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THREE DIMENSIONAL SURFACE MAPPING AND SIMULATION OF FK506 DOSE- LEVEL RELATIONSHIPS

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ABSTRACT

FK506 is a promising immunosuppressive macrolide antibiotic which appears highly effective but toxic for the treatment of organ graft rejection and a variety of autoimmune disorders. The need for therapeutic drug monitoring and individualization of dosing is underscored by its narrow therapeutic index and marked intersubject variability in its kinetics. The FK506 dose-plasma level profile is quite variable and does not appear to be linear over the dose range of 0.5-60 mg/day. Initially, an Artificial Intelligence Modelling System (AMIS) was used to learn this relationship and develop a dosing algorithm. Its accuracy and precision has been prospectively validated in clinical trials. Subsequently, we have now investigated the linearity of the relationship using a three dimensional (3-D) graphic method (SAS/Graph G3D). The surface area of the nonlinear plane observed was calculated using Design CAD 3-D. Our analyses indicate that FK506 is relatively linear over lower doses(<10mg/day) but shows marked deviation from linearity i.e. is nonlinear (e.g. 1.88 fold vs a linear fit) over the dose range of 0-50 mg/day. We conclude that this novel 3-D graphical approach should be useful as an adjunctive population screening method in the drug development process for quantitating nonlinear kinetics, estimating drug interactions and the 3-D drug surface of new chemical entities.

INTRODUCTION

The relationship between dose of a drug and plasma concentration may be variable across the useful range of doses. For some drugs such as theophylline, this relationship may be dose independent (linear) at low and moderate doses in adult patients but dose-dependent (nonlinear) at very high doses in special populations such as asthmatic children (1). Pharmacokinetic models for drug

elimination may be subdivided into three major categories: 1) linear (first order) or dose independent in which the amount eliminated is proportional to plasma concentration; 2) nonlinear (zero order) or dose dependent in which the elimination processes have a limited capacity and the amount eliminated is not proportional to plasma concentration (Michaelis-menton); and 3) a combination of both, in which parallel pathways of elimination coexist.

Several statistical and pharmacokinetic methods are often employed to assess dose proportionality and the linearity of the kinetics. The Pearson Correlation Coefficient and standard linear regression techniques assume a linear relationship which is not always the case. Compartmental models using nonlinear least squares regression and noncompartmental methods using statistical moment theory involve sophisticated computer algorithms and complex expressions that are, for the naive user, difficult to work with and hard to conceptualize. A graphical method which captures the linearity of the kinetics would be useful in demonstrating the dose-concentration relationships over the therapeutic range. In addition, a practical and quantitative system that identifies the subtle relationships between the dose given a patient and the resulting plasma level response but does not require advanced mathematics to implement, would aid the physician by providing a range of doses to achieve the desired change in plasma level and thereby decrease the amplitude and length of time of the oscillations in a patient's drug levels before an effective and safe therapeutic window is achieved.

FK506, a promising immunosuppressive drug used to control rejection in organ transplant recipients is very effective but toxic. Clinical experience has shown that it is critical to carefully control FK506 plasma levels in order to balance the opposing risks of drug toxicity and allograft rejection. The ability of the physician to adjust drug levels and individualize doses is critical for the optimal treatment of a patient. Inherent dose concentration relationships can aid or hinder a physician towards this end, and should be considered when choosing the best agent for a particular patient. In this report, a method which we have termed "three dimensional drug surface mapping" will be described and used to delineate the dose concentration characteristics of FK506 in transplant patients.

