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Concentration controlled therapy

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Abstract

Randomised concentration controlled trials (RCCT) have been used to learn about the concentration-effect relationship and to evaluate treatment strategies. They provide a model for discovering the target concentration, which is an essential prerequisite for using pharmacokinetic knowledge and measured concentrations to individualise dose. Target concentration intervention (TCI) is a rational approach to using the information from drug effect and concentration observations to achieve a clinical outcome. It employs pharmacokinetic and statistical models to learn about the patient's pharmacokinetic parameters. It differs from therapeutic drug monitoring (TDM) which uses empirical dose adjustment based on the idea of a therapeutic range. A pharmacokineticpharmacodynamic (PKPD) model can be used to describe the response to a drug. PKPD parameter variability can be divided between subject (BSV) and within subject (WSV) components. These sources of variability are either predictable (e.g. using covariates such as weight and renal function) or non-predictable and thus apparently random. Using covariates to account for subject differences may reduce the predictable component of BSV. TCI can minimize the random part of BSV but cannot reduce WSV. Safe and effective use of a drug can be defined by a criterion for acceptable variation around the target concentration (SEV). Covariates can be used to reduce overall parameter variability (BSV plus WSV) so that it is less than or equal to SEV. Covariates may be able to predict subjects who are at risk of unacceptably high WSV and thus identify people who should not be treated with a specific drug because WSV is greater than SEV. If SEV is larger than WSV, then there is an opportunity to use TCI to reduce BSV and improve the ability to predict the right dose in an individual. © 2001 Elsevier Science B.V. All rights reserved.

Keywords. Therapeutic drug monitoring; Between subject variability; Within subject variability, Safe and effective variability; Target concentration strategy

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1. Introduction

Measurement of drug concentrations to guide drug dosage has been popular for several decades. The idea is appealing that drug concentration is more closely linked to drug effects than the size of the dose but it has proven elusive to provide convincing evidence. An important factor contributing to this difficulty is the dissociation between the time course of drug concentrations at observable sites and the time course of drug effects. Advances in pharmacokinetic-pharmacodynamic models have largely overcome this problem [1-6]. The overwhelming obscuring factor in divining the dose-concentration-effect relationship is variability in drug disposition and action. This paper focuses on the scientific rationale for selecting drug concentration measurements intended to improve drug treatment by dose individualisation.

2. Concentration control

What does concentration control mean? In clinical trial methodology, it is best understood as describing a kind of experimental control for comparison of two treatments; while in patient therapy, it refers to intervention aimed at achieving a target concentration.

2.1. Concentration controlled trials

Sanathanan et al. [7,30] proposed the use of concentration rather than dose as the control for discovering if a drug was effective. They introduced the term randomised concentration controlled trial (RCCT). This concept was subsequently extended to the use of a drug biomarker as the control factor in an "effect controlled " trial [8]. The fundamental concept driving these trial designs is the recognition that the variability in the relationship between dose and response has components due to pharmacokinetics (e.g. in clearance) and pharmacodynamics (e.g. in EC50). The concentration controlled trial assigns randomly to each patient a target concentration and seeks to reduce pharmacokinetic variation by use of patient demographics (covariates) and measured concentrations to achieve the desired concentration. The effect controlled trial attempts to reduce both pharmacokinetic and pharmacodynamic sources of variability by measuring a biomarker to achieve a randomly assigned target effect. The target effect is a biomarker whose between subject variability is expected to correlate with between subject variability in pharmacodynamic parameters determining the clinical outcome.

Implementation of an RCCT involves the random assignment of patients to different control groups with different target concentrations and also requires intervention to adjust the dose in order to achieve the target concentration. This latter process implies control of the concentration but the term control here refers to the manipulation of dose rather than the assignment process. Usually, only sparse concentration data is available from each individual in a clinical trial. 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 [9,10].

The use of target concentrations reflects a treatment strategy that is amenable to confirmation using the RCCT. A target concentration of 10 mg/l for the use of theophylline in severe airways obstruction has been shown to be superior to 20 mg/l using an RCCT [11]. A limited form of RCCT compares the outcome in patients assigned to treatment using a conventional dosing regimen (which may include individualisation of the dose using covariates such as body size) with treatment individualised on the basis of measured concentrations to achieve a target concentration. Evans et al. [12] used this limited RCCT to provide dramatic confirmation of the hypothesis that concentration is a better guide to outcome than methotrexate dose by improving the 5-year survival of children with acute lymphatic leukaemia by 10%. This single strategy produced greater benefits than any single drug intervention in the treatment of cancer in the last two decades. However, the optimal target concentration for methotrexate has yet to be determined.

