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Review

Kinetic-Effect Models and Their Applications

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This article focuses on mathematical models that analyze the time course of drug effects in humans. Any such model, whether parametric or nonparametric, is termed a kinetic-effect model (KEM). These models serve to describe (interpolation) and to predict (extrapolation) the effect–time profile. KEMs are applicable to many problems in pharmaceutics, pharmacology, and clinical pharmacology.

KEY WORDS: pharmacokinetic–pharmacodynamic modeling; kinetic-effect models; *in vivo* pharmacology; oral controlled-release formulations; system analysis; stochastic control.

INTRODUCTION TO THE DIFFERENT TECHNIQUES OF KINETIC-EFFECT MODELING

Effect–time profiles can be analyzed by both parametric and nonparametric models. Parametric KEMs[2] can be classified as models following a pharmacologic or a system-analysis approach.

Parametric KEMs have the general advantage that they are capable not only of describing the data but also of making predictions. The system-analysis approach models effect–time data in terms of input and output. The analysis focuses on the system (i.e., the human organism) and the dependence of its output or response (i.e., the time course of the effect) upon the input (i.e., drug dosage). The system is calibrated using the simplest input (e.g., an intravenous bolus injection or an oral solution), and a weighting function is obtained that describes the measured output. The response to more complicated modes of input can be predicted by using the technique of convolution. This approach is comprehensively summarized by Smolen (1), who developed it during the late seventies. He also proposed to use this technique to estimate the rate of drug input from effect–time data by using deconvolution. An earlier attempt (2) to analyze effect–time data by the methods of system analysis did not utilize the technique of convolution and required sinusoidal input. This approach is impractical for the analysis of human data.

The pharmacologic approach models the kinetics of a drug response, according to functions that stem from *in vitro* receptor binding kinetics. This method requires concentration–time data in addition to the dosing history and effect–time data. The parameters express the pharmacologic properties of the drug substance (e.g., potency). The following relationship illustrates how the pharmacologic approach combines the models of pharmacokinetics (PK) and pharmacodynamics (PD):

$$D(t) \xrightarrow{\text{PK}} C_p(t) = \text{or} \neq C_e(t) \xrightarrow{\text{PD}} E(t)$$

A series of doses, $D(t)$, produces plasma concentrations which can be measured, $C_p(t)$. PK models describe this process. Depending on the type of dosing, both clearance models (in the case of steady-state infusions) and compartmental models (in the case of intravenous bolus or oral doses) are applicable. Besides $C_p(t)$ a time series of effects, $E(t)$, is measured. A variety of PD models (linear, E_{max}, sigmoid E_{max}, etc.) (3,4) is available to describe how $E(t)$ is elicited by a hypothetical concentration $C_e(t)$. The crucial step of the pharmacologic approach is the link between $C_p(t)$ and $C_e(t)$. When, after a single dose, $C_p(t)$ and $E(t)$ peak simultaneously, it might be assumed that $C_p(t)$ and $C_e(t)$ are kinetically identical and $C_p(t)$ might be used in the PD model directly. This simplification was used in KEMs of beta-adrenoceptor blockers (5).

A delay of the maximum of $E(t)$ compared to the maximum of $C_p(t)$ indicates that $C_e(t)$ and $C_p(t)$ are kinetically different or "out of phase." Theoretically one might assume that the drug molecules have to reach a deep compartment in order to elicit the effect. In reality the situation might be much more complex. It is likely that the measured effect is not a direct result of the interaction of drug molecules with the receptor (as assumed in the PD models) but an integral result of a cascade of events triggered initially by receptor binding and modified by physiologic feedback and by the measurement itself. For the purpose of modeling it is, however, convenient to postulate a compartment that is kinetically different from plasma. Initial attempts to model this very common situation assumed that the drug concentration in a peripheral compartment, which influences the kinetics in the central compartment (plasma), elicits the effect (6,7).

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[2] Abbreviations used: AUC, area under the curve; C_e, concentration which elicits the effect; C_e50, concentration which elicits a half-maximal effect, potency parameter in the E_{max} model; C_p, plasma concentration; D, dose; E, effect; E_{max}, maximal effect; F, bioavailability; KEM, kinetic-effect model; OCRF, oral controlled-release formulation; PD, pharmacodynamic(s); PK, pharmacokinetic(s).

