VOLUME 3 NUMBER 6 JDTAEH 3 [6] 411-478(1996) ISSN 1061-186X

JOURNAL of DRUG TARGETING

An International Forum on Drug Delivery and Targeting

March 1996

CONTENTS

(continued on back cover)

Journal of Drug Targeting, 1996, Vol. 3, pp. 411-415
Reprints available directly from the publisher
Photocopying permitted by license only

Editorial

An Integrated Pharmacokinetic and Pharmacodynamic Approach to Controlled Drug Delivery

DOUWE D. BREIMER

Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden University, P. O. Box 9503, 2300 RA Leiden, The Netherlands

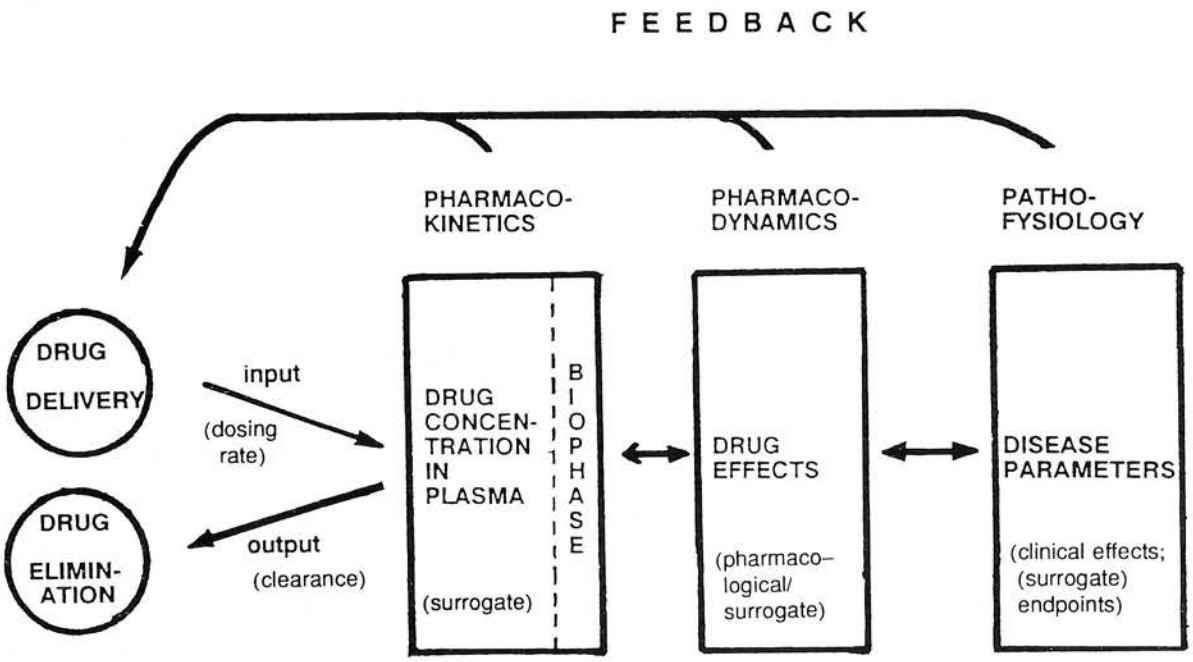
INTRODUCTION

The field of new drug delivery system research and development has come to great blossom over the past 15–20 years. Numerous systems have been designed and some have actually reached the phase of practical application. Technologically they represent major feats characterized by rate- and/or time-controlled drug release, i.e. delivery of active ingredient at a predetermined rate and/or time. These include polymeric devices and osmotic systems for the oral delivery of drugs and patches for delivery across the skin. Their release rate is most often of a zero-order nature that should lead to less fluctuating drug levels than with conventional pharmaceutical formulations. The potential therapeutic advantage of such more or less constant delivery rates have been claimed to be severalfold: in vivo predictability of release rate on the basis of in vitro data, minimized peak plasma levels and thereby reduced risk of adverse reactions, predictable and extended duration of action, reduced inconvenience of frequent redosing and thereby hence improve patient compliance. However, in relatively few cases such potential advantages have in fact proved to be of great therapeutic significance. Only too often major emphasis is placed on the relatively flat plasma level profile that is achieved (pharmacokinetics), rather than on the improved drug effect profile (pharmacodynamics in disease state).