2.2. Target concentration intervention

The term therapeutic drug monitoring has been in common use to describe the practice of sampling body fluids (almost always blood) to measure drug concentrations and propose a suitable dose for an individual. Therapeutic drug monitoring is usually referred to by its acronym TDM. Over the years it has fallen into some disrepute because it does not appear to have much clinical impact and almost no drugs developed in recent times have found TDM advantageous. TDM has become tedium.

Target concentration intervention (TCI) has been proposed as an alternative to TDM [13]. A key difference between TCI and TDM is the concept of a target concentration rather than a therapeutic range [14]. The target concentration reflects an optimal concentration, balancing effectiveness and adverse effects (Table 1). When treatment is started the target concentration is a typical value appropriate for the disease and patient characteristics such as age. The response (or lack of response) to treatment can be used to

Table 1

Drug	Target concentration	Clearance	Volume of distribution (l)
Aminoglycosides	Peak 8 mg/l ^a Css 3 mg/l	6 l/h	18
Cyclosporine ^b	150 ng/ml	17 l/h	245
Phenytoin	10 mg/l	$V_{\text{max}} = 415 \text{ mg/d},$ $K_{\text{m}} = 4 \text{ mg/l}$	45
Digoxin	2 ng/ml	9 1/h	500
Theophylline	10 mg/l	3 1/h	35

Target concentrations and pharmacokinetic parameters for selected drugs (70 kg standard individual). Css is the average steady state concentration

^a Eight hourly dosing.

^b Whole blood.

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guide the selection of an individual target concentration. However, information about target concentrations for specific drugs is still largely a matter of guesswork [14].

3. Population differences in pharmacokinetic parameters

In order to use models for dose individualisation an appropriate pharmacokinetic parameter value must be obtained for each patient. Differences in clearance between patients arise from two distinct sources. The first can be systematically related to patient characteristics (covariates) such as body size and organ function. The second is unexplained and can be described as arising apparently at random.

3.1. Parameter categories

It is helpful to distinguish three categories of a parameter such as clearance. The first category is the population parameter (CL_{pop}) which is representative of the population as a whole. This population value is usually defined with respect to some specific target group and preferably related to a set of standard values for the patient characteristics known to influence the parameter, e.g. the population value of theophylline clearance is 3 l/h in a 70-kg non-smoker (Table 1). The second category of parameter value is the typical value (CL_{tv}). This is derived from the population value by application of covariate models that reflect the predictable differences in the parameter value. The value is typical of an individual with specific covariate values, e.g. weight=60 kg, age=50 years, non-smoker. The third category of parameter is the individual value (CL_i). The individual value reflects the random differences between individuals who have similar covariates (and thus the same typical value). These differences arise from between subject and within subject differences.

3.2. Systematic differences

Typical parameter values are calculated from the population (standard) value and covariate models that reflect patient characteristics (Table 2). Covariate models are sometimes based on sound biological mechanism and theory, e.g. the relationship of weight to volume and clearance [15-17]. Other models, e.g. a linear model relating

Table 2

Covariate and typical	parameter mo	dels for	clearance
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Patient characteristic	Covariate model	Typical parameter model
Weight (Wt)	$F_{\text{size}} = (\text{Wt/Wt}_{\text{std}})^{\text{A}}$	$CL_{tv} = CL_{pop} \times F_{size} (A = 3/4)$
Creatinine	Renal Function	$CL_{tv} = CLnr + F_{cler}$
Clearance (CLcr)	= CLcr/CLcr _{std}	× Renal Function
Age	Fage = 1 + Sage	$CL_{tv} = CL_{pop} \times F_{age}$
	\times (Age – Age _{std})	
Smoker	If non-smoker, then	$CL_{tv} = CL_{pop} \times F_{smoke}$
	$F_{\rm smoke} = 1$ else $F_{\rm smoke} = FS$	

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creatinine clearance to renal clearance are biologically feasible if drug elimination is primarily due to glomerular filtration but this model is also a reasonable empirical model whatever the mechanism of renal elimination. Models predicting changes with age are strictly empirical and should not be relied upon for extrapolation outside the range of studied ages.

3.3. Random differences

The apparently random differences between individuals who have the same typical parameter values can be viewed as a reflection of our ignorance of additional factors that should be included in the covariate models. The overall variability in a parameter such as clearance is partly attributable to systematic differences (see Section 3.2). In some cases, e.g. if a drug is extensively renally cleared a substantial fraction of overall variability can be accounted for by a covariate such as creatinine clearance. More frequently, covariate models will only account for 20% or less of the difference in variability in the overall population and the variability seen between patients with the same predicted typical value (Table 3).

3.3.1. Parameter variability

The overall variability in the value of a parameter is known as the population parameter variability (PPV). PPV arises from two distinct sources — between subject and within subject. Both of these sources can be conceptually divided into predictable and random parts.

