Ambulatory blood pressure measurement : therapeutic implications

E. O'Brien* and K. O'Malley**

La mesure clinique conventionnelle de la pression artérielle a de nombreuses carences, les plus importantes étant son incapacité à indiquer la durée de l'effet d'un médicament, ou l'influence des médicaments antihypertenseurs sur la pression artérielle nocturne. On ne peut donc pas se fier à cette technique pour évaluer l'efficacité antihypertensive d'un médicament, soit en pratique clinique soit dans la recherche sur l'hypertension.

La mesure ambulatoire non-invasive de 24 heures de la pression artérielle a un certain nombre d'avantages sur la mesure conventionnelle. Dans la pratique clinique, elle fournit un profil de la pression sur une période de 24 heures, ce qui permet le choix du médicament antihypertenseur le plus approprié pour un patient donné. Dans les études sur l'effet des antihypertenseurs, la mesure ambulatoire fait la part de l'effet « blouse blanche » et, étant indépendante de la régression à la moyenne et de la réponse placebo, il est possible d'envisager des études sur l'efficacité qui ne nécessitent pas de phase placebo. En fournissant un plus grand nombre d'observations que celles obtenues par les mesures conventionnelles, la mesure ambulatoire augmente la puissance des études et réduit le nombre de patients nécessaires à des études sur les médicaments antihypertenseurs. La mesure ambulatoire de la pression artérielle de 24 heures offre la possibilité d'étudier les médicaments antihypertenseurs chez moins de patients avec plus de précision que cela n'est possible avec la mesure clinique conventionnelle, et devrait donc être obligatoire pour de telles études.

Arch Mal Cœur 1991 ; 84 (III) : 29-32.

MOTS CLÉS : **pression artérielle ambulatoire, efficacité d'un médicament antihypertensif, recherche, pratique médicale.**

Traditionally blood pressure measurement in the evaluation of antihypertensive drug efficacy has been made by conventional sphygmomanometry using a mercury or research sphygmomanometer, such as the Hawksley random zero sphygmomanometer, and static semi-automated or automated devices. Observer error is one of many limitations of conventional measurement in the assessment of antihypertensive drug efficacy is [1, 2]. The Hawksley random zero sphygmomanometer was designed to overcome observer bias in studies of antihypertensive drug efficacy and epidemiological studies. However, a number of recent studies have shown that the instrument systematically gives lower readings than the standard mercury sphygmomanometer [3-6] and it can no longer be recommended for blood pressure measurement in its present design.

Self-measurement of blood pressure has been used to assess antihypertensive drug efficacy, both in clinical practice and research but the technique has a number of limitations [7], foremost among which is the inaccuracy of the automated and semi-automated instruments available. In recent years the number of devices available commercially has risen rapidly but most have been shown to be less accurate than the mercury sphygmomanometer [8].

In addition to these methodological problems, conventional measurement has a number of inherent features which call into question its role in assessing antihypertensive drug efficacy. These include random variation, regression to the mean, the defence reaction and a placebo response, all of which render the assessment of antihypertensive drug efficacy difficult [1].

Ambulatory blood pressure measurement over 24 hours has given new insights into blood pressure behaviour and is bringing about such a reappraisal of previously held concepts on hypertension that diagnostic and therapeutic decisions in practice are being critically evaluated [9]. Similarly, in clinical research 24-hour ambulatory blood pressure measurement is providing exciting possibilities for the study of blood pressure behaviour, especially in the assessment of antihypertensive drug efficacy [10]. The advantages of 24

(*) Blood Pressure Unit Beaumont Hospital, Dublin, Ireland.
(**) Department of Clinical Pharmacology, Royal College of Surgeons, Dublin, Ireland.

(*Tirés à part* : Dr E. O'Brien).

Work cited in this paper from our Unit has been supported by grants from the Charitable Infirmary Charitable Trust, the Health Research Board, the Irish Heart Foundation and the Royal College of Surgeons.

hour ambulatory measurement over conventional techniques may be considered in relation to the ability of the technique to detect drug effect that may not be evident with conventional measurement, to provide information on the duration of antihypertensive drug effect, its role in improving the design of studies of antihypertensive drug efficacy, and the ability of the technique to demonstrate the effect of drugs on nocturnal blood pressure and the potential problems associated with excessive lowering of blood pressure.

