LEADING ARTICLE

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Using Pharmacokinetic-Pharmacodynamic Relationships to Predict the Effect of Poor Compliance

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Abstract

Since it is difficult to improve patient compliance to drug prescriptions, an alternative is to select a drug with less consequences for poor compliance, that is, a drug that has the capacity of 'forgiveness'. Forgiveness is the property of a drug which, when compared with another medicine with different pharmacokinetics and/or concentration-effect relationships, blunts the consequences of missing one or two doses in a row, or has a greater variability in the timing of intake. Simulations show that drugs with a concentration-effect relationship modelled with an effect compartment, for example a delayed response, have more forgiveness. A marker of forgiveness would be of some help for doctors deciding which drug to prescribe to patients who are poor compliers.

1. Poor Compliance with Drug Therapy

Compliance with therapy is defined as the degree of coincidence between a person's behaviour and the prescription instructions given by their physician.[1] It has been observed for centuries that compliance with doctors' prescriptions is not always perfect, whatever the markers for compliance used. The interest in compliance stems from the fundamentals of pharmacology: that there is for all drugs a dose-effect relationship, related to a concentration-effect relationship at the site of action, which is mediated through the interaction of drug with receptor. Thus, if less than the prescribed dosage is taken, the effect will be less than expected, and if more is taken, the effect will be greater and deleterious effects may occur.

The shape of the dose-effect relationship explains the varying effect of taking less (or more) than the prescribed dose, as illustrated in figure 1. Missing 20% of the prescribed dose when the expected effect is at or near the plateau will change little in the treatment efficacy (A), whereas one or two pills missed at the maximum slope of the dose-effect curve could halve the effect (B).

The idea of a continuous, increasing, relationship between dose and effect is quite old, much older even than the discovery of receptors, and is the basis of drug discovery, development and practice. The existence of this relationship has been confirmed by the progress in pharmacokinetics and pharmacodynamics since the beginning of the last century, as explained in all textbooks of pharmacotherapy. However, for most drugs and their expected clinical effects we do not know precisely the shape of the relationship shown in figure 1, which remains, in these cases, mostly speculative. Nevertheless, this relationship is the rationale for the current belief that poor compliance could alter the effective-

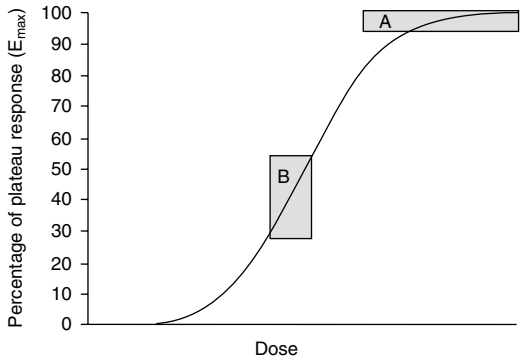

Fig. 1. Relationship between dose and effect, expressed as a percentage of the maximal response.

ness of a prescription. As such, the dose-effect relationship, whether precisely known or pure guesswork, remains the underlying compulsory assumption of any research on the consequences of less than optimal compliance behaviour. In parallel to the expected pharmacological effects and clinical efficacy, a similar reasoning can be made for concentration-dependent adverse effects: their incidence increases with dose or concentration, and the same relationship as that shown in figure 1 is assumed, and sometimes empirically observed.[2]

One challenge in studying varying compliance, from whatever perspective, including its consequences for the expected efficacy, is that no single feature can express it. First, there is no single category of noncompliers, but a spectrum of variable compliance with, roughly, five patients in about six who do not comply satisfactorily and one patient in about six complying poorly, taking less than 40% of prescribed doses with long and widely variable administration intervals.[1] Secondly, several patterns of less than full compliance can be defined: (i) delay in the beginning and/or the termination of treatment; (ii) intake of nonprescribed drugs; (iii) omission of one or several doses; (iv) errors in the size of the dose to be taken; and (v) inappropriate and irregular timing in administration. Thus, instead of noncompliance, it seems more appropriate to speak of poor compliance.

Simple statistics can summarise a patient's compliance history, although none incorporate all the features of compliance. Different markers may be calculated: the percentage of days with accurate dose intake (or compliance rate), the percentage of prescribed doses taken, the percentage of drug holidays (days without drug intake), the time variability in drug intake, the percentage of too short or too long administration intervals, the median and quartiles of administration intervals.

