Trough/Peak Ratios for Antihypertensive Agents
The Issues in Perspective

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1. Background

In 1988, the Cardiovascular and Renal Drugs Advisory Committee of the US Food and Drug Administration (FDA) met in the company of leading experts to consider proposed guidelines for the clinical evaluation of antihypertensive drugs. Whilst the draft guidelines covered many aspects of the development of an antihypertensive drug, the most pivotally important component of the proposals that were subsequently promulgated were those relating to trough to peak ratios of blood pressure response.

These guidelines were formulated because of concern that there was increasing evidence that relatively short-acting drugs were having their durations of action prolonged by giving larger doses than were necessary or desirable. This had arisen because, until comparatively recently, the clinical development and licensing of an antihypertensive drug was based largely on the magnitude of the blood pressure reduction at the end of the steady-state dosage interval (trough). Thus, an agent was deemed suitable for once-daily administration if it could be shown to produce a statistically significant clinically relevant reduction in blood pressure 24 hours after the previous dose. It was recognised that this approach was flawed in that it focused attention on a single time-point with little regard being given to the antihypertensive response throughout the rest of the dosage interval.

Problems associated with this reliance on a single time-point were apparent in a study of the relatively short-acting dihydropyridine calcium antagonist isradipine. In this study, when ambulatory blood pressure monitoring was used, it was noted that patients who had had their dosages titrated based on clinic (trough) blood pressures were hypotensive around the time of peak drug concentrations. Conversely, it was also noted that patients whose dosages were titrated at the time of peak blood concentrations did not have an adequate blood pressure response at the end of the dosage interval.

2. The Definition of Trough to Peak Ratios

To try to create a more definitive index of the duration of antihypertensive activity, the FDA guidelines proposed an arithmetic indicator based on a trough to peak blood pressure response ratio. The guidelines indicated that, in addition to maintaining a ‘useful’ antihypertensive effect at the end of the dosage interval, the trough effect should be at least half of the peak effect, once appropriate adjustment had been made for placebo effects. Note that the guidelines do not define ‘useful’. Furthermore, it was suggested that if the net effect of the drug was relatively modest (for instance, a reduction of 5mm Hg at peak), a larger trough to peak ratio of two-thirds of the peak effect would be required. Since drugs with such modest effects are unlikely to consistently achieve a trough to peak effect ratio of 50% in a significant proportion of patients, the two-thirds ratio is largely irrelevant.
Fig. 1. The profile of blood pressure in a representative untreated hypertensive patient, the normal range of 24-hour blood pressure (shaded area) and the profile in the patient following administration of 2 hypothetical drugs, 1 with a favourable trough to peak response ratio of 60% and the other with a trough to peak response ratio of 40%.

The concept underlying the trough to peak ratio is illustrated in figure 1. This represents the diastolic blood pressure response to 2 hypothetical antihypertensive drugs. The first, drug A, has a favourable trough to peak ratio of 60% and the second (B) has an unfavourable ratio of 40%. Both exhibit their maximal response 4 to 6 hours after administration, and the figure shows the effect of these 2 drugs on the diastolic blood pressure profile of a typical hypertensive patient.

Using the established criterion, it is apparent from figure 1 that both these drugs would be considered to be equipotent as both reduce diastolic blood pressure by 12mm Hg at trough response. However, in the case of drug A (trough to peak ratio 60%) the blood pressure profile of the hypertensive patient is normalised, with a relatively smooth and consistent profile maintained within the established range for normotensive individuals and, additionally, the effect is superimposed on and maintains the normal circadian pattern of blood pressure.

In contrast, with drug B there is a more profound response, such that the blood pressure is reduced to well below the normal range for a significant proportion of the normal 24-hour dosage interval. If the aim were to avoid this hypotensive response, it would be necessary to reduce the dosage of drug B, but this would result in a reduced effect at the end of the dosage interval (trough) and, perhaps more importantly, a failure to adequately control the early morning rise in blood pressure.

It is, thus, apparent that the FDA guidelines offer an arithmetic index which defines the duration of action of an antihypertensive drug and, hence, the selection of an appropriate dosage interval. It is not in itself a measure of antihypertensive efficacy, but may usefully become so when combined with an assessment of the magnitude of antihypertensive response.

3. Determination of Trough to Peak Ratios

The determination of definitive trough to peak ratio for any antihypertensive drug is potentially confounded by inadequate study design. Of these inadequacies, it appears that the most important is the failure to recognise the potential of placebo and/or circadian effects to confound the determination. Ignoring placebo effects can completely alter the interpretation of a study designed to characterise trough to peak ratios, such that almost invariably the ratio is inappropriately enhanced.[2]

This shortcoming was apparent when calculation of trough to peak ratios were made for felodipine in its extended release formulation.[2] For systolic blood pressure it was originally calculated that for both 10 and 20mg of felodipine extended release (ER) the trough to peak ratios were satisfactory at 56 and 61%, respectively. However, as illustrated in figure 2, this failed to take account of a significant placebo response, such that when the figures were corrected for placebo effects, the corresponding values were 33 and 50% for 10 and 20mg felodipine ER, respectively.

Although the 2 are inextricably linked, circadian variability in blood pressure is potentially