METHODS

Steady-state trough FK506 plasma levels were measured in 142 adult heart, liver and kidney allograft recipients who were transplanted under primary FK506 immunosuppression at the University of Pittsburgh medical Center during the time period from January 1, 1990 to December 31, 1990. The patients included in the analysis represented the full spectrum of functional graph status typical for a tertiary care facility. The main criteria for inclusion was the availability of consecutive doses of FK506 and corresponding plasma levels obtained after the patient had achieved steady-state i.e. at least three days of administration of the current dose at constant intervals (e.g. every 12 hours) and at least 24-36 hours after administration of a new dose (e.g. every 12 hours for two doses). It was assumed that steady-state FK506 levels (e.g. 2-3 x T1/2 or at least 75-90% of the true Css) had been achieved based on an average plasma terminal half-life in this patient population of 8-12 hours (2). An open one compartment linear pharmacokinetic model provided a reasonable fit of the plasma level versus the time profile during continuous IV therapy and after oral doses. FK506 concentration in plasma was measured by a monoclonal antibody-based ELISA method as previously described (3). The coefficient of variation of this assay is 17.0% at 1.4 ng/ml; 14.4% at 2.9 ng/ml and 12.0% at 5.7 ng/ml.

To assess the nature of this relationship between the % change in dose and the % change in level, we adapted and modified a simple graphical technique described by Sarrazin et al, 1980 (1) where the % change in FK506 dose was plotted against the corresponding % change in FK506 plasma level at steady-state. Dose and corresponding drug concentrations were then entered into an artificial intelligence system designed to "learn" the expected dose-plasma level relationships for FK506. Using the knowledge-base system as a model, an FK506 dosing algorithm was developed which incorporated the learned dose-plasma level relationships. This information was linked with patient factors known to influence clinical dosing decisions such as liver and renal function, concurrent steroids and rejection status. A prospective clinical study was then conducted which confirmed the accuracy and precision of this dosing algorithm (4). A three-dimensional plot of the learned relationships was implemented using a computer-assisted drawing package (SAS/Graph G3D). Deviation from

linearity (nonlinearity) in the three-dimensional model was calculated as the observed increase in the surface area between the linear plane and the corresponding nonlinear plane (plane of best fit). The surface area of the nonlinear plane was calculated using the software package DesignCAD 3-D, which uses surface integrals to make the surface area calculation (5).

RESULTS

A scattergram that depicts the observed relationship between a given FK506 dose and the corresponding FK506 plasma level at steady-state is shown in figure 1. The FK506 dose-plasma level response profile is variable and does not appear to be simply linear over the dose range of .5-60 mg/day. Repeated PK profiles consisting of three steady-state FK506 trough levels in 17 stable patients during maintenance therapy at 4 mg/day of FK506 have shown only minimal intrasubject variability i.e. CV of 36 percent. This is further supported by the fact that the average CV in the FK506 assay is approximately 20 percent. This is in sharp contrast to the observed wide total variability (inter/intrasubject) in these same patients i.e. CV of 91 percent. To determine the effect of within patient variability on the dose-level relationship, three steady state levels at three different doses were obtained for 8 patients. To investigate this relationship, an unbalanced repeated measures analysis with an unstructured covariance matrix was used (6). These results are consistent with our interpretation that the overall marked interpatient variability observed in steady-state trough levels (7 fold range) previously reported by Venkataraman, et al (2) can be largely explained by nonlinear pharmacokinetics. Furthermore, the significant intrasubject variability observed in achieved steady-state trough levels in patients receiving a range of doses i.e. 4-20 mg/day can also be explained by nonlinear PK.