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But there are other situations where either a two-compartment model is not supported by the $C_p(t)$ data or the concentration in the peripheral compartment is out of phase with $E(t)$. For such situations Sheiner and co-workers (8) developed the "effect-compartment model." It was assumed that the effect compartment had a very small volume and that only very small amounts of drug would enter this compartment and would be excreted directly to the outside. Therefore the effect compartment is essentially a mathematical trick and does not alter the kinetics of the other compartments. Under the further assumption that the drug concentration in the effect compartment, C_e, equals C_p at steady state, the KEM of Sheiner *et al.* needed only one additional parameter, k_{eq}, a first-order rate constant, which describes the rate of equilibration of drug between the central and the hypothetical effect compartment. Equations to calculate $C_e(t)$ according to this model have been published (3) for many different PK models and drug inputs.

A technique to analyze concentration- and effect-time data with a nonparametric model was introduced recently (9). Nonparametric "modeling" of the concentration-time data is performed by simply connecting data points. Pairs of concentration and effect measurements are plotted in temporal order to investigate whether C_p and C_e are identical. If this so-called "hysteresis plot" shows a significant area between the ascending and the descending parts of the curve, a parametric link model is introduced [identical to the one described above (8)] to predict C_e from C_p. The optimal estimate of k_{eq} is the one that minimizes the area within the hysteresis loop.

This type of KEM cannot predict an effect-time profile resulting from an altered dose, but it can describe effect-time and C_e-effect relationships that do not, for one reason or another, comply with classical PK and PD models.

APPLICATION OF THE NONPARAMETRIC KEM TO THE TESTING OF BIOEQUIVALENCE

Bioequivalence testing of different formulations of the same drug substance traditionally involves the comparison of the AUCs of the $C_p(t)$ profiles, of the rates of absorption, and of the time points when C_p reaches its maximum. The idea behind these tests is that only formulations with identical $C_p(t)$ profiles can produce the same therapeutic profile and are therefore "bioequivalent." This requirement may, however, be too stringent. Nonlinear relationships between concentration and effect (e.g., the E_{max} model) make it possible that different $C_p(t)$ profiles give rise to identical $E(t)$ profiles.

Provided that the measurable effect is closely related to the therapeutic effect, the comparison of $E(t)$ profiles should provide sufficient evidence of bioequivalence. Effect measurements could be performed both after single doses and within a dosing interval after steady state has been reached. The AUC of the $E(t)$ profile within a dosing interval or the time period during which $E(t)$ exceeds a certain value could serve as measures of bioequivalence.

The interpolation between individual effect measurements and the filtering of random noise could be accomplished by a nonparametric KEM.

Testing bioequivalence by this method could also involve patients where effect measurements could be performed more frequently than concentration measurements (e.g., in the case of hemodynamic effects). This approach could, at least for some drugs, establish therapeutic equivalence. The future will show whether regulatory authorities accept it.

APPLICATIONS OF THE PARAMETRIC KEM (PHARMACOLOGIC APPROACH)

Comparison of Drug Potency

The potency of a drug can be determined in humans by a series of infusions which lead to different steady-state concentrations and by simultaneous effect measurements. The relationship between concentration and effect (PD model) can then be analyzed directly.

This approach is seldom applicable, and investigators try to define drug potency after single bolus doses by measuring the so-called "dose-effect relationship." But the question arises: When, after the dose, should the effect be measured? The potency parameter (ED_{50}) determined in this manner is dependent not only upon the drug substance and the type of effect, but also upon the time of the measurement. The ED_{50} cannot be compared between different drugs, because of their PK differences.

The individual PK properties of the drugs can be included when the potency is compared by means of a parametric KEM. The PK model and link model, if necessary, are optimized for an individual drug, whereas the PD model is the same for all drugs to be compared. The sensitivity parameter (e.g., the slope of a linear PD model) or potency parameter (C_e50 of a E_{max} model) can then be compared. $C_p(t)$ and $E(t)$ data collected after a single bolus dose are sufficient.

A retrospective comparison of the potency of different beta-adrenoceptor blockers has been published recently (10). More conclusive results would, however, be obtained from a crossover study within one group of individuals. Furthermore, the rank order according to *in vivo* potency could be compared with the rank order resulting from *in vitro* receptor binding studies. This comparison could help to identify the receptors involved (11).

