Why ABPM Should Be Mandatory in All Trials of Blood Pressure – Lowering Drugs

PEER REVIEWED

INTRODUCTION

Traditionally, blood pressure (BP) has been assessed with the auscultatory technique introduced into clinical medicine at the end of the 19th century. Despite being inaccurate and misleading, this technique has survived largely unchanged for over 100 years. It is salutary to reflect that since Riva-Rocci and Korotkoff introduced the technique we have landed men on the moon, orbited Mars, invented the automobile and airplane, and, most importantly, revolutionised the technology of science with the microchip. Why, we might ask, has medicine ignored scientific evidence for so long and thereby perpetuated an inaccurate measurement technique in both clinical practice and hypertension research?[1]. The same sentiment has been expressed by Floras: "As a society, we are willing to contemplate widespread genomic or proteomic subject characterisation in pursuit of the concept of 'individualised medicine.' By contrast, blood pressure measurement is one of the few areas of medical practice where patients in the twenty-first century are assessed almost universally using a methodology developed in the nineteenth"[2]. Quite apart from the inaccuracy of the auscultatory technique, one of its major limitations is that it can only provide a snapshot of BP behaviour, usually under circumstances that may adversely affect the level of BP. To overcome these serious methodological shortcomings, the technique of ambulatory blood pressure measurement (ABPM) has been developed to provide automated profiles of BP behaviour over 24 hours. When we consider that the phenomena of white coat hypertension, nocturnal dipping, and morning surge cannot even be suspected with conventional BP measurement and that the technique can give no indication of the duration of antihypertensive drug effect, it is a matter of some wonderment that researchers can persist in using the technique. It is indeed worrying that the editors of scientific journals and their peer reviewers can give scientific credence to studies performed with a discredited technique. We must question also why the bodies that regulate the approval of antihypertensive drugs have not made BP measurement over 24 hours mandatory for studies of drug efficacy and why the pharmaceutical industry funds studies that do not provide ABPM[3].

ADVANTAGES OF ABPM

There are several advantages of 24-hour ABPM over conventional BP measurements in demonstrating the efficacy of BP-lowering drugs, which include the following.

Detection of white coat responders

The white coat effect, whereby the circumstance of measurement causes a temporary rise in BP, can cause a very significant rise in clinic BP, and a reduction in BP during a clinical trial can be attributed erroneously to drug efficacy rather than to attenuation of the white coat effect[4]. Although a white coat effect may be evident in the first hour of ABPM (and possibly also in the last hour) when the patient is in the medical environment[5], the average BP measurements during the daytime and night-time periods are devoid of the white coat influence. More than 20 % of patients with borderline hypertension diagnosed by clinic BP measurement have normal daytime ABPM[6]. If patients with white coat hypertension are included in a pharmacological study, as is often the case when patients are recruited by clinic BP measurement, we might expect as many as one-fifth of these patients not to have sustained hypertension and to be unsuitable for the study[7].

Absence of placebo response

Unlike clinic BP measurement, 24-hour ABPM is virtually devoid of a placebo effect[3]. The absence of a placebo effect with non-invasive ABPM allows the opportunity of simplifying the design and conduct of efficacy studies of antihypertensive drugs. For example, in randomised placebo-controlled trials, ABPM performed before and repeated at the end of the treatment period may suffice, making the crossover design with its risks of carryover effects and the need for prolonged placebo administration unnecessary. ABPM may also remove the need for a runin phase to exclude normotensive patients and detect truly hypertensive patients[3]. This significant advantage overcomes the ethical problem of keeping patients with hypertension off treatment for weeks or months[3,8].

Reduction in patient numbers

It is becoming more difficult to recruit patients for pharmacological trials, especially for studies aimed at determining the efficacy of drugs in mild hypertension. The average BP over 24 hours is three times more reproducible than are clinic BP values, and this allows the number of patients needed in parallel and crossover design studies to be reduced without loss of statistical power[3,9].

Provision of a 24-hour profile

ABPM provides a profile of BP behaviour over the 24-hour period rather than the snapshot provided by clinic BP. This profile allows assessment of the efficacy of antihypertensive drugs over not only the entire 24-hour period but also during windows of the 24-hour cycle[10,11]. For example, the 24-hour period can be divided into white coat, day-time, siesta, vesperal (evening), night-time, and matinal (early morning) windows. A number of patterns may be observed in these windows: white coat hypertension and white coat effect, siesta dip, dipping, Non-dipping, reverse dipping, excessive dipping, and morning surge in the nocturnal period. As the mechanisms involved in determining BP at different times may differ, not surprisingly drugs can have different effects on these different windows[3,12].

Assessment of blood pressure variability

The most important measures of circadian variation are the nocturnal dip and the morning surge[13]. Nocturnal hypertension (or a non-dipping pattern) is the most important finding associated with increased target organ involvement and increased cardiovascular morbidity and mortality. Recently, BP variability has been shown to be an important prognostic marker that is likely to become a target for antihypertensive drug treatment[14,15]. The prognostic impact of BP variability is largely dependent on the variability of BP over time, but the many measures of variability that may be obtained from ABPM make this an interesting alternative, especially for assessing the effect of antihypertensive medication on this parameter[16].

