Target concentration intervention: beyond Y2K

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Target concentration intervention (TCI) is proposed as an alternative conceptual strategy to therapeutic drug monitoring (TDM). It is argued that the idea of a therapeutic range has limited the interpretation of measured drug concentrations and diminished the anticipated clinical benefit to patients by use of an oversimplified pharmacodynamic model. TCI on the other hand embraces pharmacokinetic and pharmacodynamic concepts and uses the idea of a target effect and associated target concentration to make rational individual dose decisions.

Keywords: target concentration intervention, therapeutic drug monitoring

Target Concentration Intervention (TCI) and Therapeutic Drug Monitoring (TDM)

The Y2K problem

In her lead article for this series Shenfield [1] seeks a role for therapeutic drug monitoring (TDM) beyond the year 2000. Her discussion and that in ensuing articles [2–4] focus almost exclusively on the measurement and interpretation of drug concentrations in relation to a 'therapeutic range'. I contend that 'therapeutic drug monitoring' and 'the therapeutic range' are the year 2000 (Y2K) problem for clinical pharmacologists. The Y2K problem arose from a limited perspective on how to represent dates in computer storage. Only the year index within a century is stored and it is assumed that the century and millenium are understood by default. TDM manifests a limited perspective by using concentrations with the unstated assumption that the effects arising from those concentrations are understood by default. The therapeutic range limits attention to concentrations within empirically chosen bounds.

Target concentration intervention

It is time to pay attention to the concentration effect relationship and to think about the broader strategy of how to individualize drug treatment with the aid of drug concentration measurements. TDM has become tedium because of its focus on the passive concept of 'monitoring' and its failure to explicitly take drug effects into account. The synthesis of pharmacokinetic (PK) and pharmaco-

dynamic concepts (PD) provides a sound intellectual framework for using all available information about the patient and the disease in order to interpret effect and concentration observations. Successful interpretation will lead to a positive decision to select the best dose to achieve the desired therapeutic effect. This is target concentration intervention (TCI) [5].

Target concentration intervention is a treatment strategy. As such it is comparable with other forms of treatment and can be evaluated using broadly similar techniques (*vide infra*). TDM has rarely been evaluated as a treatment strategy. Most commonly forecasting methodologies are compared to see if they can predict future concentrations (or effects) but to my knowledge no formal tests of alternative therapeutic ranges have ever been performed.

Target concentration and therapeutic range

Sheiner & Tozer [6] proposed the target concentration strategy (TCS) as an algorithm for rational dose individualization but this idea has rarely been recognized. The essential feature of the algorithm is to use a *target concentration* rather than a range. The goal is to achieve this target using initial doses based on typical pharmacokinetic parameters for the individual predicted from patient specific factors (covariates) such as body size and renal function. Drug concentration measurements are used solely to individualize the PK parameters in order to predict future dosing. TCS does *not aim* to have the *measured* concentration equal to the target concentration. This is a key distinction from TDM which *aims* to have the *measured* concentration within the therapeutic range. TCS explicitly uses a PK model to understand what makes the patient an individual while TDM offers no

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Target	Dose model
Initial peak	Loading dose = Target concentration $\times$ volume of distribution
Average steady state	Maintenance dose rate = Target concentration $\times$ clearance

Table 1 Simple dose models for target concentrations.

direct guidance and leaves the prescriber to use any method to get the concentration within range.

The therapeutic range concept suffers from two strategic deficiencies. First the idea of a range introduces uncertainty into exactly how to prescribe the desired dose. It is of course impossible to administer simultaneously a range of doses yet a range is the inevitable consequence of aiming for a range of concentrations and the prescriber must use some process to choose a specific dose. TDM and the therapeutic range give no guidance for making this choice.

On the other hand, the target concentration is directly linked to a specific dose for an individual –not a range of doses. Dose predictions are usually simple applications of elementary PK principles [7] (Table 1), e.g. if the target is the steady state average concentration then the dose rate is simply the product of the individual estimate of clearance and the target concentration. Aiming for a specific target provides unambiguous guidance for the prescriber. The target concentration is separated from the concentration–effect relationship. The intellectual process required to choose a target concentration is independent of any consideration of pharmacokinetics. Selection of a target concentration requires an understanding of the concentration–effect relationship, i.e. pharmacodynamics, for both desired and undesired effects. The target concentration is chosen to optimize the balance between these effects.