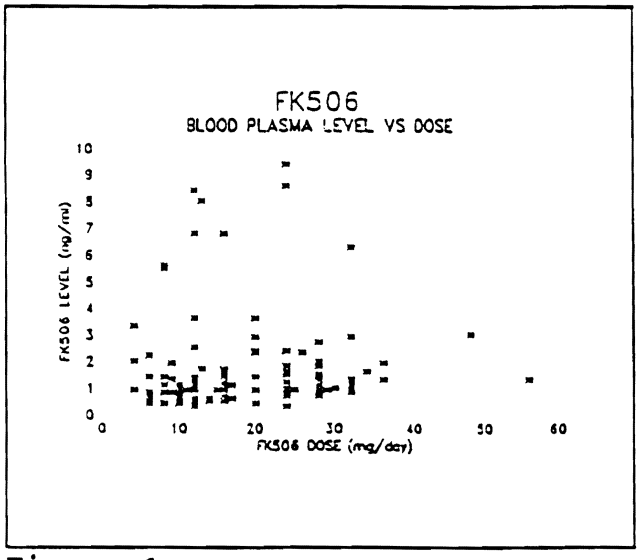

Figure 1

If FK506 exhibited simple

linear kinetics and dose proportionality, the changes depicted

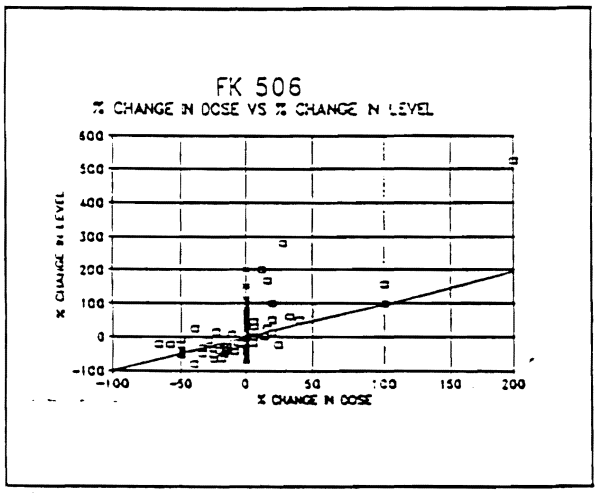

Figure 2

in figure 2 would be proportional and scattered equally about the line of unity.

The relationship between current dose, new dose and the percent change in FK506 level is shown in figure 3. It can be seen

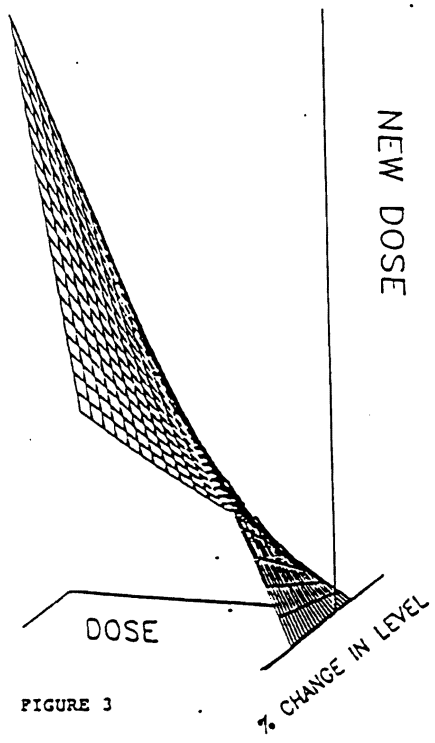

FIGURE 3

that there is relative linearity in this system in the low dose range (dose < 10 mg/day). However, there is a rapid and disproportionate increase in the systems response at higher total daily doses indicative of nonlinear pharmacokinetic behavior. Notice the disproportional increase in the surface area between the nonlinear model and a linear plane (figure #4). In this model the degree