In figure 1 the inter-relationship between drug delivery, pharmacokinetics, pharmacodynamics and pathophysiology is shown schematically.

In this scheme it is clearly indicated that drug concentration in plasma is no more than a ''surrogate'' for pharmacological and clinical effects, the relevance of which can only be judged if the relationship between pharmacokinetics and pharmacodynamics (PK/PD) is well established. In other words, only on the basis of quantitative information of this relationship the desired optimal drug concentration time profile can be defined. This is then to be translated into desired characteristics of the drug release profile from the delivery system (feedback, see figure 1). In fact, what is needed is pertinent information on the kinetics of drug effects and its (potential) dependence on the rate and time of drug input. This is what controlled drug delivery should be aiming at: optimal drug treatment through rate and time programmed drug delivery. Therefore in the design and development of such systems at least two fundamental questions should be asked and answered prior to their further development (Breimer, 1993a):

1. a *clinical pharmacological* one in terms of the optimal rate and timing at which the drug should be delivered; this requires profound knowledge of the concentration-effect relationship of the drug in man and its dependence on disease and rate and time profile of drug input (e.g. continuous versus pulsatile as extreme input profiles);
2. a *pharmaceutical technological one* in terms of the most suitable system that can provide the required rate and time specifications via the desired route of administration; this requires knowledge on the capacity, flexibility, rate and time programming possibilities.



Currently these questions are often studied in the reverse order, i.e. new drug delivery systems looking for a suitable drug candidate. Ideally, however, relevant clinical pharmacological studies are undertaken in man with the drug candidate looking for a suitable delivery system. This requires PK/PD modelling experiments with rate and time controlled drug input as important variables to be studied. Rate-controlled delivery systems of a generic type may be useful tools in this respect (Breimer et al., 1984; Soons et al., 1989).

PK/PD MODELLING

The relevance of PK/PD modelling for drug research and development in general is beginning to be well appreciated (Peck et al., 1992). Its primary objective is to identify some key properties of a drug *in vivo*, which allow the characterization and prediction of the time course of drug action under physiological and pathophysiological conditions. The modelling of direct pharmacological effects usually consists of three components: 1. a pharmacokinetic model, characterizing the time course of drug (and metabolite) concentrations in blood or plasma; 2. a pharmacodynamic model, characterizing the relationship between concentration and intensity of effect; 3. often, a link model that serves to account for the frequently observed delay or other time effects of the pharmacological effect relative to the plasma concentration (Holford and Sheiner, 1981). This approach of ''effect compartment modelling'' has proved to be very successful for quite a number of drugs; for several others no delay in drug distribution from plasma to the site of action has been observed and therefore a link model is not needed. Alternative, more physiologically and mechanistically based models have been proposed which are in particular relevant to indirect pharmacological effects, i.e. when the delay between plasma-concentration and effect is largely determined by slowly developing or declining (secondary) effects, rather than by slow distribution to the site of action (Jusko et al., 1994).

The most important lesson to be learnt from PK/PD modelling exercises for the field of drug delivery is that the time course of drug effects can be and generally is quite different from the time course of drug concentrations. In other words, without PK/PD information the effect time course cannot be predicted on the basis of pharmacokinetics alone. For example, a short plasma elimination half-life will not necessarily imply short duration of action. This has clearly been recognized as early as 1966 in pioneering studies by G. Levy, showing that the decrease of pharmacological effect intensity of several reversibly acting drugs is a function of the slope of the drug's intensity of effect versus log concentration relationship (in the linear part) and

the drug's elimination rate constant (Levy, 1966). Two drugs with similar elimination half-lives but very different slopes in concentration-effect relationships will have very different durations of effect. In terms of drug delivery this implies that for the compound with the steeper slope a controlled delivery system may well be indicated, whereas this is not the case for the compound with an intrinsically long duration of action. Examples can be found among the β-blocking agents, e.g. pindolol versus propranolol (Carruthers et al., 1985). Of course, there are also cases where duration of action is much more dependent on plasma kinetics if effect slopes between two compounds are relatively steep and similar, e.g. nifedipine versus amlodipine. Here, controlled delivery is indicated for nifedipine (elimination half-life 2–4 hours) but not for amlodipine (elimination half-life 35–50 hours).