Between subject variability (BSV) is the variability from person to person in the average value of the parameter in each individual. If an individual is studied on more than one occasion then the variability in the occasion specific individual parameter

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Drug	PPV%	BSV ^a %	WSV%	Source
Artemisinin	70	45 ^b	53	Sidhu and Ashton, 1988 [20]
Drug A	64	57	29	Karlsson and Sheiner, 1993 [21]
Metoprolol	64	53	35	Lunn and Aarons, 1997 [22]
Riluzole	56	51 (42 ^b)	22	Bruno et al., 1997 [23]
Felodipine	47	34 ^b	33	Wade and Sambol, 1995 [24]
Ceftazidime	44	36 (18 ^b)	40	Frame et al., 1999 [25]
Drug B	41	28 ^b	20	Karlsson and Sheiner, 1993 [21]
Drug B	38	33	19	Jonsson et al., 1996 [26]
Moxonidine	27	22	15	Karlsson et al., 1998 [27]
Fenoterol	20	12	16	Bouillon et al., 1996 [28]
Theophylline	16	10	13	Upton et al., 1982 [29]
Average ^c	41	32	25	

Table 3					
Sources of variability in	drug	clearance	with	approximate	CV%

^a Includes variability predictable from covariates.

^b Excludes variability predictable from covariates (assumed if not stated in original).

^c Average computed from sums of variances using BSV including variability predictable from covariates if available.

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around the average individual value defines the within subject variability (WSV). More strictly, WSV should be divided into within occasion (WOV) and between occasion variability (BOV). The interval that is long enough to allow a reliable estimate of clearance defines an occasion. WOV for a parameter such as clearance is for all practical purposes not possible to estimate so that BOV and WSV are essentially synonymous. Variation in clearance within the occasion may indeed occur, e.g. due to variation in organ blood flow, but apart from exceptional experimental conditions this variability cannot be observed.

There is a component of both BSV and WSV that can be explained by differences in patient characteristics. The contribution of predictable between subject variability (BSVP) to overall variability will depend on the distribution of characteristics in the population as well as the influence of the covariate model on the parameter. It may also be possible to predict subjects who have differences in within subject variability. This predictable component (WSVP) does not help to predict the parameter in a specific individual but could indicate which individuals would be expected to have more difficulty with a drug because of greater variability.

Both between subject and within subject variability have apparently random components that reflect lack of knowledge about the causes of differences. The random BSV is known as BSVR and the random WSV is known as WSVR.

Some estimates of PPV, BSV and WSV for drug clearance are shown in Table 3.

4. Safe and effective variability

Both the target concentration and the therapeutic range try to express something about the optimal concentration for treatment of a patient. The target concentration implies a single optimal value but says nothing about the loss from deviations from the target. The therapeutic range implies that all concentrations within the range are equally "optimal" and usually it is understood that any concentration outside of that range is highly suboptimal and reflects inadequate treatment.

When applying TCI using the target concentration strategy [18], it is not usually necessary to explicitly decide on the loss from deviation from the target concentration. Any attempt to individualise dosing which gets the *predicted* concentration closer to the target concentration is better than doing nothing. With the therapeutic range approach, it is satisfactory to have a *measured* concentration within the range but unsatisfactory if it is outside.

Formal approaches to describe the balance between the desired therapeutic effect and adverse effects have been suggested previously [19]. The essential components are to define the concentration–effect relationship for therapeutic and adverse effects and decide on a utility function to measure the trade off between positive and negative effects. The definition of safe and effective variability (SEV) will necessarily include some element of subjectivity even after a utility function is defined. The prescriber will need to interpret the concentration–utility curve to decide the minimum level of utility that is appropriate. Because the utility curve has an inverted U shape there will be two concentrations defining the lower and upper concentrations within which utility is acceptable.

Variability criterion	Dosing strategy
PPV < SEV	Give everyone the same dose
PPV>SEV PPVR <sev< td=""><td>Use patient characteristics (covariates) to adjust dose</td></sev<>	Use patient characteristics (covariates) to adjust dose
PPVR>SEV WSV <sev< td=""><td>Use target concentration intervention to adjust dose</td></sev<>	Use target concentration intervention to adjust dose

Criteria for using patient characteristics or target concentration intervention to decide on a dose

A less formal approach has elements of the target concentration and therapeutic range ideas and also recognises the probabilistic nature of being able to achieve the target concentration given random variability in a parameter such as clearance. Suppose the prescriber would be satisfied if 90% of expected concentrations lay within 50% of the target concentration. The $\pm 50\%$ range around the target concentration therefore defines a 90% confidence interval. If the distribution of expected concentrations is approximately lognormal then this range of concentrations would be expected if the standard deviation of expected concentrations was about 25%. This standard deviation provides an estimate of safe and effective variability (SEV). Recall that the lowest variability in concentrations in an individual is limited by the size of within subject variability (WSV). If WSV were greater than 25% then it would not be possible to meet the criterion for safe and effective use. On the other hand, if WSV was less than SEV it would be possible to use TCI to reduce individual variability around the target concentration so that it lay within the range defined by SEV. Thus, the relative size of SEV and WSV provides an objective criterion for deciding if TCI could have any role in individualising dose.