The second deficiency of the therapeutic range concept is the implicit assumption that all concentrations within the range are equally desirable. This assumption implies a 3 step concentration effect relationship. Below the lower end of the range the patient will get no benefit, anywhere within the range the patient will be OK and above the upper end the patient will experience unaccept-

able toxicity. This is patently naïve but is the apparent model used by TDM practitioners today.

PK, PD and disease progress

The full target concentration strategy requires the selection of a target effect then the target concentration to achieve that effect. The target effect may vary with time as the disease state changes. The time course of disease progress (disease kinetics) has had little quantitative study but it is just as important a part of the process as the pharmacodynamic and pharmacokinetic aspects [8].

Target effect

What do we know?

Table 2 illustrates the rather sparse information we have about the pharmacodynamics of drugs which are commonly associated with TDM. Only theophylline has been sufficiently characterized to predict the concentration effect relationship. Note that $E_{\max}$ for theophylline reflects the maximum improvement from baseline [11]. If $E_{\max}$ was achieved, the actual PEFR would be the sum of the baseline PEFR and $E_{\max}$. Incorporation of a disease progress model gives a more complete picture [10] at different times and concentrations.

How can we find out?

Defining the concentration effect relationship using clinically relevant effects is challenging. It has become increasingly common to describe the clinical pharmacology of a drug based on the use of a biomarker and while this may be helpful for guiding drug development the pharmacodynamics of a clinical endpoint are needed

Drug	Target effect	$E_{\max}$	EC_{50}
Aminoglycosides	'Cure'	?	?
Cyclosporine	'Prevention of rejection'	?	?
Phenytoin	'Prevention of seizures'	?	?
Digoxin	'Control of atrial fibrillation'	?	?
Theophylline [9, 10]	'Normal PEFR'	344 l min ⁻¹	11 mg l ⁻¹

Table 2 Target effects and pharmacodynamic parameters for selected drugs. $E_{\max}$ is the maximum effect due to the drug, EC_{50} is the concentration producing 50% of $E_{\max}$. PEFR is peak expiratory flow rate.

to apply TCI. The population modelling approach has been used to understand concentration effect relationships and can be used with a variety of measures of clinical effect [12]. The easiest to model are those based on a continuous measure of effect, e.g. PEFR. However, clinical endpoints are more commonly categorical, e.g. cure of infection, prevention of organ rejection, or perhaps based on frequency of an event, e.g. seizure frequency. Methodology now exists that can incorporate a common pharmacokinetic-pharmacodynamic approach to all these measures [13].

Target concentration

What do we know?

The target concentrations shown in Table 3 are mainly guesses based on the usual therapeutic range. The theophylline target concentration (10 mg l^{-1}) has been tested prospectively and shown to produce a useful change in peak expiratory flow rate with a reduced risk of nausea and vomiting compared with a target of 20 mg l^{-1} [9].

If an individual target effect (TE) is known the target concentration (TC) required is predictable from:

$$TC = \frac{EC_{50} \cdot TE}{E_{\max} - TE}$$

e.g. to achieve a TE of 200 l min^{-1} increase in PEFR for theophylline a target concentration of 15 mg l^{-1} is required.

How can we find out?

The estimation of pharmacokinetic parameters for TCI focuses primarily on clearance and volume of distribution. The population approach to pharmacokinetics is the natural method for describing these parameters and important covariate influences. An automated approach to discovering covariate models has been described recently [14].

Interpreting concentrations and effects

Sources of variability

When concentrations are measured in order to guide future dosing there is an implicit assumption that the way the patient differs from an average patient is captured in this measurement, and that the patient will remain predictably different in the future. There are two sources of variability in PKPD parameters that need to be considered when deciding if concentration or effect measurements can help with predicting future dose needs. Parameter variability is made up of a between subject component (reflecting systematic differences between people) and a within subject component (reflecting random changes within a person). For example, if the percentage coefficient of variation for variability in clearance is reported as 70% this implies a total variance of a lognormal distribution of about 0.5 (i.e. 0.7^2). This is the population parameter variability (PPV) which is the sum of between subject variability (BSV) and within subject variability (WSV). For practical reasons, the within subject component is usually estimated as the interoccasion variability (IOV) [15]. This can be thought of as a description of the likely within subject random variation in clearance from the time of estimating clearance from a measured concentration using TCI, until the next occasion or dose, when the target effect from the new dose prediction is expected. WSV for clearance is a measure of the minimum variability in average steady state concentration that can be achieved by using TCI. If the variance associated with WSV is 0.1 then BSV must be 0.4 ($PPV = 0.5 = WSV + BSV$). These correspond to a CV% of 31% (square root of WSV) within individuals and 63% (square root of BSV) between individuals. The steady state concentration in an individual will therefore vary by about 31% from one occasion to another (BSV) in contrast to a 70% variation (total) if comparing the concentrations from different individuals. On average, TCI can expect to achieve target effects by learning about and accounting for the way an individual

Table 3 Target concentrations and pharmacokinetic parameters for selected drugs (70 kg standard individual). C_{ss} is the average steady state concentration.

