Editorial review

Ambulatory blood pressure measurement in the evaluation of blood pressure lowering drugs

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Introduction

Since the indirect measurement of blood pressure based on the principle of arterial occlusion using a forearm cuff was introduced by Scipione Riva-Rocci in 1896 [1] and subsequently modified to incorporate auscultation by Nicolai Korotkoff in 1905 [2], this technique has been the universal method used in the assessment of blood pressure in medial practice. Most of the evidence showing that the antihypertensive drugs in everyday use lower blood pressure derives from studies of clinic blood pressure measured by this technique [3–5]. However, it is well known that casual blood pressure measured in the clinic may be influenced by a number of factors and as long ago as 1904, Theodore Janeway, writing before Korotkoff had reported the now accepted auscultatory method of measuring blood pressure, showed that stress could raise blood pressure [6].

Factors influencing blood pressure measurement

Apart from potential error and inconstancies in technique [7], random variation of blood pressure readings is large; in one study a series of 40 readings from individuals on 20 different occasions showed a within-subject range of 25–39 mmHg [8]. Moreover, there is the circadian variation of blood pressure whereby blood pressure reaches its highest level at mid-morning, to fall thereafter throughout the day to its nadir in sleep with a rise again before waking [9].

Another confounding factor is the alarm or alerting reaction whereby the mere presence of the physician performing the measurement can induce substantial increases in blood pressure [10]. This phenomenon is also present, albeit to a lesser degree, when blood pressure is measured by a technician [11] or a nurse [12]. Recently, Pickering and his colleagues reported that 21% of 292 patients with borderline hypertension diagnosed by clinic measurement had normal daytime ambulatory pressure [11]. These patients with 'white coat' hypertension did not show any generalized increase in blood pressure lability or exaggerated pressor response while at work. In a study of 638 patients with hypertension we found that using the World Health Oorganization level of hypertension (blood pressure $\geq 160/95$ mmHg) 89% of these patients would have been diagnosed hypertensive by the family practitioner, 65% by the hospital clinic and 46% by ambulatory blood pressure [13].

When attempting to ascertain the effect of drugs on blood pressure, good trial design can reduce the influence of factors affecting the measurement technique and blood pressure behaviour. Multiple recordings of blood pressure may reduce error from random variation, and taking blood pressure at the same time of day throughout a study should minimize errors associated with circadian variation. A cross-over design in which recordings are performed by the same doctor or nurse in the same room under standardized conditions reduces, but does not necessarily remove, error from the alarm reaction.

Assessing blood pressure lowering 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-h cycle, often without reference to the time of drug administration, is taken to indicate therapeu-

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tic efficacy through the day. It is, of course, difficult, if not impossible, to demonstrate the duration of drug effect with clinic measurement as repeated readings are tedious to perform both for the patient and investigator. In any event, the methodology of conventional blood pressure measurement in many of these studies leaves much to be desired [14]. However, with the increasing use of new formulations of drugs that permit once and twice daily dosage in an effort to improve compliance [15], it is now more important than ever to be able to assess accurately the duration of drug effect. Furthermore, studies using ambulatory techniques have demonstrated the naivety of assessing the response to antihypertensive treatment by conventional clinical measurement alone [16]. To overcome the limitations of infrequent clinic measurements in assessing the efficacy and duration of action of antihypertensive drugs, self-measurement and ambulatory measurement have been used.

Self-measurement of blood pressure

Since Brown's observation in 1930 that blood pressure measured in the home was lower than that recorded by a doctor [17], the discrepancy between pressures recorded in the home and the clinic has often been confirmed [18–20]. Assessed against clinic measurements, blood pressure recorded in the home is accurate whether measured by patients [20] or their relatives or friends [21], and the technique can detect small average changes in blood pressure [22]. The usefulness of self-measurement of blood pressure in the assessment of the effects of therapy has been shown in several studies [19,23,24]. However, the technique has the disadvantage of being dependent on the ability of the subject to measure his or her blood pressure. Also, the patient's over-reaction to the normal fluctuations in blood pressure associated with daily living may cause psychological distress and affect the results in an unpredictable fashion [25]. The technique is further limited in that it is dependent on the subject's participation and cannot, therefore, give multiple readings during the day or any assessment of nocturnal blood pressure.