Provision of derived measures

A number of indexes may be derived from ABPM. For example, the ambulatory arterial stiffness index, which is calculated from systolic and diastolic pressure over 24 hours, independently predicts stroke and cardiovascular fatality risk[17]. Analysis of hourly mean BPs and changes over 24 hours allows determination of the efficacy of a drug at half-hourly time points, thereby showing the optimal dosing regimens for a particular drug. Traditional trough-to peak ratio can be calculated as well as the more recent ABPM-derived smoothness index[3,18].

Identification of drug induced hypotension

ABPM allows ready identification of drug-induced hypotension, particularly in association with a postprandial fall in BP and during a siesta dip—phenomena that are particularly common in the elderly. Antihypertensive drugs with a prolonged duration of effect, or administered frequently, may cause a profound reduction in nocturnal BP in some patients, which may lead to myocardial ischemia and infarction[3,19]. Hypotension induced by excessive medication in patients with coronary arterial disease can induce episodes of overt and silent ischemia[20].

Identification of adverse effects of drugs on BP

The increasing interest in the cardiovascular safety of drugs has tended to concentrate on the effects drugs may have in inducing adverse electrocardiographically detectable abnormalities[21]. However, the unwanted effects of drugs for general noncardiovascular use as well as those with specific cardiovascular indications can elevate or, more commonly, reduce BP, especially in the elderly and often in specific periods of the 24-hour profile, such as the postprandial (or siesta window) or the nocturnal period. Such phenomena can only be detected with ABPM.

TECHNOLOGICAL DEVELOPMENT OF ABPM

ABPM, which has been available in one form or another for some 30 years, has been advocated for studies of BP-lowering drugs for almost as long, but it has been slow to find acceptance[22]. Although assessing the BP-lowering efficacy of antihypertensive drugs over the 24-hour period is a logical scientific premise, the ability to do so has been dependent on technological developments. The first advance was the introduction of a direct intra-arterial technique for the measurement of BP continuously over the 24-hour period[3,23]. The data on antihypertensive drug efficacy provided by studies using this system were particularly valuable because they provided continuous BP measurement over the 24-hour period, but use of the technique was limited by safety and ethical considerations[3]. Efforts were focused, therefore, on developing a device that would record ambulant BP noninvasively and, in the 1960s, the Remler device, which was capable of measuring BP intermittently during the daytime period, provided clinicians with a new technique for evaluating antihypertensive drugs[3,24]. This device yielded interesting information on drug efficacy but was limited by having to be operated by the patient, which precluded recording of nocturnal BP. The next technological advance was the introduction of fully automated devices that could measure BP intermittently at predetermined intervals over the 24-hour period[25]. This class of devices, among which the SpaceLabs series has been dominant, has allowed clinical scientists to assess not only the BP-lowering efficacy of drugs but also their influence on circadian patterns such as nocturnal BP and the morning surge[3]. The latest technological development has been the provision of a software system that can analyse the data from ABPM and provide not only statistical data on mean levels of BP throughout the 24-hour period but also indexes of BP and the relationship of drug effect to the time of ingestion and the association of drug level with BP lowering[26].

These developments in ABPM have brought a new dimension to the interpretation of studies of BP-lowering efficacy. By providing a profile of BP behaviour over demarcated windows of the 24-hour period, ABPM has demonstrated the deficiencies of clinic BP measurement. First, a number of studies have shown that ABPM can be in agreement with clinic BP measurements[3]. In such studies, where a clinic fall in BP was confirmed by ABPM, the latter also demonstrated what conventional BP measurement can never show, namely, the pattern of an antihypertensive effect over the dosing interval. Second, studies have demonstrated that clinic BP measurement can fail to detect the BP-lowering effect demonstrated by ABPM[3]. Third, it has been shown that whereas reductions in clinic BP may be significant, ABPM may be either non-confirmatory or show that the clinic BP reduction coincides only with a brief period of BP reduction on ABPM[3]. Finally, one of the major advantages of ABPM in studies of antihypertensive drug efficacy is that the degree of BP control achieved by an antihypertensive drug may be determined not only over the entire 24-hour period but also within windows of the circadian profile. For example, studies have shown that patients who appeared to have well-controlled BP on routine clinic measurement had uncontrolled BP during the early morning hours[3]. There are many studies showing that an elevated nocturnal BP or a diminished nocturnal fall in BP is associated with poor cardiovascular outcome both in populations and in patients with hypertension[3,13]. Isolated nocturnal hypertension, which may be present in 7 % of patients with hypertension, can be diagnosed only with ABPM, and its presence in patients on antihypertensive drug trials could have an important influence on the assessment of 24-hour efficacy of BP-lowering drugs[27].

