 0.9 mcg/mL; theophylline: RMSE = 2.3, 1.2 mcg/mL.[18] In a prospective randomized concentration controlled clinical trial of primary FK506 prophylaxis in renal transplantation, wide intersubject variability

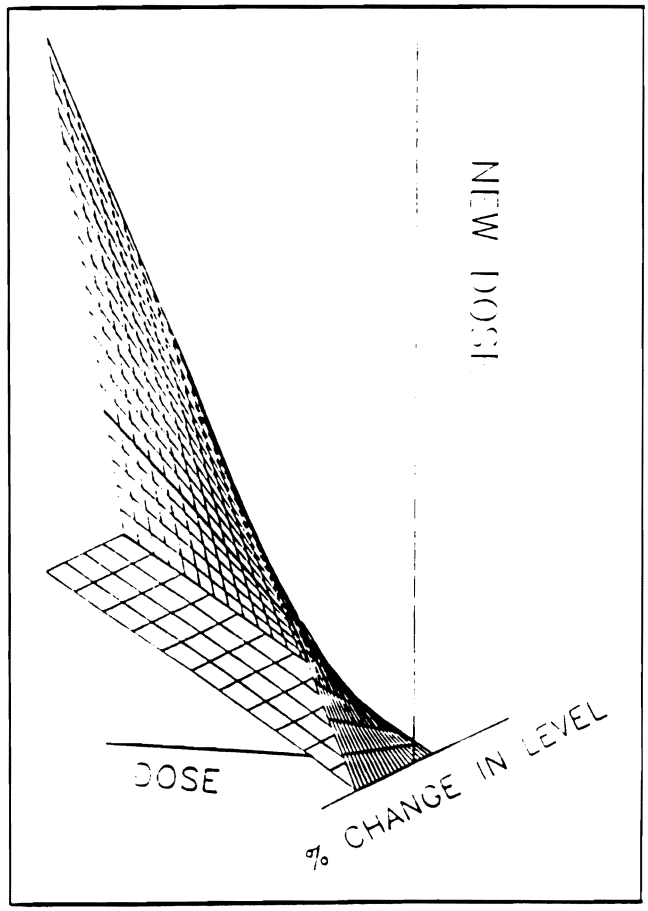

Figure 4. A three-dimensional plot of the modeled relationship between the three variables (current dose, new dose and percent change in FK506 level) is shown. The disproportionate increase in the surface area between nonlinear plane and a linear plane with increasing doses of FK506 can be readily seen.

exists in PK parameters (e.g. clearance, bioavailability), such that population or patient specific PK parameter values derived from pre-transplant or post-transplant PK profiles are not reliable in accurately predicting or achieving target steady-state drug levels (Qais Mekki, personal communication). It seems unlikely that these feedback methods can significantly improve upon the performance achieved by the IDS especially given the nonlinearity in FK506 kinetics.

This IDS has other important potential benefits besides improved performance for achieving target levels. Because this IDS requires no previous computer experience and is user friendly, it should help minimize the learning curve and facilitate standardization of care. This is especially true for the physician prescribing a drug like FK506 for the first time with large PK variability and a narrow therapeutic index. Similar to the introduction of an effective new immunosuppressive drug such as CsA with concurrent therapeutic drug monitoring in renal transplantation, the addition of FK506 to the therapeutic armamentarium coupled with this IDS should also translate into a significant cost-benefit advantage.[19] Preliminary studies at the University of Pittsburgh suggest that the cost of liver transplantation under FK506 compared with CsA may be reduced by half or more due to shorter hospital stays (16.1 vs. 35.9 days).[20]

The IDS also offers potential benefits to the new drug development process. In the case of new drugs for disorders such as AIDS, cancer, or acute refractory organ rejection, it may not be feasible to do standard intense PK sampling early in drug development to estimate the PK profile, dose proportionality and bioavailability. As we have shown, the IDS combined with the 3D graphic method requires only single steady-state plasma samples for each dose level analyzed. PK-PD analysis using only trough levels should be informative since steady-state FK506 trough levels closely correlate with the area under the curve. Therefore it should be possible to extract information from observational databases to estimate the response surface of a new drug and assess its linearity or nonlinearity. This 3D graphic method should also be capable of estimating the change that occurs in the surface area of the plane when there is a drug-drug interaction.

Finally, this IDS is user friendly and intuitive. It has been routinely used by transplant physicians without prior computer training or experience. To run the program, the physician is simply asked to make choices from menus to answer questions about a patient's condition that are relevant to any transplant patient receiving immunosuppressive drugs. For example, if a patient exhibits signs of drug toxicity (nephrotoxicity) and has no evidence of rejection, then a reduction in FK506 dosage is indicated. However, the physician must choose the new target drug level based on the current FK506 level and renal function. The only keyboard input required is to enter current FK506 doses and levels and the new target level. The IDS predicts the recommended dose based on the patient's previous dose-level history. The IDS can also be used to predict the next FK506 level given the current dose, current level and the new FK506 dose. In short, dosing recommendations and adjustments are tailored to the individual patient.

In conclusion, the experience gained with this IDS in several hundred transplant patients and more recently in autoimmune patients indicate that an intelligent PC based, user friendly dosing system can efficiently optimize FK506 therapy. It also provides a practical and cost effective method for implementing concentration controlled clinical trials. Furthermore, it is probable that patients can learn to use this program as well and become more active participants in clinical decision making in a manner analogous to patient-controlled analgesia. Through maintenance of safe and effective therapeutic drug levels which can be tailored to the individual patient, this IDS should result in even greater reductions in health care costs by reducing the likelihood of drug-limiting toxicity while improving the likelihood of remaining free from rejection and therefore reducing the duration of hospitalization.[20] Current studies are underway to validate this and more precisely measure its pharmacoeconomic impact.

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