Non-invasive ambulatory treatment

The first step towards achieving a profile of blood pressure during normal activity was the development of a portable apparatus for direct recording of blood pressure in 1969 [26], which allowed assessment of the antihypertensive effect of blood pressure lowering drugs over a 24-h period [27,28]. However, being invasive, ethical considerations limit the application of this approach. Therefore, much effort has been directed to the development of non-invasive measuring devices which can be used repeatedly in the same patient. The early devices required participation by the subject who had to inflate the cuff at prescribed intervals and were therefore limited to daytime recording [29], but now fully automated recorders are available with automatic cuff inflation allowing the recording of blood pressure over 24-h [30,31].

There are certain disadvantages, however, with non-invasive ambulatory measurement. The cost of the equipment is high, maintenance costs are often substantial, and the finance for a technician may have to be taken into consideration [32]. There is then the problem of accuracy. Devices should not be purchased (ideally they should not be marketed) unless the manufacturers provide independent validation of accuracy, preferably published in a reputable journal [33] and this is rarely done. Because of the variation in the methodology and statistical analysis of validation studies of ambulatory devices, it is not easy to make dogmatic assertions about the accuracy of the many devices now available. However, the American Association for the Advancement of Medical Instrumentation has recently published a standard for electronic and automated sphygmomanometers [34] which is now being used for assessing new devices [35] and the British Hypertension Society is preparing a standardized protocol for validation which will permit comparison between studies, and hopefully allow prospective purchasers to make reasoned decisions on the basis of independent assessment.

The placebo effect of measurement

The existence of the placebo effect in the treatment of a variety of diseases is a well-substantiated phenomenon [36]. Because clinic blood pressure falls in response to placebo in most hypertensive patients [37,38], placebo control has routinely been incorporated into the design of antihypertensive drug studies. An important observation with ambulatory blood pressure measurement is that blood pressure monitored intra-arterially is not subject to the placebo effect [39]. While non-invasive ambulatory measurement has been found to be free of placebo effect in most studies [40–43], this has not been the experience in all cases [44]. The absence of a placebo effect with indirect ambulatory monitoring, if confirmed, would greatly simplify the design and conduct of efficacy studies of antihypertensive drugs. For example, many studies employ a randomized placebo-controlled cross-over design, on the basis that a comparison between treatments in the same subject is more precise and requires fewer subjects than a comparison between subjects. In such studies, a wash-out period before patients, cross-over treatments is recommended to reduce the possibility of a treatment/period interaction [45]. However, if there was no placebo effect with ambulatory blood pressure monitoring, then measurement performed before and repeated at the end of the treatment period would suffice, making the cross-over design with its risks of carry-over effects unnecessary. In fact, this approach has been adopted by Raftery and his colleagues for the last 7 years using direct intra-arterial ambulatory blood pressure measurement [46–50].

Ambulatory measurement and antihypertensive drug efficacy

For the past decade it has been our policy to incorporate ambulatory measurement into the study protocols of blood pressure lowering drugs [51–56]. Initially, we used daytime ambulatory measurement in double-blind, cross-over studies of drug efficacy. From the results of these and other similar studies a number of patterns emerge.

Firstly, ambulatory blood pressure may be in agreement with clinic blood pressure measurements [56–61]. In such studies, where a clinic fall in blood pressure is confirmed by ambulatory blood pressure measurement, the latter also demonstrates what conventional measurement can never show, namely the pattern of an antihypertensive effect over the dosing interval.