It should furthermore be understood that if the relationship between concentration and effect is of a sigmoidal nature, i.e. a maximum is reached with higher concentrations, there will be no decline of drug effect intensity in spite of decreasing plasma-concentrations until the range is reached where the slope will determine the time course of declining effect. An example of this is omeprazole, which seems to be absorbed and eliminated rapidly, but exhibits profound proton pump blocking effect for at least 24 hours.

Observations in studies where pharmacological effect intensity only gradually increases after rapid i.v. injection have triggered the concept of ''effect compartment'' modelling. This often reflects a slow access of the drug to the site of action (effect compartment), but can also be caused by processes secondary to drug-receptor interaction which operate at a different than instantaneous time scale. Several examples of drugs exhibiting ''distribution delays'' are known, like some benzodiazepines, neuromuscular blocking agents, digoxin. Examples of drugs exhibiting ''effect delays'' include corticosteroids, oral anticoagulants, growth factors, cytokines and probably several other regulatory protein and peptide drugs. Again, for such compounds controlled drug delivery cannot be based on their (often rapidly fluctuating) plasma kinetics; PK/PD information is essential to achieve optimal results. It should also be noted that with such compounds no rapidly changing effects with time can be achieved, which might occasionally be desirable for chronotherapeutic reasons.

A clear example of the application of PK/PD modelling to optimize controlled drug delivery is represented by somatostatin in suppressing growth hormone levels in acromegaly (Mazer, 1990). It was shown that continuous subcutaneous infusion is the optimal delivery regimen. Once the PK/PD relationship is established and validated under different conditions, also simulation experiments of various controlled delivery regimen may be quite helpful for this purpose.

TIME DEPENDENCE

PK/PD relationships are usually established in clinical pharmacological studies in healthy subjects under relatively standardized conditions. For this information to be relevant for controlled drug delivery, it is very important that its potential rate and time dependence be elucidated. It is for example not true that the maintenance of constant concentrations (steady-state) through zero-order input rate is always associated with a constant pharmacological effect intensity. Theory, as outlined under PK/PD modelling, dictates that this should in principle be the case. However, tolerance development and circadian variation in the (patho)physiological systems to be influenced, are two important factors that may cause major deviations. A well-known example of tolerance development is that of continuous delivery of nitroglycerine by the transdermal route. On the other hand it is now reasonably well established that this can be prevented if delivery takes place at 12 hours' on-off cycles; in other words, time programming in drug delivery is needed to avoid tolerance development. Relatively simple PK/PD studies (i.v. infusion studies with different duration and different intervals) with nitroglycerine at an early stage of patch development could have provided this very relevant piece of information. Then transdermal nitroglycerine treatment could have been optimal from the beginning onwards. With respect to circadian variability, also well-documented examples are available. For example, continuous i.v. infusion of famotidine (a H2-blocking agent) leads to constant plasma levels, but constant effect levels (high pH in the stomach) are only reached between 2 a.m. and 1 p.m. After 1 p.m. a very considerable decrease in pH is seen. This is most likely caused by food intake and intrinsic diurnal variation in H+-secretion. Similar results have been obtained during continuous infusion with ranitidine. In terms of drug delivery this clearly implies the need for time control of different delivery rates at different times of day, if indeed a continuously high pH should be desirable.