Drug	Target concentration	Clearance	Volume of distribution
Aminoglycosides*	Peak 8 mg l^{-1} $C_{ss} 3 \text{ mg l}^{-1}$	6 l h^{-1}	18 l
Cyclosporine**	150 ng ml^{-1}	17 l h^{-1}	245 l
Phenytoin	10 mg l^{-1}	$V_{\max} = 415 \text{ mg day}^{-1}$, $K_m = 4 \text{ mg l}^{-1}$	45 l
Digoxin	2 ng ml^{-1}	9 l h^{-1}	500 l
Theophylline	10 mg l^{-1}	3 l h^{-1}	35 l

*8 hourly dosing. **Whole blood.

is systematically different (BSV) from another apparently similar person. It can not influence WSV. If the acceptable variability in concentration for safe and effective use of a drug is greater than PPV then TCI is unnecessary. If acceptable variability is less than WSV then TCI cannot make use of the drug safe and effective. TCI has its place when acceptable variability lies between PPV and WSV.

Bayesian forecasting

The key feature, in the clinical setting, of pharmacokinetic interpretation of drug concentrations is the very limited number of observations. Typically only one concentration is available and even with the simplest of models there will be at least two parameters (clearance and volume of distribution) to be estimated and of course there will be some inevitable measurement error and model misspecification. The best approach to extract useful information from such limited data is to use a Bayesian estimation method for the parameters. Programs are quite widely available for this purpose and have been known for a long time to be at least as good as an experienced clinician in terms of the precision of achieving the target concentration [16, 17]. The essential information required for Bayesian estimation is usually provided in the output of a population analysis, i.e. the population values of the parameters, covariate models which predict typical values from the population prior to starting treatment and estimates of the variability in the typical parameters and the measurement and model misspecification error.

Trial designs for TCI

The target concentration approach lends itself to evaluation by comparing the clinical outcome associated with different target concentrations. Note that information about the target effect and corresponding target concentration learned from such a trial reflects a typical patient. It can be a guide for initiating and managing treatment but both the target effect and target concentration may require revision in light of the response of an individual patient.

Two target concentrations of theophylline (10 and 20 mg l⁻¹) have been compared in the treatment of severe airways obstruction and it was shown that therapeutic benefit in terms of PEFV was similar with both targets but side-effects, particular nausea and vomiting, were worse at 20 mg l⁻¹. A target concentration of 10 mg l⁻¹ was therefore recommended [8].

A target concentration approach has been advocated for cyclosporin [18, 19] but no clear target has yet been identified. A target AUC, which is really just a target concentration in disguise, has been suggested for amino-

glycosides but no formal test of the proposed target has been made [20].

The theophylline target concentration was evaluated using a randomized concentration controlled trial (RCCT [21, 22]). Standard dose controlled trials compare two or more different doses of a drug which are randomly assigned to each subject. A concentration-controlled trial compares two or more target concentrations that are randomly assigned to each subject. It is important to note here that control refers to the experimental design feature that allows comparison of treatments. It does not refer to the process of adjusting the concentration in an individual in order to attempt to achieve the target concentration.

The precision of adjustment of concentrations is a factor that may influence the power of an RCCT but the intensity of this process may vary from a single measurement to intensive sampling profiles. The latter has been used in what might arguably be cited as the most impressive application of TCI. The 5 year survival rate in acute lymphoblastic leukaemia increased from 66% to 76% when TCI was applied to methotrexate treatment [23]. This is better than any new single drug cancer treatment that has been developed in recent years. The methotrexate study compared a TCI approach, with intensive sampling feedback, to one based on size adjusted dosing. The target concentration was based on the maximum tolerated value in earlier tolerability studies.

Conclusion

The year 2000 is nigh. The challenge for clinical pharmacology is to devise and execute RCCTs that will test alternate target concentration strategies and move beyond the methodological issues of dose adjustment algorithms and the blinkered viewpoint of the therapeutic range.

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