Therapeutic efficacy

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This session was devoted to the application of ambulatory blood pressure monitoring (ABPM) to evaluate the therapeutic efficacy of antihypertensive treatment. Several aspects of this large field have been discussed, but others, no less important, need to be treated and clarified in the future.

In the position paper, Dr B. Waeber reviewed several published reports showing a discrepancy between the results of blood pressure reduction under treatment, according to the method used to assess blood pressure, casual or ABPM, with a smaller decrease in patients with 'normal' ABPM values. He also emphasized the importance of analysing data from the whole group of patients but also in some definite subgroups, such as patients with 'clinic' or 'white-coat' hypertension, responders and non-responders, patients with normalized blood pressures and so on. This data analysis must consider the effect of placebo, which seems to be less on non-invasive ABPM than on the casual measurements. In other respects, evaluation of the compliance with treatment, assessed by an objective method, could improve the analysis of blood pressure profiles, according to the precise time of drug intake. This approach might be helpful in the chronotherapy field.

The response of ABPM to antihypertensive therapy guided by clinic blood pressure was analysed in a study by Fagard *et al.*; their results indicate the limits below which blood pressures measured by ABPM do not decrease under treatment when the decision to institute or to intensify drug treatment is based on clinic blood pressure measurement. Under angiotensin converting enzyme inhibitor and calcium antagonist treatments, with or without hydrochlorothiazide, this minimum ABPM result averaged 128/88 mmHg for daytime, 106/73 mmHg for night-time and 119/81 mmHg for the whole 24 h, with upper 95% confidence limits of 137/93, 115/78 and 127/86 mmHg, respectively. It is important to note here that the finding of different minimum ABPM results in the day and night periods might constitute an argument that antihypertensive treatment must respect the circadian cycle of blood pressure and that the well-known 'initial level' law used to analyse blood pressure reduction could differ from day to night. This interesting approach needs to be investigated, using other drugs and several doses in order to clarify the attractive notion of a 'minimum level'.

The reproducibility of ABPM and its sensitivity to placebo were analysed in detail by Asmar *et al.* in a multicentre French study using a cross-over design, which allows one to analyse the reproducibility or the regression of the mean separately from the 'proper' effect of placebo. They showed for a group of patients that ABPM are more reproducible than clinic blood pressure measurements and that administration of placebo is accompanied by a significant reduction in clinic blood pressure but not in ABPM result averages with virtually superimposable hourly blood pressure values. Using an individual approach, based on the clinic blood pressure placebo response, they showed that placebo affects both the casual and the ambulatory measurements, mainly during the daytime; clinic and ABPM measurements are less reproducible in the placebo responder patients than in the whole group; and placebo responders present lower baseline ABPM results, which remain within the normal range, than do the non-responders. These results confirm that non-invasive ABPM is sensitive, but less so than clinic blood pressure measurement, to the proper effect of placebo, which is independent from any alerting or familiarization reaction, and suggest that clinical trials must include placebo and patients with high ABPM results.

If the data analysis must always be performed in the whole study population, Dr B. Waeber emphasized that complementary analyses in some subgroups of patients may provide interesting information. In fact, for the evaluation of treatment efficacy, including in the analysis patients with 'clinic' or 'white-coat' hypertension can lead one to underestimate the efficacy of the test compound. Indeed, the major classes of antihypertensive drugs have little effect in this subgroup of patients. He also showed that the trough : peak ratio can be extremely erratic in non-responder patients. Thus, the analysis of antihypertensive drug trials should be restricted not to groups of patients but rather to individual patients. So, on the basis of which average values must the 'responder' patients be defined when using ABPM? Studies are needed to establish this definition clearly.

Concerning the trough : peak ratio, Dr P. Meredith showed that trough : peak effect calculations must be performed according to an appropriate methodology for an acceptable level of accuracy and reproducibility. In order for a study to define the trough : peak ratio appropriately, he emphasized the importance of considering the antihypertensive effect of placebo and the circadian variability in blood pressure which is particularly likely to compromise the interpretation of the peak effect. The study design should incorporate a placebo group, provide an adequate placebo running-in period and specify that individual patients be studied under carefully standardized conditions. Thereby, and only if the trough : peak ratio is appropriately defined and calculated, can it be considered a good parameter characterizing the duration of action of an antihypertensive drug. Most reports showed that the 2 h average values used to calculate the peak effect and to smooth the intracircadian blood pressure variability may represent a good compromise. This needs to be clarified and established in further specific studies.

The use of ABPM in the evaluation of the non-responder patients was analysed by J. Redon, who showed that about 40–50% of treated patients with poor control of office blood pressure have a 'normal' ABPM result and that antihypertensive treatment fails to reduce ABPM values when the pretreatment level of an awake patient was lower than 90 mmHg for diastolic blood pressure. This emphasizes the target to achieve in terms of blood pressure level and reduction under treatment using ABPM.

Several important points concerning the application of ABPM to evaluate the therapeutic efficacy of antihypertensive treatment have been discussed and clarified. More studies are needed to analyse other points. In fact, in addition to the average values, the impact of antihypertensive treatment on other parameters obtained using ABPM (e.g. blood pressure variability, circadian profile and early morning increase) could provide further information concerning the mechanisms of treatment and organ damage. Elsewhere, the use of non-invasive ABPM in chronotherapeutic assessment needs to be specified. What is the ambulatory blood pressure target to achieve for reducing hypertension-induced morbidity and mortality? Is the prognostic significance of ABPM during treatment greater than that of office blood pressure measurement? Only collecting data from trials and prospective studies will help to answer these questions and thus to delineate guidelines concerning the exact role which should be played by ABPM in the assessment of antihypertensive treatment.