Explanation of the Duration of Drug Action

An obvious application of a KEM is the prediction of the duration of drug action. It is a quite general observation that drug effects last longer than concentrations can be measured in plasma. This is, first, a result of the relationship between the drug potency and the detection limit of the assay used to determine plasma concentrations. Moreover, plasma levels may decline faster than the effect. This indicates a nonlinear relationship between C_e and effect. The flexibility offered by parametric KEMs (the combination of different PK and PD models) makes it possible to analyze virtually any set of $C_p(t)$ and $E(t)$ data. Hypotheses about irreversible receptor binding and unknown active metabolites with slow elimination are generally not required.

A typical case are the beta-adrenoceptor blocking drugs. It was discovered quite early (5) that the reduction in exercise-induced heart rate was linearly related to the logarithm of the plasma concentration. The slope of this correla-

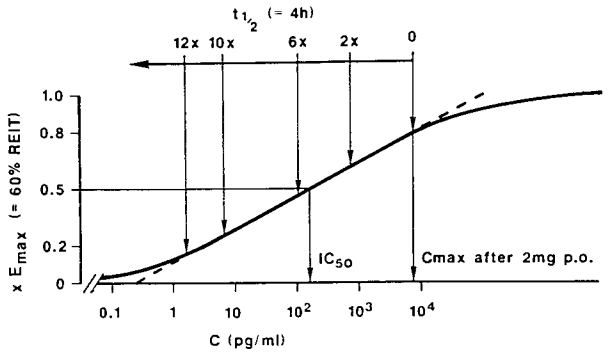

Fig. 1. The concentration–effect relationship of a beta-adrenoceptor blocker (bopindolol) is shown. The effect (reduction of exercise-induced tachycardia) on the ordinate is expressed as a fraction of the maximal effect E_{max}. The plasma concentration is plotted logarithmically on the abscissa. The auxiliary abscissa at the top illustrates the decline in concentration after a single dose in terms of multiples of the elimination half-life ($t_{1/2}$). Two days after the dose (after 12 × $t_{1/2}$) there is still an effect (10% of E_{max}) left [with permission (12)].

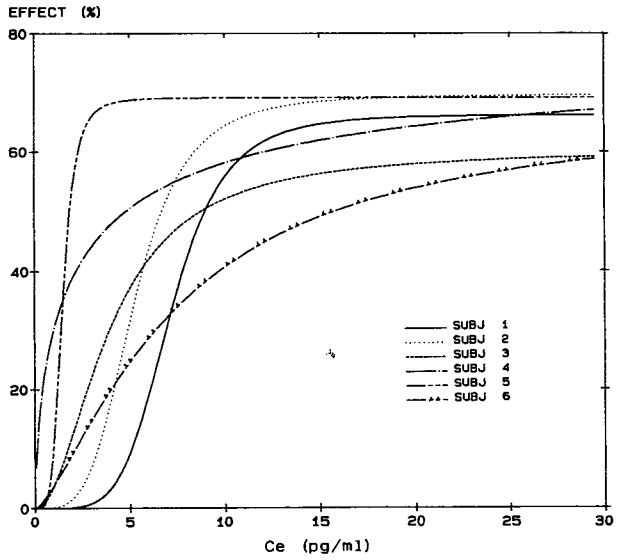

Fig. 2. The *in vivo* concentration (C_e)–effect relationship of the dopamine agonist CQP201-403 is simulated for six healthy volunteers. The KEM consists of a two-compartment PK model, an effect compartment (8), and a sigmoid E_{max} model. The effect is the reduction (percentage) in plasma prolactin levels compared to baseline [with permission (13)].

tion determines just how much slower the effect declines compared to C_p. A rather extreme case is illustrated in Fig. 1.

Simulation of Dosing Regimens

One of the attractions of parametric KEMs is that they can be used to make predictions beyond the limits of the study during which the $C_p(t)$ and $E(t)$ data were gathered. It is useful, as a first step, to plot the C_e–effect relationship and to realize its idiosyncrasies. Figure 2 shows an example of a drug whose PD behavior is described by a sigmoid E_{max} model. The PD model has a sensitive part at low concentrations (0 to 5 pg/ml), where a small change in C_e results in a dramatic change in effect. At higher concentrations (above 15 pg/ml) further increases leave the effect almost unchanged.