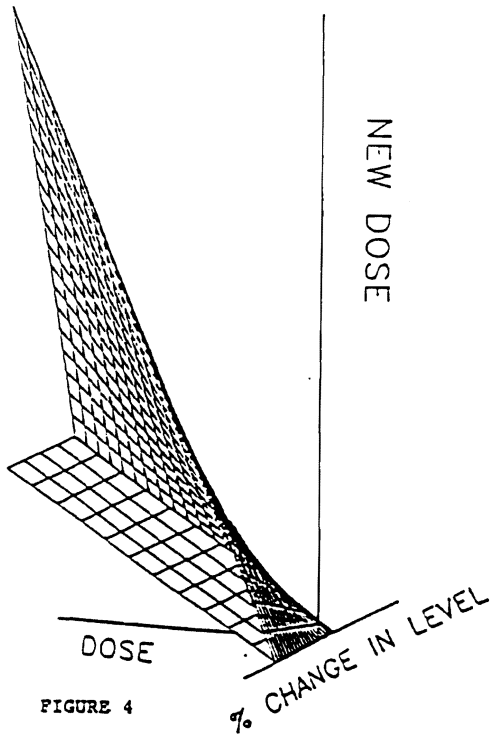

FIGURE 4

of nonlinearity was calculated as the nonlinear surface area divided by the linear surface area and was 1.88 over the normal dosing range (0-50 mg/day). This means that the surface area of the FK506 nonlinear

plane of fit is 1.88 times greater than if it were a linear system, providing an index of its deviation from linearity. This deviation from linearity especially at doses above 10 mg/day helps to explain why FK506 doses can not be used alone to guide therapy without monitoring drug levels as well.

DISCUSSION

We have shown that the use of Artificial Intelligence Modelling System (AIMS) can be an informative tool for understanding very complex, dynamic biological systems such as the FK506 dose concentration relationship. The accuracy and precision of the learned relationships derived from this approach have been prospectively confirmed in clinical studies in transplant recipients (4). The three dimensional graphic representation of this relationship reported here provides a practical and quantitative method for characterizing the kinetic behavior of FK506 over a wide dosing range which is independent but complimentary to standard pharmacokinetic models and methods of analysis. We believe that this graphical method has significant clinical and regulatory implications.

The information derived from this technique combined with the FK506 dosing algorithm should be useful for physicians using effective but toxic agents like FK506 with known or suspected plasma drug level related dose-limiting toxicities. It should help physicians improve the therapeutic index or safety margin of these drugs by avoiding toxic episodes associated with high drug blood levels. This graphical method should be of special interest in the case of pediatric therapy with FK506 since children consistently require more than twice the total daily dose of FK506 compared to adults in order to achieve the same plasma level and thus are in the more nonlinear portion of the plane (7). This graphical method can also be envisaged in quantifying the change that occurs in the surface area of the plane when there is an interaction with other drugs (cyclosporine, ketoconazole, erythromycin, etc).

In addition, this method should be of interest to drug developers and regulatory agencies who are concerned with the appropriate, expeditious and efficient pharmacokinetic-pharmacodynamic characterization of a new drug entity over its proposed dosing range. In the case for example of a promising new therapy for a life-threatening disorder i.e. AIDS, cancer, malignant tachyarrythmias or acute refractory organ rejection, it may not be ethical

or feasible to do standard dose proportional studies or standard intense full sample pharmacokinetic studies in the target population early in drug development to estimate the linearity of a drug's kinetics. However, the graphical method described here for FK506 requires only a pair of steady-state plasma samples for each dose level analyzed. It is therefore likely that this method could be used to screen population/observational databases to estimate the three-dimensional drug surface of a new drug entity.

In the case of observational databases, this method could certainly generate hypotheses to be tested similar to what has been demonstrated for population modelling approaches such as NONMEM (8). In fact, it might be used in conjunction with these population methods to sort out the inter/intraindividual variability in the kinetic parameters and identify important covariates contributing to the variability. In this regard, attention to study design such as providing for intrapatient dose escalation would be desirable to facilitate the mapping of the dose-concentration-clinical response surface as well. Moreover, in the context of randomized controlled studies, it could be used as an adjunct to standard pharmacostatistical methods such as noncompartmental statistical moment theory for delineating dose proportionality and bioavailability. Finally, since this method provides an objective index of linearity over the useful dose range it could serve as a means by which drugs belonging to the same class might be compared.

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Biography

John McMichael is the Director of Applied Medical Informatics at the University of Pittsburgh Transplantation Institute. His research interests include the use of Artificial Intelligence in Pharmacokinetic and Pharmacodynamic modelling, and Intelligent Dosing Methods.