Also the severity of disease may be quite different at different times during a 24 hours' cycle. Dethlefsen and Repges (1985) studied the incidence of

severe asthmatic attacks in more than 1500 patients and found that these occur predominantly in the early morning hours and not during day-time. It is therefore questionable whether drug treatment of asthma with theophylline controlled release preparations, which aim at a plasma level profile as constant (flat) as possible for 24 hours, is most optimal. Indeed, Staudinger (1990) has shown that a time-controlled theophylline formulation aiming at maximal drug concentrations during early morning hours exhibited better improvement of lung function than a zero-order release product. PK/PD is clearly time-dependent under such circumstances, and this should be investigated in the context of appropriate experimental protocols leading to relevant information with respect to time specifications for controlled delivery. The fields of chronopharmacology and chrono(patho)physiology are rapidly emerging and should be taken seriously by those engaged in drug delivery research (Hrushesky et al., 1991).

RATE DEPENDENCE

The other very important variable that may influence both pharmacokinetics and pharmacodynamics is the rate of drug input (absorption rate for conventional formulations). Differences in such rates will usually result in differences in peak times (t_{max}) and peak concentrations (C_{max}) and thereby in intensity of drug effects. Since high peak levels are sometimes associated with too intensive effects, a potential advantage of controlled delivery is that these can be avoided. This may well be explained in the context of the same PK/PD relationship for an entire concentration range, independent of the rate at which concentrations are reached. However, there may be instances where the *rate of change* of plasma concentration as determined by the rate of input, may be of major influence on the PK/PD relationship. In other words: at one plasma concentration differences in effect intensity may be observed, dependent on the rate at which they were reached. The best documented example in this respect is nifedipine. This calcium channel blocker was originally marketed in a capsule formulation, from which it is rapidly released and absorbed and later on also in a sustained release tablet formulation. Extent of bioavailability from the two preparations is comparable (average value of about 50%), but there is a profound difference in plasma level versus time profile (Kleinbloesem et al., 1984a). The capsule preparation leads to rapid and relatively high peak concentrations, whereas the tablet gives a relatively flat plasma level profile. In fact the latter is an example of a ''flip-flop'' situation: the rising part of the curve represents drug elimination, whereas the decreasing part is a reflection of the delayed release and absorption of nifedipine.

Interestingly, it was observed that the increase in heart rate (side-effect) was far less with the tablet than with the capsule in all subjects, whereas with both preparations a slight blood pressure lowering effect was achieved in the normotensive subjects. This observation was further substantiated in a subsequent study in which nifedipine was administered rectally by the OSMET—osmotic pumps to healthy subjects for 24 h (Kleinbloesem et al., 1984b). Concentrations rose relatively slowly and steady-state was reached after 6–10 h; there was no increase in heart rate at all and a smooth decrease in blood pressure was noted. This led to the hypothesis that the rate-of-increase of plasma concentration nifedipine (rather than absolute concentration) is a determinant factor for the drug's haemodynamic effects. Clear evidence for this was obtained in a study in which nifedipine was given by two i.v. regimens, each to produce the same steady-state concentration, but attained gradually (infusion protocol) or rapidly (injection-infusion protocol). No increase in heart rate occurred with the slow regimen, whereas a substantial and long-lasting increase was seen with the rapid regimen (Kleinbloesem et al, 1987). In the former case a gradual decrease in blood pressure was observed, whereas in the latter case hardly any blood pressure lowering effect occurred. Clearly, control of the rate of drug input is an essential feature in nifedipine therapy: side-effects can be avoided and desirable effect enhanced in this way.

It seems not unreasonable to claim that the enormous success of Procardia XL, which is nifedipine in an oral osmotic once-daily formulation, is based on the principle of this clear dissociation of undesirable (increase in heart-rate) and desirable (blood pressure lowering) effects. Current sales figures of this product of over one billion dollar per year on the American market, make this the most successful controlled drug delivery product ever. It clearly illustrates what competitive advantage can be achieved if the concept of a controlled delivery profile has a solid PK/PD basis which is further substantiated by clinical studies. This issue also gives rise to interesting questions concerning bioequivalence assessment of similar nifedipine formulations. Can this be based on pharmacokinetic

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.