CURRENT REGULATORY RECOMMENDATIONS IN CLINICAL TRIALS

It is abundantly evident from an extensive review of the literature[3] that the scientific argument for using ABPM in all studies assessing the efficacy or long-term protective benefits of BP-lowering drugs is irrefutable and there can no longer be a case for performing such studies using clinic BP as the measure by which efficacy is judged. Indeed, the recommendations of the regulatory bodies on the use of ABPM in trials of antihypertensive drugs generally concur with this view, but there is nonetheless a certain ambivalence that is now scientifically unacceptable. The US Food and Drug Administration guidelines, which are still in draft form, state: "The effect of the drug over the duration of the dosing interval has generally been evaluated in recent years with ABPM studies (which can incorporate dose response elements and an active control), but studies that measure blood pressure at approximate peak and at trough (pre-dosing) blood levels can also be used"[28,29]. The document also suggests that ABPM is "perhaps" not subject to bias. The primary purpose of the guideline is to obtain values for the trough-to-peak ratio regardless of how BP is measured.

The current European Medicines Agency (EMA) guidelines unequivocally recommend ABPM in clinical trials: "As ambulatory blood pressure monitoring (ABPM) provides a better insight to blood pressure changes during everyday activities and is better standardised than casual readings, ABPM is required for the evaluation of new antihypertensive agents"[30,31]. However welcome scientifically this recommendation may be in principle, the requirements for ABPM stipulated by the EMA are nevertheless in need of considerable refinement.

FACILITATING THE USE OF ABPM IN CLINICAL TRIALS

The use of ABPM in clinical practice and research has been hampered by both manufacturers and researchers having concentrated on the development and means of validating the accuracy of devices—the hardware—rather than directing attention to presentation and analysis of data—the software—so as to make the technique more user friendly and acceptable to clinicians and researchers. The Conway Institute, University College Dublin, in association with dabl Limited, has been endeavouring to redress this imbalance and has developed the dabl ABPM system to facilitate the wider use of ABPM in the clinical management of hypertension[1,10,11,26,32,33]. The use of this custom-designed software system for the analysis of ABPM has facilitated the application of ABPM in primary care by showing clearly on a standardised plot the windows of the 24-hour profile, the normal bands for systolic and diastolic BP, and the recorded levels of BP throughout the 24- hour period as well as a computer-generated interpretive report. Together with central hosting of data, the dabl ABPM system has provided valuable demographic information in research[13,17,34] and it is now used in many centres internationally.

The analysis of ABPM data and the reported diagnoses by the dabl ABPM system have been shown to be more accurate than reporting of ABPM data by expert observers[33].

A number of practical obstacles have militated against the wider use of ABPM in pharmacological studies, especially in prospective multi-centre trials. These include lack of familiarity with the technique, the need for trained personnel, the need to standardise the methodology, the need for electronic collection and monitoring of data so as to be able to inform investigators in real time of the success or otherwise of ABPM recordings, and the cost of the procedure, which, though higher than conventional BP measurement, provides so much additional information that the benefits make the procedure very cost effective. Finally, the goal levels for reduction of both daytime and nighttime BPs need to be determined and real-time analysis and transmission to the investigators of the target ABPM levels achieved has to be feasible.

The dabl ABPM system has now been developed to incorporate the basic requirements that are needed for ABPM to be implemented in studies of antihypertensive drug efficacy. These include the capability of assimilating a number of parameters over the 24-hour period and also within the windows of the 24-hour period so as to provide a comprehensive analysis of clinic and ABPM parameters; provision of real-time analysis of ABPM data so as to be able to alert the investigator to the validity or otherwise of the ABPM; and organisation of ABPM data so as to permit ongoing analysis and flexibility of the system so that it can be adapted to accommodate studies of differing design.

CONCLUSION

Conventional clinic BP measurement is influenced by many factors, which limit the applicability of this technique for research into drug efficacy. More importantly, clinic BP measurement cannot provide a comprehensive assessment of duration of effect, or of the effect of antihypertensive drugs on sleeping pressure. The benefits of ABPM in the assessment of the efficacy of drug treatment are now so well established that its use should be mandatory in all pharmacological trials of antihypertensive drug efficacy. From the scientific viewpoint, it is now time to utilise the technique to obtain a fuller understanding of the patterns of drug-induced lowering of BP than was ever possible with conventional clinic BP measurement. The following was written in 1991: "The time has surely come when antihypertensive drug efficacy studies that do not assess blood pressure over 24 hours should no longer be acceptable"[35]. That this plea has not become reality some 20 years later must be seen as an indictment of clinical science.

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Eoin O'Brien is Professor of Molecular Pharmacology at the Conway Institute of Biomolecular and Biomedical Research, University College Dublin. He has published many scientific papers on hypertension research, especially in the areas of blood pressure measurement, ambulatory monitoring and the management of hypertension in the elderly. **Email: eobrien@iol.ie**