On the Trough-to-Peak Ratio of Drug Effect in Antihypertensive Trials

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Blood pressure in hypertensives (treated or untreated) varies over the course of the day, and, although animal models and human intervention studies have demonstrated that the ill effects of hypertension are mediated by the pressure itself, and not by some confounder, it remains unknown what time-related function of pressure (simple mean, root-mean-square, duration of pressure above some threshold, and so on) might be the best predictor of hypertension-related morbidity.

There is no accepted means of describing the time course of blood pressure, let alone a difference between two such descriptions, which might then be a description of the time course of a drug effect. In a document dated 1988, the US Food and Drug Administration (FDA) defined the trough-to-peak drug-effect ratio and indicated that drug approval would be granted only when values of this statistic were satisfactory.

The FDA's belief in the importance of the time-course of drug effect has grown stronger over time, but the idea that only drugs with certain trough-to-peak ratios could be approved was discarded by the FDA within months of its appearance. In recent years, more promising means of assessing the time-course of drug effect have begun to take shape. Am J Hypertens 1996;9:105S–107S

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Blood pressure varies over the course of the day. Typically, blood pressure is higher when the subject is awake and upright. Superimposed upon this broad pattern (especially during wakefulness) are scattered peaks related to exogenous or endogenous stress. A casual office cuff measurement of blood pressure is a sample from this continuous curve. Perhaps surprisingly, this tiny nonrandom sample is often sufficient to detect drug effects, and all of our common wisdom about the prognostic importance of blood pressure is based on such samples.

The morbid effects of hypertension are not known to be correlated with particular features of the daily blood pressure curve. For example, it is tempting to compress the 24 h curve into a scalar 24 h average, but such data reduction may lose important prognostic information. A constant mean arterial pressure of 90 mm Hg is probably different in effect from a pressure that is 150 mm Hg by day and 30 mm Hg by night.

Understanding the pressure-prognosis linkage would be valuable for many reasons, not least of which being that such understanding might change our ideas about the desired time-course of effect of antihypertensive drugs. For example, suppose it were known that the ill effects of hypertension are all mediated by the extreme peaks of pressure, and that moderate hypertension, as detected by average daily pressure or by spot office measurement, is harmless except insofar as it is associated with higher and more frequent peaks. If this were true, a patient might reasonably choose an antihypertensive regimen whose effect is seen during only that portion of the day during
which higher or more frequent peaks were expected to occur.

No such knowledge exists. In its absence, physicians—and the US Food and Drug Administration (FDA)—have sought guidance from the (few) antihypertensive trials whose endpoints were not just reduction of blood pressure, but reduction in the irreversible deleterious changes of stroke, infarction, or death. Each of the regimens shown to provide any of these clinical benefits turns out to provide blood-pressure reduction that is present, at least to some degree, around the clock; shorter-acting regimens have not been similarly studied. With this in mind, regulators and physicians have generally played on the (presumed) safe side, and they have approved and adopted regimens that share this latter property. That is, they have required and expected each dose of one of these regimens to have an antihypertensive effect that lasts through the time ("trough") of the next dose.

To make the trough effects more prominent without inconveniently shortening the dosing interval, one might simply increase the dose, even though the peak effects might then become excessive or even dangerous. How can one be sure that this has not happened? One needs a means of describing the time-course of drug effect. The ratio of drug effect at trough to drug effect at peak (the "trough-to-peak ratio") could (when it can be computed) be the simplest possible such descriptor.

The earliest public mention of the trough-to-peak ratio appeared in an FDA document dated 9 May 1988, "Proposed Guidelines for the Clinical Evaluation of Antihypertensive Drugs." This was nominally a draft document, but it was in fact widely circulated. In discussion of the time-course of drug effect, the document stated that

based on its presumption that an antihypertensive drug should retain most of its peak effects at trough, the Division [of Cardio-Renal Drug Products] has determined that the drug effect at trough (measured as the difference from the placebo effect) should be no less than one-half to two-thirds of the peak effect, depending on the magnitude of the effect. The time-effect relationship also may be examined through the use of automated blood pressure monitoring equipment. The Agency has not yet determined precisely how such information will be interpreted, and suggestions for evaluative approaches are encouraged.\(^1\)

The draft guideline was soon tested. On 3 November 1988, members of the Cardio-Renal Advisory Committee were presented with data showing that when thrice-daily nicardipine is used for the treatment of hypertension, the trough-to-peak ratios of drug effect are all less than 30%. Committee members were not specifically asked to recommend approval or nonapproval of nicardipine in this regimen, but they were encouraged to voice opposition to approval if that would have been their recommendation. None did. Because excessive effect was not observed at peak, and because Committee members explicitly acknowledged that the linkage between antihypertensive therapy and its benefits is not really understood, the Committee recommended only that labeling describe the wide swings in drug effect that are likely to be observed when thrice-daily nicardipine is used.\(^2\)

The trough-to-peak ratio seemed to have died in its cradle. Had it perhaps been misconceived from the outset? Why had it at first seemed so attractive?

Trough-to-peak ratios are of established value in pharmacokinetics. When a drug is administered periodically (say, daily), serum concentrations rise and decline along curves that can be reliably approximated by sums of simple exponentials. When the postabsorptive portion of the curve is acceptably approximated by a single exponential, knowledge of the trough-to-peak ratio is sufficient to define the shape of that portion of the curve. The pertinent troughs and peaks here are, of course, the troughs and peaks of drug concentration, not those of drug effect.

