SPECIAL ISSUE: Trough to peak ratios

(Guest Editor: JA Millar)

EDITORIAL

Trough to peak ratio: time for reappraisal?

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This issue of the *Journal of Human Hypertension* contains six papers on practical and theoretical issues surrounding the concept of the trough to peak (T:P) ratio for antihypertensive drugs. With the exception of the paper by Henry Elliott, the papers were submitted to the Journal within weeks of each other and were recognised as being of great topical interest. I was asked by the Editor to compile the papers and write this overview, and Henry was invited to summarise his view of the ratio's current standing, as a major contributor to the field. All papers except Elliott's were submitted to the Journal's normal refereeing process.

Like many people on the periphery of the T:P ratio debate, I had proceeded for some years on the assumption that the ratio was little more than a marketing gimmick, with little science or application to clinical medicine. Indeed, it has been and continues to feature prominently in some promotional material. I regarded the topic as one that I should perhaps bone up on one evening when I had little else to do. My mind was focussed in 1996 by an invitation to speak at a sponsored medical meeting. The company concerned was concerned about inroads into its existing ACE-inhibitor market by a newer ACE inhibitor whose T:P ratio was apparently perfect (ie, unity). I asked myself a series of questions which eventually took shape as the paper in this issue, but on recourse to the literature it became apparent that while I was temporising others had been thinking deeply about the T:P ratio, and had raised crucial questions about its derivation, theoretical meaning, and practical application. However, none to my knowledge has seriously questioned the assumption that the T:P ratio should be as high as possible (the theoretical maximum is unity,

measurement problems aside), or have suggested that antihypertensive drugs with a high T:P ratio may in fact be disadvantageous. As I point out, the advantages and problems of T:P ratio are probably disease-specific. For example, there is no theoretical reason to suppose that a lipid lowering drug with a high T:P ratio on plasma cholesterol would be potentially hazardous due to cholesterol lowering, although the possibility of increased toxicity at higher than necessary concentrations would remain a valid concern. Indeed, it is of interest that the T:P ratio concept has not been extended explicitly to other areas of therapeutics.

Though it has intuitive appeal, T:P ratio turns out to be more complex than it appears at first sight. This is essentially a consequence of the high variability of blood pressure (BP). The papers published here demonstrate that neither peak nor trough are as easy to measure as one might suppose, and there is always the inevitable question about the validity of the baseline against which drug effects on BP are measured. To what extent should one attend to theoretical problems posed by minute-to-minute and diurnal BP variability, the effects of awakening and rising, and variations in patient compliance? What are the confidence limits on published ratio values? What is the relevance of the ratio in patients who do not respond to the drug? The answers to these questions are complex, a fact which militates against using the ratio as the sole standard of efficacy or as a sufficient criterion for deciding whether a drug may be given once daily. The papers present two possible approaches to these questions. The first is to improve measurement of BP, by improving either BP analytical techniques (see Diamant *et al*) or by practical solutions to various environmental determinants of BP variability (see papers by Morgan *et al*). The second, exemplified by Elliott's paper, seems to be to regard the ratio merely as a

simple means of determining the reasonableness of once-daily dosing for antihypertensive drugs. He implies that to ask detailed questions of the measurement and significance of the ratio is to undermine its simple utility. Certainly, one can say that the T:P ratio is nothing if it is not a practical help to ordinary physicians in daily practice. If it turns out that advanced mathematical manipulation of BP data is a necessary condition for accurate determination of the T:P ratio and for practical application, then it is unlikely to find wide application in everyday clinical decision-making. On the other hand, being obliged to confront BP variability in this context forces us to think about its wider diagnostic and therapeutic implications, a necessary and positive step.

Morgan *et al* have clearly proceeded along a similar route as myself. In two papers they cite the shortcomings of the T:P ratio and make some practical suggestions on how they may be overcome. In general, their suggestions are suitable for practice at regional hospital level but some are applicable to individual practice. Diamant and colleagues describe an elegant technique for overcoming at least in part the problem of BP variability, based on Fourier analysis. This technique will not be available to most practitioners, and it should have its main application in measuring T:P ratios accurately for marketing or regulatory purposes rather than in individual patients. These three papers and my own agree that T:P ratios may be underestimated for many useful antihypertensive drugs if non-responders are included in the analysis, and it appears that most investigators (but not Diamant *et al*) agree that T:P ratio should be determined only in patients who respond to the drug concerned.

Martell and colleagues have calculated T:P ratios

for two ACE inhibitors with different durations of action on ACE. Their paper shows how 24 h ambulatory BP monitoring and clinic BP readings can give very different results and that the T:P ratios of a short-acting drug (captopril) given twice daily and a long-acting drug (lisinopril) given once daily may be similar. The paper raises certain methodological questions, such as whether the peak response to captopril was measured during the first or second 12-h dose interval, when systematic differences in BP due to the sleep/wake cycle are likely, the relative timing of the office measurements, and the extent to which the data are responsive to drug dose (only single doses were studied).

In the debate about T:P ratio, the absence of 'hard' outcome data as a function of the ratio should be noted. Elliott has said elsewhere: 'If strict criteria for evidence-based medicine are demanded then it is not possible to provide definitive proof that antihypertensive drugs providing full 24-h control will lead to improved outcomes relative to agents which provide incomplete 24-h blood pressure control.'¹ It seems to me that this is an important point. Other apparently logical assumptions in medicine have ultimately been shown to be false, for example the apparently logical but false assumption that reversal of hypertension with drugs will abolish the hypertension-specific risk. The role and optimum value of the T:P ratio both remain to be established and physicians should bear this in mind when making clinical decisions and choosing antihypertensive drugs.

Reference

- 1 Elliott HL. Benefits of twenty-four-hour blood pressure control. *J Hypertens* 1996; **14** (Suppl 4): S15–S19.