DETECTION OF ANTIHYPERTENSIVE DRUG EFFECT

One of the most surprising aspects of research into the efficacy of antihypertensive drugs, is the readiness with which a blood pressure lowering effect observed at one moment in the 24-hour cycle, often without reference to the time of drug administration, has been taken to indicate therapeutic efficacy throughout the day. For the past decade it has been our policy to incorporate ambulatory measurement into our study protocols of blood pressure lowering drugs [10]. The most important lesson to be learned from such studies is that many preparations which would have been declared as quite efficacious blood pressure lowering agents by conventional measurement were shown by ambulatory measurement to have a far less impressive pattern of activity.

DURATION OF ANTIHYPERTENSIVE DRUG EFFECT

Ambulatory measurement provides what was only previously obtainable with direct invasive intra-arterial measurement - an assessment of antihypertensive drug effect over 24- or 48-hours. Until recently interest in this aspect of 24 hour measurement centered on the desirability of being able to demonstrate that a drug was efficacious for the appropriate period related to dosing. This facility proved useful in demonstrating that drugs possessed or did not possess the duration of action claimed for them. With recent interest in the potential danger of excessive lowering of blood pressure with antihypertensive medication [11], the role of 24 hour blood pressure monitoring in detecting such reduction in pressure, especially during the nocturnal period, may prove to be an important one.

DESIGN OF ANTIHYPERTENSIVE DRUG EFFICACY STUDIES

White coat responders

The white coat phenomenon, now a well-recognized entity, is best characterised by ambulatory techniques of measurement. Pickering and his colleagues have shown that more than 20 % of patients with borderline hypertension diagnosed by clinic measurement have normal day-time ambulatory blood pressure [12]. This has considerable implications in clinical practice. If patients with white coat hypertension are included in a study, as is often the case when patients are recruited by the conventional clinic measurement, we might expect as many as one fifth of these patients not to have sustained hypertension [12] and to be, therefore, unsuitable for the study.

Placebo response

An important difference between conventional and ambulatory blood pressure measurement is the absence of a placebo response with the latter, whether measurement is invasive or non-invasive [1]. The absence of a placebo effect with non-invasive ambulatory measurement allows the opportunity of greatly simplifying the design and conduct of efficacy studies of antihypertensive drugs by simply measuring ambulatory blood pressure before and at the end of the treatment period thus dispensing with the need for a cross-over design placebo control.

Regression to the mean

Regression to the mean has the potential for increasing the number of responders in antihypertensive drug studies, especially in patients with higher levels of blood pressure, such as the elderly, and a control placebo group is, therefore, necessary to permit assessment of the number of true responders to the drug [13]. Ambulatory measurement does not regress to the mean by which is meant that subjects with high pressures do not exhibit a fall in pressure and that those in whom pressures are low do not show a tendency to raise their pressure with repeated measurement [14]. This being so, ambulatory measurement may further enhance the likelihood of entering into a study only those patients with genuine hypertension.

Sample size

Conway and his colleagues have shown that the multiple measurements obtained with ambulatory recording the power of as study is increased and the numbers of subjects may be greatly reduced [15].

NOCTURNAL BLOOD PRESSURE "LOAD AND LEESE"

White has shown that an excessive "load", as denoted by the percentage of systolic or diastolic measurements above normal during a 24 hour period, predict

left ventricular enlargement [16]. There is now evidence that treated hypertensive patients whose blood pressures are lowest have the highest incidence of myocardial infarction [17, 18]. For this reason we must now direct our attention, not only to the efficacy of blood pressure reduction in studies of antihypertensive drugs but also to the magnitude of this reduction, the "leese" of pressure, as we have termed it, denoting excessive release or reduction in pressure [1]. Reviewing the evidence that lowering blood pressure may increase the risk of myocardial infarction has led Berglund to make the recommendation that until further evidence is available clinic diastolic blood pressure should not be reduced below 85 mmHg [11] but he did not give consideration to the potential effects of blood reduction at different times throughout the 24 hour cycle.