One would like to describe the time-course of drug effect (pharmacodynamics) as concisely as one can describe the time-course of drug concentration (pharmacokinetics). Unfortunately, this is not an easy transition. The serum concentration of a molecular species is a simple matter of analytic chemistry; to measure such a concentration at a given time in a given patient, one needs access to the patient for only as long as it takes to obtain the specimen. Frequent sampling may be necessary in order to capture a short-lived peak, but during most of the dosing interval, concentrations will usually be changing with a time-scale measured in hours. Single-subject data may be sufficient; when it is not, precision can be increased by aggregation of data from multiple subjects, using well-known statistical methods.

When one moves from pharmacokinetics to pharmacodynamics, the concrete notion of drug concentration must be replaced by the abstract notion of "drug effect." The drug effect in a given patient at a given time is defined as the difference between the actual measurement (of, say, sitting diastolic blood pressure) made at that time and the measurement that "would have been made" in the absence of drug. Even in the same patient, and even in the total absence of drug effects, blood pressure measurements may be widely disparate over short periods. To estimate the observation that "would have been made" at a given
time under contrafactual conditions, one must have experience with other patients (in a parallel-group trial), or with the same patient at different times (in a cross-over trial). In either event, measurements of drug effect are inextricably bonded to aggregation and statistical inference, and the methodology of analysis is not mature.

One might hope that the drug effect \( E(t) \) could be a linear function of serum concentration

\[
E(t) = kC(t)
\]  

(1)

Unfortunately, the relation of concentration to effect is often saturable, and in any event nonlinear, so one can't really do any better than

\[
E(t) = f(C(t))
\]  

(2)

where \( f \) is the appropriate sigmoid function.

Equation 2 is unduly optimistic. It's just not always true that the drug effect at any given time is uniquely determined by the serum drug concentration at that time. In the specific case of antihypertensive therapy, drug effect is often codetermined by the (time-varying) drug concentration and the (also time-varying) levels of endogenous substrates, such as angiotensin and catecholamines. A given drug may block (or potentiate) the action of some of these substrates but not others. At best, one is left with

\[
E(t) = g(C(t), S_1(t), S_2(t), \ldots, S_n(t))
\]  

(3)

where the \( S_i(t) \) functions are substrate levels.

Even equation 3 is an oversimplification. There may be arbitrary lags between the serum concentration of a drug and its effect, so prediction of the drug effect \( E(t) \) may require taking account of a few hours' history of the drug and substrate levels. In this event, no closed-form expression may be possible. By way of demonstration of this complexity, drug effect will sometimes be seen to rise even though the drug concentration is falling; the peaks and troughs of drug effect will not necessarily be respectively simultaneous with the peaks and troughs of concentration.

If one is trying to describe the time-course of drug effect using only such information as can be gleaned from the estimates of drug effect at two times during the dosing interval, then it is mathematically prudent to choose the two times to be those two at which the drug effects will be maximally different. Notwithstanding the observations of the previous paragraph, the times of pharmacokinetic peak and trough might be reasonable candidates. If the times of measurement will be the investigators' main opportunities to observe patients receiving an experimental drug, then the time of pharmacokinetic peak \( (t_{\text{max}}) \) is of particular interest, because excessive dosing is most likely to manifest itself (in the case of an antihypertensive, as hypotension) around \( t_{\text{max}} \).

The pharmacokinetic trough following a dose given in an oral regimen is not generally reached until some time after the next dose has been administered, but few investigators attempt to identify this time \( (t_{\text{min}}) \) or to measure the drug effect at it. Investigators (and the FDA) have assumed that drug effects measured just before dosing are reasonable approximations to those that might be made at \( t_{\text{min}} \), and the FDA now accepts a nonzero antihypertensive drug effect just before dosing as an adequate surrogate endpoint for benefit.

When the two readings are arithmetically combined into a single scalar, then different combinations preserve different fragments of the original information. The trough + peak sum, for example, is directly proportional to the drug-effect area under the curve (AUC), but this AUC has no established regulatory or therapeutic interpretation. The trough-to-peak ratio, when close to unity, lets one know (for what it is worth) that the curve is nearly flat. In each case, some of the (scant) information present in the two numbers (trough drug effect, peak drug effect) is lost when the two numbers are reduced to one.

Attempting to describe a 24-h drug-effect curve by any method relying on just two points may be ill-fated. Ambulatory blood pressure monitoring (ABPM) enables one to record 24-h blood pressure curves, and to combine such curves into curves of drug effect. To date, the only widely-used descriptions of such curves have been graphs (discussed qualitatively or esthetically) and shapeless 12- and 24-h means, but more informative descriptions are being developed. Even before better quantitative descriptions appear, ABPM is qualitatively better than casual cuff measurements in locating and quantifying peaks of drug effect, when transient but important adverse effects may be detected.

The notion of the trough-to-peak ratio successfully drew attention to the process of choosing a dosing interval, and to some of the factors (other than patient convenience and marketing advantage) that must influence that process. As better descriptors of the time-course of drug effect become available, the trough-to-peak ratio will have outlived its usefulness.

REFERENCES