Secondly, conventional clinic measurement may fail to detect the blood pressure lowering effect, demonstrated by ambulatory measurement [51,55,62,63]. The studies showing this phenomenon used smaller numbers (six patients [51]; 11 patients [55]; 12 patients [62]; seven patients [63]), and for this reason their power to detect differences between treatments with clinic measurement was low. However, the greater number of observations available with ambulatory measurement, by reducing within-subject variability, greatly increases their power. For example, applying the power calculations for cross-over studies described by Hills and Armitage [45] to the data from one of these studies [55], it can be shown that eight patients would be required if ambulatory measurement was used to assess blood pressure lowering effect (to achieve a power of 85%), whereas 30 patients would be needed with clinic measurement. Ambulatory blood pressure measurement may also afford a means of determining patients likely to respond to drug treatment. In a recent study diltiazem decreased average whole-day blood pressure by 18/13 mmHg in patients whose clinically diagnosed hypertension was confirmed by pre-treatment 24-h blood pressure, but by only 0/1 mmHg in those whose 24-h pressures were normal [64]. This suggests that there are differing antihypertensive responses among patients diagnosed as hypertensive in the clinic, and those in whom hypertension is confirmed by 24-h ambulatory measurement. Given the increasing demands for and the high costs of studies of blood pressure lowering agents, the potential of ambulatory blood pressure to demonstrate clinically significant reductions using smaller samples than those required using clinic measurement [41] or by determining responder status, has important implications.

Finally, reductions in clinic blood pressure may be significant, but ambulatory blood pressure measurement may be either non-confirmatory [44,52,53,65–67], or show that the clinic reduction coincides only with a brief period of ambulatory reduction [54]. Thus, in a study of the antihypertensive efficacy of verapamil in the elderly evaluated by ambulatory blood pressure measurement where clinic blood pressure assessments were carried out within 4 h of dosing, a marked effect on clinic measurement was observed; ambulatory measurement revealed that control was poor for the remainder of the expected duration of the drug's action [54]. However, in other studies using ambulatory measurement [44,52,53,65–71] this loss of blood pressure control was not observed, raising another possibility, namely that the physiological basis of blood pressure elevation in the clinic may be different from that outside the clinic and that the dose of an antihypertensive agent effective in lowering clinic blood pressure may not be effective in reducing ambulatory blood pressure. This hypothesis is supported by the observation that nitrendipine reduces blood pressure effectively in the clinic, but this effect is blunted on ambulatory measurement during work periods [66], possibly due to increased adrenergic activity associate with work. Similarly comparison of the β-blocker timolol with methyldopa showed similar significant reductions in clinic measurement, but ambulatory blood pressure was significantly reduced with timolol only [65]. Likewise, both the β-blocker, betaxolol, and verapamil reduced clinic blood pressure, but only betaxolol significantly reduced ambulatory blood pressure [67]. These studies suggest that β-blocking drugs have a sustained effect on ambulatory blood pressure not shared by drugs with other modes of action. Of considerable practical importance is the fact that many preparations would have been declared as quite efficacious blood pressure lowering agents by conventional measurement, whereas ambulatory measurement showed a pattern of activity that was far less impressive.

Future prospects for ambulatory measurement

Ambulatory blood pressure measurement in the words of Norman Kaplan, is 'an idea whose time has come' [68]. It is also moving into a new phase of development. In most of the studies cited, ambulatory measurement was carried out over a 12–16 h period simply because the devices used were not fully automated thus making night-time measurements impractical. With the new generation of ambulatory recorders, it is possible to obtain 24-h ambulatory measurement which provides not only further evidence of the duration of drug effect but also demonstrates the circadian rhythm of blood pressure. This latter facility, quite apart from being of value in the assessment of antihypertensive drugs, may also have important prognostic implications. 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) [69]. 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 [70]. While the prognostic and therapeutic implications of these findings require further evaluation, they provide cogent evidence in favour of assessing the effects of antihypertensive therapy on sleeping blood pressure, an area where we feel further research is urgently required.

Conclusions

The benefits of ambulatory blood pressure monitoring in the assessment of the efficacy of drug treatment are now well established. Conventional clinic measurement is influenced by many factors which make the technique unsuitable for research into drug efficacy, but more importantly, clinic measurement cannot provide assessment of duration of effect, nor of the effect of antihypertensive drugs on sleeping pressure. If it can be confirmed that non-invasive ambulatory blood pressure measurement is free of any placebo effect, then it is possible that the design of antihypertensive drug studies could be greatly simplified. The

greatest potential for ambulatory blood pressure measurement in assessing drug efficacy may be its ability to reduce significantly the numbers of patients needed in such studies. The time has surely come where studies of antihypertensive drug efficacy which do not assess blood pressure over 24 h should no longer be acceptable.

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