There is some evidence that hypertensive patients who do not have a nocturnal fall in blood pressure (non-dippers) are at greater risk than the majority who show a significant reduction in nocturnal blood pressure (dippers) [19, 20]. Moreover, it has been recently demonstrated that end-organ damage, as judged by left ventricular size, is more severe in non-dippers than in dippers [21]. The possibility also exists that antihypertensive drugs with a prolonged duration of effect, or administered frequently, may cause a profound reduction in nocturnal blood pressure in dippers, and that such hypotension might lead to myocardial ischaemia and infarction [22]. While the therapeutic and prognostic implications of these findings require further evaluation, they provide cogent evidence in favour of assessing the effects of antihypertensive therapy on sleeping blood pressure.

EFFECT OF DIFFERENT DRUGS ON CIRCADIAN PATTERN

Because of the potential importance of diurnal blood pressure rhythm, we analysed retrospectively 2,859 24 hour ambulatory records over a 3 year period to determine if currently used antihypertensive had different effects on the 24 hour circadian pattern [23]. The most important points to emerge from this analysis were : *firstly*, hypertensive patients on beta-blockers had a significantly smaller nocturnal systolic dip than hypertensives on no medication and this tendency was also present for diastolic pressure, though it did not reach statistical significance ; *secondly*, hypertensives on ACE inhibitors had markedly accentuated systolic and diastolic dipping patterns compared to untreated hypertensives and patients on beta-blockers. Hypertensive patients treated with calcium antagonists or diuretics had similar diastolic and systolic dipping patterns to the untreated groups. These small but significant differences between the mean dips of the groups resulted in quite marked alterations in the distribution of dipper/non-dipper status. Whatever the explanation for these varying effects of different groups of antihypertensive drugs, which need to be assessed in more detail in prospective studies, the fact that some drugs may accentuate nocturnal dipping, that others may blunt the normal nocturnal fall in blood pressure and that others have no effect on diurnal rhythm, raises important questions in assessing antihypertensive drug effect and in choosing a drug for an individual patient. In patients with an accentuated dip, it may be advisable to use shorter acting drugs to be taken in the morning or to prescribe drugs which are known not to affect nocturnal pressure. On the other hand hypertensive non-dippers require smooth blood pressure reduction throughout the 24 hour period, and it may be advantageous to attempt to restore a normal circadian pattern by using drugs known to be efficacious in reducing nocturnal pressure.

24-hour non-invasive blood pressure measurement is now passing from the research sphere to clinical practice and it offers such advantages in the diagnosis and management of hypertension that it must before long become indispensable to the assessment of the hypertensive patient. In research, the time has come when studies of antihypertensive drug efficacy which do not assess blood pressure over 24 hours should no longer be acceptable.

Summary

Ambulatory Blood Pressure Measurement Therapeutic Implications.
E. O'Brien and K. O'Malley

Conventional clinic measurement of blood pressure has many deficiencies, among which the most significant are its inability to indicate the duration of drug effect, or the influence of antihypertensive drugs on nocturnal blood pressure. The technique is, therefore, unreliable for assessing antihypertensive drug efficacy, either in clinical practice or hypertension research.

Non-invasive 24 h ambulatory blood pressure measurement has a number of advantages over conventional measurement. In clinical practice it provides a profile of blood pressure over the 24 h period permitting the selection of the most appropriate antihypertensive drug for the individual patient. In studies of antihypertensive drug effect, ambulatory measurement detects white coat responders and, being free of regression to the mean and the placebo response, it is possible to consider efficacy studies which need not have a placebo phase. By providing considerably more observations than can be obtained with clinic measurement, ambulatory measurement increases the power of studies making it likely that fewer numbers of patients are needed for antihypertensive drug studies. 24 h ambulatory blood pressure measurement offers the opportunity to study antihypertensive drugs in fewer patients with greater accuracy than is possible with conventional clinic measurement and should be a mandatory requirement for such studies.

Arch Mal Cœur 1991 ; 84 (III) : 29-32.