Simulations of $E(t)$ after multiple doses (Fig. 3) reflect this PD relationship. When a rather high dose (0.025 mg daily) is selected, a very stable $E(t)$ profile is obtained. Incremental dose reduction causes little change initially, but at a certain dose (0.010 mg daily) the effect fluctuates considerably. This happens when the concentrations reach the sensitive part of the PD model (Fig. 2). However, caution is advisable because the parameters of the KEM may not remain stable during the following extrapolations: single dose–multiple dose, small dose–big dose, and healthy volunteer–patient. Nevertheless, simulations can introduce an element of rational planning which is especially useful during the clinical development of new drugs.

Investigation of Kinetic and Dynamic Instabilities

Simulations of instabilities of the PK and PD characteristics of a drug, which may occur after multiple doses, can help to interpret variability in the results of clinical studies. As an example Fig. 4 shows the influence of a sudden drop in bioavailability on the $E(t)$ profile. The disturbance occurs during the third dosing interval, and it is evident that the resulting changes are minor as long as the dose is high enough to keep concentrations in the insensitive part of the PD model (Fig. 2). A case of PD instability is shown in Fig. 5. The $E(t)$ profile after a single dose (left panel) is compared to a multiple-dose situation (right panel) where the drug has lost potency by different degrees. A reduction in potency or tachyphylaxis is equivalent to a shift of the sensitive part of the PD model (Fig. 2) toward higher concentrations. The result is an $E(t)$ profile that fluctuates widely during the dosing interval (Fig. 5).

The simulations in Figs. 4 and 5 also explain the advantage of selecting a rather high dose for a drug under clinical development. The higher dose tends to alleviate PD variability when the underlying PD model is nonlinear. As a re-

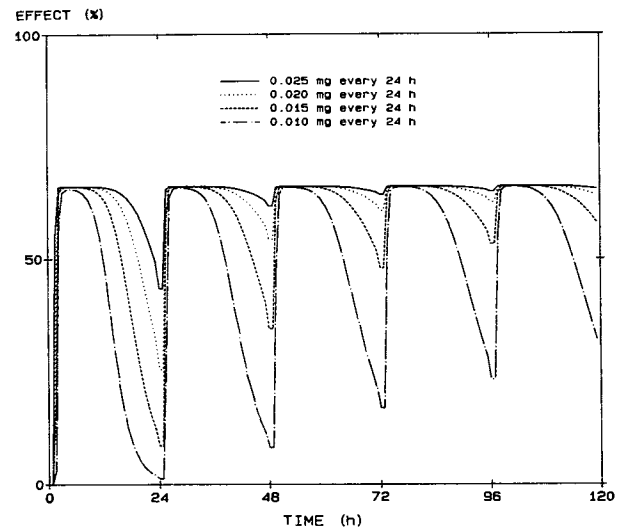

Fig. 3. Simulation of different dosing regimens of the drug CQP201-403. The KEM is taken from subject 1 in Fig. 2 [with permission (13)].