SEV is also helpful in evaluating the value of covariate model predictions of typical parameter values. If overall parameter variability (PPV) is greater than SEV, the drug would not be safe and effective if all patients were treated with the same dose even if the median concentration from this dose was the target concentration.

The use of patient characteristics with covariate models for the parameter can reduce predictable subject variability (BSVP). Covariates can also be used to identify the size of the random WSV so that only the random population parameter variability (PPVR) remains. If PPVR is less than SEV then the drug can be considered safe and effective if doses are adjusted based on individual characteristics. These considerations lead to the criteria for dose individualisation and concentration controlled therapy shown in Table 4.

Acknowledgements

Table 4

I wish to acknowledge helpful discussions with Mats Karlsson (University of Uppsala) and Steve Duffull (University of Queensland) in developing the concepts of within subject variability and compiling Table 3.

Appendix A. Discussion 12

A. Breckenridge: Just picking up the point that Bill Evans was making yesterday, I guess you've got to build in some kind of pharmacogenomic factor into this as well, because it may well be that the concentration in different groups of patients may be quite markedly different.

N. Holford: Pharmacogenomic information helps us to predict how individuals differ from each other, and it removes one component of between-subject variability. If we have pharmacogenomic information, we can individualise the average dose for the individual. But we still need to have target concentration intervention to predict the random component.

G. Levy: I continue to be concerned about pharmacodynamic variability. I mean, even theophylline, they've got data showing that effective concentrations vary substantially with other drugs even more. And of course as you know, that led me to consider effect-controlled dosing, which is sort of consistent with medical practice; how do you feel about that?

N. Holford: I tried to indicate that this talk was about that category of drugs, where we don't have bio-markers for effect-control therapy. I think effect-control therapy is the standard of therapy where there is a bio-marker available—like blood pressure, cholesterol, or international normalized ratio (INR) for warfarin. This talk is really about the case where we don't have those bio-markers, and then we have to rely upon some other measure and there's a narrow window where concentration could be helpful.

W. Evans: Help me a bit with the WSV. I got the message that if that were large, then TDM or TCI might not be as useful. Do you differentiate between within-subject variability that's sort of random, versus that's caused by some factor, for example, drug interactions. You can have a lot of within-subject changes in the clearance of a drug because you put a patient on phenytoin or phenobarbital and induce metabolism, or you put them on an inhibitor. And it would seem that TCI or TDM would be useful in identifying when that's happening, when somebody might not realise that a person's diet or something is changing their clearance.

N. Holford: When I introduced the topic of between-subject variability and withinsubject variability, I said there were two ways of splitting this up. You can consider predictable factors and are random factors, which can be divided between subject and within subject. There is a predictable component of a drug interaction, which is a component of within-subject variability. You can make an average prediction of what the impact of that will be. But there is still some component of it that's random.

W. Evans: I don't disagree with you, but I think the predictable component of that becomes predictable after it's discovered and appreciated. How do you learn that new drug X induces drug C's clearance unless you're doing something to observe that and find it out, then you can move into the predictable category.

N. Holford: All the random stuff is the unknown, so by recognising a signal, maybe from a single individual patient, and thinking there might be a problem and doing explicit studies is how we move from the random to the predictable.

P. Joubert: Having been in Pharmaceutical Industry drug development for the last 10 years, I have become convinced of the utility of concentration effect relationships, and

defining things within relevant populations and getting a handle on risk benefit ratios. From my clinical days, I still see as you have rightly pointed out, that a purely doing drug concentration monitoring is very poor surrogate of effect, but for certain drugs that is all we have. Again, from my very distant digitalis days, you could substantially change the pharmacodynamics of digitalis without touching the concentrations, keeping them absolutely constant. We placed people into whole body counters and changed their whole body potassium with either diuretics or potassium supplements, and could markedly change the effects of digoxin on the ECG. I guess once we can get surrogates that are closer to the effect compartment, and measuring the effects, there might be a time where therapeutic drug monitoring might totally disappear as a therapeutic tool.

N. Holford: You've essentially stated that obvious; if we've got effects we can monitor, then we don't need to concentration. The concentrations are only a substitute for the effects. Essentially it's a substitute for not having the effect; so, bring the effects into the picture and we don't need the concentrations for individualisation of treatment.

M. Reidenberg: Just back to the compliance issue; a concentration of zero tells me something. This is where just looking for effect to adjust dose won't work.

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