Références

1. O'Brien E, O'Malley K, Cox J, Stanton A. Ambulatory blood pressure monitoring in the evaluation of drug efficacy. Am Heart J 1990 (in press).

2. O'Brien E, Tan KS, Atkins N, Mee F, O'Malley K. Training and assessment of observers for blood pressure measurement. J Human Hypertens 1991 ; 5 : 7-10.
3. Evans JG, Prior IAM. Experience with the random-zero sphygmomanometer. Br J Prev Soc Med 1970 ; 24 : 10-5.
4. De Gaudemaris R, Folsom AR, Prineas RJ, Luepker RV. The random-zero versus the standard mercury sphygmomanometer : a systematic blood pressure difference. Am J Epidemiol 1985 ; 121 : 282-90.
5. Parker D, Liu K, Dyer AR, Giumetti D, Liao Y, Stamller J. A Comparison of the Random-Zero and Standard Sphygmomanometers. Hypertension 1988 ; 11 : 269-72.
6. O'Brien E, Mee F, Atkins N, O'Malley K. Inaccuracy of the Hawksley Random Zero Sphygmomanometer. Lancet 1990 ; 336 : 1465-8.
7. Cox JP, Julius S, O'Malley K, O'Brien E. Self-measurement of blood pressure. In : E. O'Brien, K. O'Malley. Blood Pressure Measurement. Elsevier. Amsterdam : Handbook of Hypertension, 1991 (in press).
8. O'Brien E, Atkins N, Mee F, O'Malley K. Inaccuracy of seven popular sphygmomanometers for home measurement of blood pressure. J Hypertens 1990 ; 8 : 621-34.
9. O'Brien E, Fitzgerald D, O'Malley K. Blood pressure measurement : current practice and future trends. Br Med J 1985 ; 290 : 729-34.
10. O'Brien E, Cox J, O'Malley K. Ambulatory blood pressure measurement in the evaluation of blood pressure lowering drugs. J Hypertens 1989 ; 7 : 243-7.
11. Berglund G. Goals of Antihypertensive Therapy : Is There a Point Beyond Which Reduction Is Dangerous ? Am J Hypertens 1989 ; 2 : 586-93.
12. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension ? JAMA 1988 ; 259 : 225-8.
13. Bulpitt CJ. Responders and Non-Responders to Antihypertensive Treatment. Drugs 1988 ; 35 (suppl 6) ; 142-6.
14. Fitzgerald DJ, O'Malley K, O'Brien ET. Reproducibility of ambulatory blood pressure recordings. In : Weber MA, Drayer JIM. Ambulatory blood pressure monitoring. New York : Springer-Verlag, 1984 ; 71-4.
15. Conway J, Coats A. Value of ambulatory blood pressure monitoring in clinical pharmacology. J Hypertens 1989 ; 7 (suppl 3) ; S 29-S 32.
16. White WB, Dey HM, Schulmann P. Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild to moderate hypertension. Am Heart J 1989 ; 118 : 782-95.
17. Cruickshank JM, Thorp JM, Zacharias FJ. Benefit and potential harm of lowering high blood pressure. Lancet 1987 ; (suppl I) : 581-4.
18. Alderman MH, Ooi WL, Madhavan S, Cohen H. Treatment-Induced Blood Pressure Reduction and the Risk of Myocardial Infarction. JAMA 1989 ; 262 : 920-4.
19. O'Brien E, Sheridan J, O'Malley K. Dippers and Non-dippers. Lancet 1988 ; ii : 397.
20. Pickering TG. The Clinical Significance of Diurnal Blood Pressure Variations : Dippers and Nondippers. Circulation 1990 ; 81 : 700-2.
21. Verdecchia P, Schillaci G, Guerreri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990 ; 81 : 528-36.
22. Floras JS. Antihypertensive treatment, myocardial infarction and nocturnal myocardial ischaemia. Lancet 1988 ; ii : 994-6.
23. Stanton AV, Atkins N, O'Malley K, O'Brien E. Circadian blood pressure and antihypertensive drugs. Am J Hypertens 1990 ; 3 : 107A.