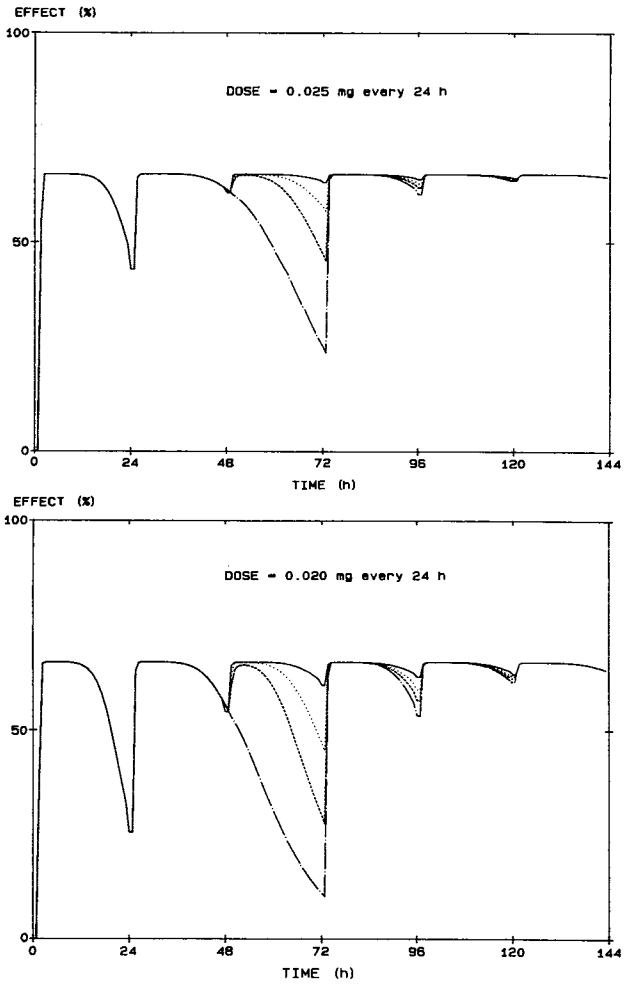

Fig. 4. Simulation of the influence of a sudden drop in bioavailability (F) on the effect–time profile of CQP201-403. The instability (——, F unchanged, system undisturbed; · · · ·, 0.5 × F; ---, 0.25 × F; -·-·, dose is completely missing) occurs only during the third dosing interval and the system recovers thereafter. The KEM is taken from subject 1 in Fig. 2. The upper and lower panels show equivalent simulations of different dosage regimens [with permission (13)].

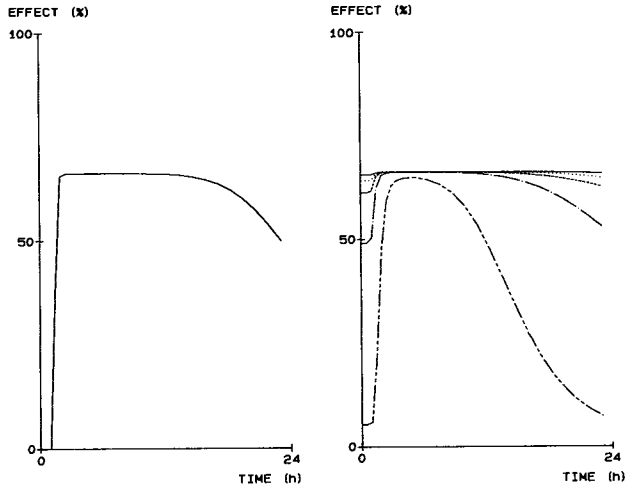

Fig. 5. Simulation of a PD instability. The left panel shows the $E(t)$ profile after a single dose of 0.025 mg CQP201-403. The right panel shows $E(t)$ profiles after multiple doses when tolerance (tachyphylaxis) has developed. Tolerance is expressed as an increase in the potency parameter C_e50 of the PD model: ——, C_e50 unchanged, system is undisturbed; · · · ·, 1.25 × C_e50; ---, 1.50 × C_e50; -·-·, 2.00 × C_e50; ——, 4.00 × C_e50. The KEM is taken from subject 1 in Fig. 2 [with permission (13)].

sult, statistically significant results can be obtained with fewer subjects.

The stability of PK and PD parameters after multiple doses can be demonstrated by testing the predictive performance (14) of a KEM which uses parameters estimated from single-dose data. If the predictive performance is poor (producing estimates with a significant bias), the $C_p(t)$ and $E(t)$ data obtained after multiple doses can be modeled separately and the PK and PD parameters can be compared with the single-dose situation.

Design of Oral Controlled-Release Formulations

Progress in pharmaceutical technology makes it possible to design an oral once-a-day formulation for virtually any drug substance. If a drug substance has a short elimination half-life, then an oral controlled-release formulation (OCRF) will make drug release in the intestine the time-limiting step. The development of an OCRF is traditionally orientated toward an optimal $C_p(t)$ profile. It seems more logical to design an OCRF directly according to a desired $E(t)$ profile. This strategy was applied during the development of an OCRF for the dopamine agonist mesulergine (15).

The following objectives were given at the beginning. (i) Plasma concentrations of OCRFs should, for safety reasons, not exceed the levels obtained after dosing the normal form, which contained 0.5 mg mesulergine. (ii) The normal dosing regimen was 0.5 mg twice a day; the OCRF should be given once a day and should contain 1.0 mg. (iii) Ideally the $E(t)$ profile should stay above 60% inhibition of the baseline plasma prolactin during multiple dosing.