The diversity of the pattern of poor compliance and the difficulty in improving compliance through changes in patients' behaviour have led to more focus on the drug itself. Not all drugs have the same relationship between dose and concentration, and concentration and effect, respectively. The idea that the consequences of noncompliance vary with the particular drug has initiated research aimed at characterising which drugs are more demanding than others in terms of compliance. This has led to the concept of 'forgiveness'. For instance, drugs with a very narrow therapeutic index (for example antiarrhythmic agents) would be preferred with forgiveness, i.e. with the capacity that missing (or repeating) one or a few doses will not be of consequence for the expected efficacy (or safety). Finally, a difficulty in exploring the potential consequences of less than optimal compliance is our inability to link the pharmacological effect of a drug with its efficacy on a clinical outcome. Although many models are potentially appropriate, there is, in most cases, very little evidence available to select the best one.[3]

2. Capacity for Forgiveness

A drug for which a dose can be missed without having too much effect on the expected benefit and safety of the prescription is said to have the property of forgiveness. The notion of treatment forgiveness has been defined by Urquhart[4] as the property of a drug, given as a repeated treatment, to forgive the omission of one dose, or several doses in a row, without a loss of efficacy. Some intuitive examples come to mind: (i) drugs that are stored somewhere in the body in a releasable

form;[5] (ii) drugs with a very long elimination half-life, so the steady-state blood concentration does not change very much when a dose is missed;[5] (iii) drugs with an indirect effect model, i.e. a delayed effect compared with blood concentration; and (iv) drug regimens at the plateau of the dose-effect curve (see figure 1). The last situation depends on the prescription, whereas the former depend on the drug itself and its interactions with the body. These cases are considered in this article. They should be investigated with proper approaches in order to confirm the anticipated forgiveness and to provide a formal framework for identifying drugs with this capacity. We will limit the derivation to efficacy, although a similar approach can be applied to concentration-dependent adverse effects. Following the last remarks of the previous section, we will assume that a sustained pharmacological effect, with a given average value, is required for the expected clinical efficacy.

3. Labelling for Compliance

Knowledge of the consequences of poor compliance for a particular drug belongs to the general framework of prescription information, as does other information in the drug data sheet. Such knowledge is useful for doctors to manage compliance and to allow them to put emphasis on drugs with low forgiveness. Recommended dosage regimens are chosen for all drugs from extensive clinical experience during phase II and III trials. Although it is likely that compliance is better in clinical trials, this has never been documented, and the safety and therapeutic implications of poor compliance are rarely explored during clinical trials. Thus, dosage recommendations reflect a set-