As the first step theoretical *in vivo* release profiles were chosen that had the potential to render the OCRF both safe and effective (Fig. 6). Release profiles in area II were re-

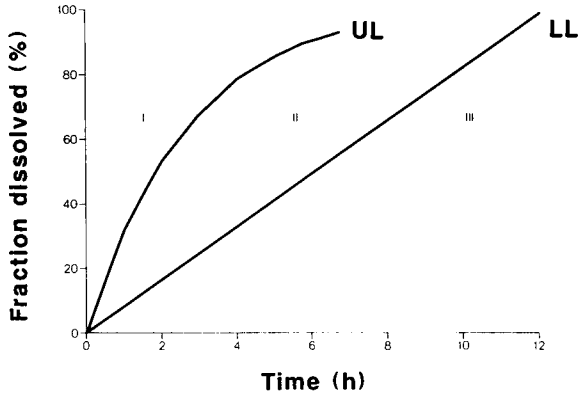

Fig. 6. Release profiles for an OCRF of mesulergine. The profiles describe a theoretical release *in vivo*. OCRFs with a release according to the lower limit (LL) and upper limit (UL) are subjected to further simulations in Figs. 7 and 8. Areas I, II, and III are described in the text [with permission (15)].

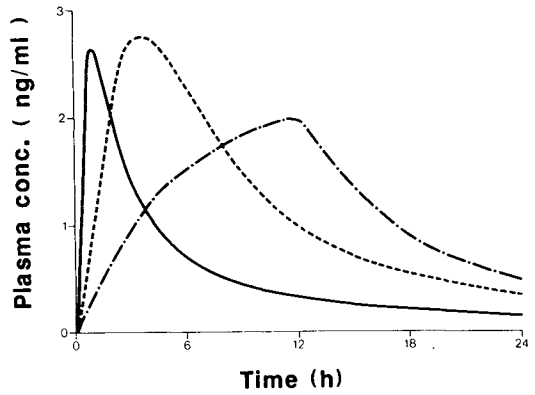

Fig. 7. $C_p(t)$ profiles after a single oral dose are displayed. The two OCRF (---, UL; -·-·, LL) containing 1.0 mg mesulergine are compared to the normal form (——) containing 0.5 mg [with permission (15)].

garded optimal, and the upper limit (UL) and lower limit (LL) of this area characterized two OCRFs for which further simulations were performed (Figs. 7 and 8). Release profiles in area I were too fast to be safe, and profiles in area III were too slow, with the chance that the form was excreted before all the drug content was released.

In the second step $C_p(t)$ profiles were simulated for a single dose of OCRF(UL) and OCRF(LL) using the convolution technique (Fig. 7). The release profile of OCRF(UL) was designed to prevent plasma concentrations from exceeding those obtained after 0.5 mg in a normal form.

Finally, the convolution technique was used again to simulate $C_e(t)$ profiles after multiple doses for both OCRFs. The $C_e(t)$ profiles were translated into $E(t)$ profiles (Fig. 8) by applying the appropriate PD model (sigmoid E_{max}). In spite of marked differences in the $C_p(t)$ profiles (Fig. 7), both OCRFs showed very similar $E(t)$ profiles (Fig. 8) which were well within the desired range. The parameters of the KEM for these simulations were obtained from a study of single oral doses of mesulergine in healthy volunteers (15). Therefore the same precautions as listed above apply.

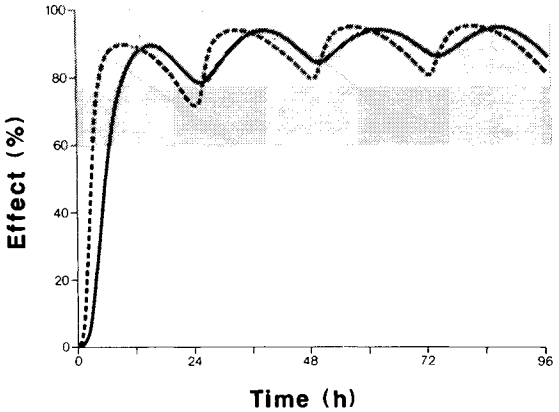

Fig. 8. $E(t)$ profiles after multiple daily doses of OCRF (UL, ---) and OCRF (LL, ——). The effect is the reduction (percentage) in plasma prolactin levels compared to baseline. The shaded area indicates the therapeutically desired effect [with permission (15)].

The OCRFs were unfortunately never tested in humans because the clinical development of mesulergine was stopped for toxicological reasons. The approach was repeated for another dopamine agonist (bromocriptine), and the OCRFs produced the expected effects in healthy volunteers (N. Mazer and J. Drewe, III World Conference CPT 1986 poster demonstration No. 219).

APPLICATION OF THE SYSTEM-ANALYSIS APPROACH TO STOCHASTIC CONTROL

The idea to use the principles of control theory (16) for the optimization of drug dosage in an individual patient has evolved quite recently (17) and systems of different levels of sophistication (18) have been developed. The basic components of a closed-loop stochastic control system with automatic feedback are displayed in Fig. 9 as a block diagram.

Stochastic control is a process that seeks an optimal balance between adapting the parameters of the KEM and controlling the patient's response (output) by adjusting the drug dosage (input). The control operates continuously because the patient is subject to unknown disturbances from the environment and from within him- or herself. These disturbances alter the way the patient responds to the drug and also add random noise to the response. A filter identifies this random component of the raw output and subtracts it, leaving the measured output. In parallel the KEM simulates the behavior of the patient by translating the drug input via transfer functions into predicted output. The discrepancy between the predicted and the measured output causes the adaptor to adjust the parameters of the KEM. The degree of this adaptation is determined by the controller, which also is capable of altering the predicted output by changing the drug input. Moreover, the controller compares the measured output with the desired output. The dual task of adapting the model and optimizing the measured output according to the desired output is at the core of the stochastic process. The desired output is the result of an algorithm (optimization criterion) that takes into account the previous dosing history, the likelihood of side effects, the status of the patient, and possibly the ad hoc judgment of a physician.

Prototypes of such and similar systems are tested in clinical situations where continuous control is required, such as control of blood pressure in intensive care, control of the depth of anesthesia and degree of muscle relaxation

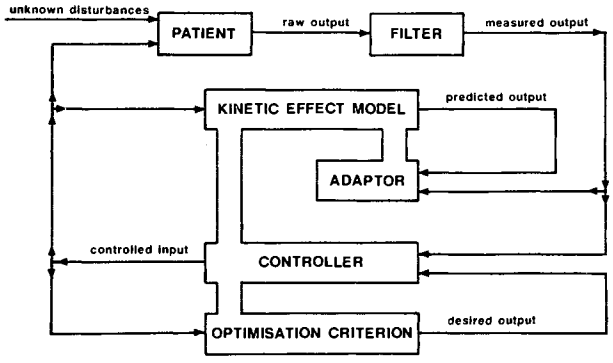

Fig. 9. Block diagram for a stochastic control system to optimize drug therapy for an individual patient.

Table I. Comparison of Methods Related to Clinical Pharmacokinetics and to KEM

Problem	Methods and criteria	
	Clinical pharmacokinetics	KEM
Design of a dosing regimen	Proof of linear PK	Proof of stability of PD
	Clearance, C_p at steady state	$E(t)$ at steady state
	Elimination half-life	Duration of effect
	Optimal range of C_p	Therapeutically desired effect
Design of controlled-release formulations	Optimal $C_p(t)$ profile	Optimal $E(t)$ profile
Test of bioequivalence between different formulations	Comparison of AUCs and absorption kinetics	Comparison of $E(t)$ profiles
Individualization of drug therapy	Therapeutic drug monitoring	Control system with effect as feedback

during surgery, control of postoperative pain relief, and control of blood glucose in diabetes (for a review see Ref. 17). The applications are limited, at present, to disease states where output can be frequently sampled and to intravenously administered drugs with a short duration of action and a rapid elimination.

CONCLUSION

The problems that might be solved by applying techniques related to KEM are presently tackled by methods of clinical pharmacokinetics. Table I shows a comparison of the two methods with respect to topics addressed in this article. In most cases pharmacokinetics and KEM will complement each other. But for some problems, such as the test of bioequivalence and the individualization of therapy, the KEM will provide unique solutions.

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