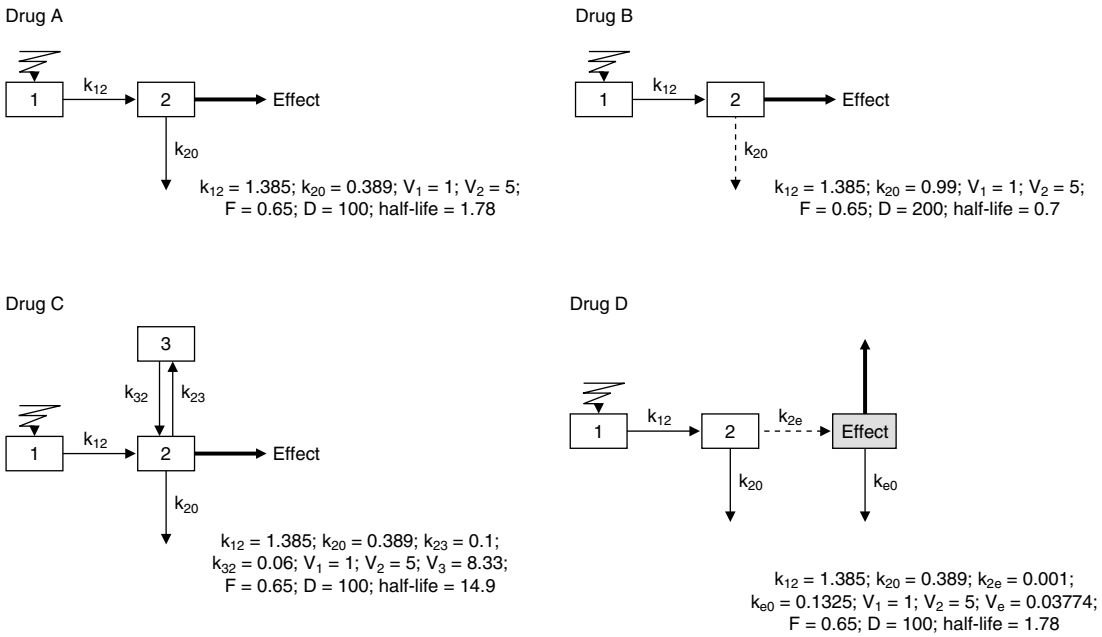

Fig. 2. Four drugs, A, B, C and D, with different pharmacokinetic-pharmacodynamic models (see figures 3 and 4). For drugs A, B and C there is a direct relationship between the concentration in the central compartment 2 and effect: $E(t) = 2 \bullet C_2(t)$. For drug D, the effect compartment causes an indirect pharmacokinetic-pharmacodynamic relationship: $E(t) = C_e(t)$. **1** = absorption compartment; **2** = central compartment; **3** = peripheral compartment; **e** = effect compartment; $\mathbf{C_x(t)}$ = concentration in compartment x at time t; **D** = dose; **E(t)** = effect at time t; **F** = bioavailability; $\mathbf{k_{xy}}$ = intercompartmental transfer rate constant; $\mathbf{k_{x0}}$ = elimination rate constant from compartment x; $\mathbf{V_x}$ = volume of compartment x (all expressed in arbitrary units).

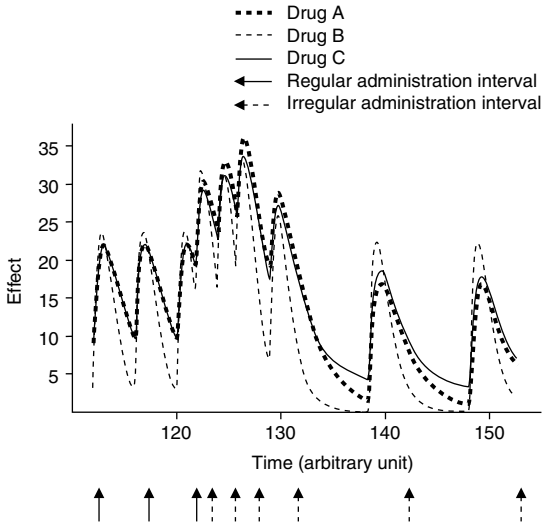

Fig. 3. Examples of the impact of pharmacokinetics on forgiveness. Drug B has a half-life half that of drug A; drug C has a peripheral compartment and the same half-life as drug A.

ting of drug use that may be different from current medical practices.

It would be a great help for a prescriber to know whether he/she could authorise or should restrict variability in the time interval between two consecutive administrations and the dosage errors which should not be exceeded for each drug. In the interests of both accuracy and full disclosure, drug labelling should include some information on the consequences of the major patterns of noncompliance. In addition to meeting the ethical standard of full disclosure, labelling that includes such information would also provide a rational basis for efforts to improve patient compliance, the outcome of treatment and the quality of ambulatory care. In this perspective, the concept of forgiveness looks promising.

4. Prediction of the Effect of Poor Compliance and Forgiveness

The only approach that can be used to predict the effect of poor compliance for different drug-specific pharmacokinetic-pharmacodynamic relationships is *in silico* studies.[6] This approach will be used here to prove that forgiveness occurs in particular pharmacokinetic and pharmacodynamic situations. It involves a computer simulation starting from the mathematical models used to describe the kinetics of an *in vivo* pharmacological response. Usually, the models considered involve a pharmacokinetic model, a pharmacodynamic response model with a pharmacodynamic effect summary. This intermediate pharmacodynamic effect can also be related to a clinical effect using physiological models or statistical models (such as logistic regression, for example).

The results of these simulations allow us to predict therapeutic failure or rebound effects on clinical outcomes, when the model linking the pharmacological and clinical effect is known or can be guessed, or only on the expected pharmacological effect when it cannot, during recurrent drug holidays (i.e. two to three or more sequential days without drug administration), variability in administration intervals or variability in pharmacokinetic properties, assuming the superposition principle applies. For a given drug, knowledge of its pharmacokinetic-pharmacodynamic relationship is required to identify its capacity for forgiveness. In addition, we will illustrate the relationship between the pharmacokinetic-pharmacodynamic characteristics of a drug and its capacity for forgiveness.

5. Examples

We compared the time dependence of the pharmacological effect of four drugs with different pharmacokinetic and pharmacodynamic properties. The main features of their pharmacokinetic and pharmacodynamic models are shown in figure 2. Drugs A, B and C differ by their pharmacokinetic features: B has an elimination half-life half that of A, and C is stored in a peripheral compartment that will blunt variations of the concentration of the drug in the central compartment. Drug D differs from all others by its indirect relationship between concentration in the central compartment and effect, modelled by an effect compartment.[7,8] Drugs A, B and C have a direct pharmacokinetic-pharmaco-

dynamic relationship, i.e. their site of effect is the central compartment.

The pharmacological effect over time is obtained by computation (figure 3 and figure 4). The comparison started after steady state (more than 10 half-lives) has been reached through regular drug administration, i.e. full compliance. Poor compliance is simulated by irregular administration intervals. We did not use simulation to account for variability of model parameters, which should be done if one has to compare real drugs.

5.1 Pharmacokinetic Forgiveness

In figure 3, the comparison between drugs A, B and C suggests that a longer half-life and a peripheral compartment are better for forgiveness, since the variation of the effect is much greater with drug B.

5.2 Pharmacodynamic Forgiveness

In figure 4, the improvement of forgiveness with an indirect concentration-effect relationship is striking. The effect compartment smooths the variation of the effect due to irregular drug intake intervals. Thus, drugs with indirect concentration-effect relationships have a better capacity for forgiveness as compared with those with direct concentration-effect relationships, since the peak effects are lower (less adverse effects) and trough effects are higher (more sustained clinical efficacy). Furthermore, the 'smoothing' effect of the indirect relationship appears to be greater than that resulting from increased half-life or a peripheral compartment (compare figures 3 and 4).

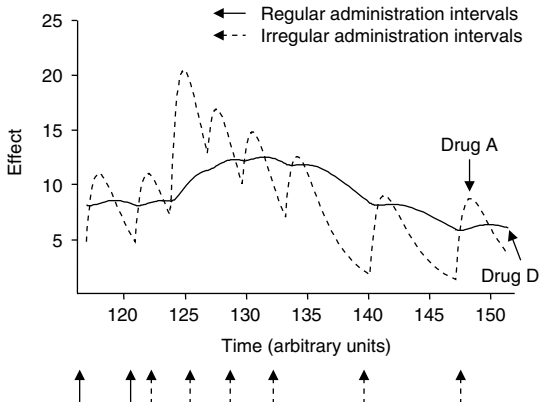

Fig. 4. Examples of the impact of concentration-effect relation on forgiveness. The unshaded area under the concentration-time curve shows drug A with a direct concentration-effect relationship [$E(t) = C_2(t)$] and the shaded area under the concentration-time curve shows drug D with an indirect concentration-effect relationship [$E(t) = C_e(t)$]. $\mathbf{C_2(t)}$ = concentration in central compartment at time t; $\mathbf{C_e(t)}$ = concentration in effect compartment at time t; **E(t)** = effect at time t.

6. Conclusion

Intuitively, poor compliance with a short half-life drug will induce lower trough concentrations when the administration interval is increased, and higher peak concentrations when the administration interval is decreased. If the drug has a direct effect model, this will lead to a less sustained pharmacological effect and a higher rate of concentration-dependent adverse effects at peak drug concentrations. The above computations and simulation support these intuitive thoughts, and added that, more generally (everything else being equal), drugs with an indirect effect have a more sustained pharmacological effect.

The major conclusion from the above derivation is that drugs may differ greatly in terms of capacity for forgiveness, depending on their pharmacokinetic and pharmacodynamic properties, i.e. their specific chemistry, metabolism and mechanism of action. Therefore, ideally, physicians should be able to select the proper drug, for instance in narrow therapeutic range situations and/or for patients who are more likely not to comply with the prescribed regimen, on its capacity for forgiveness. However, in order to achieve that in practice, prescribers should have access to appropriate indicator(s) of forgiveness.

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