Trough-to-peak ratio of indapamide 1.5 mg sustained-release coated tablets assessed by ambulatory blood pressure monitoring

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Summary

Trough/Peak Ratio (T/P) of indapamide 1.5 mg sustained-release form assessed by ambulatory blood pressure monitoring (ABPM).

Because of the high variability of casual blood pressure measurements, ambulatory blood pressure monitoring (ABPM) has become a complementary clinical tool for evaluating antihypertensive treatment. Nevertheless, there is still a lack of practical guidelines to interpret the data. A review of the literature shows that ABPM efficacy data are analyzed differently, especially the trough-to-peak ratio proposed by the Food and Drug Administration. Published trough-to-peak ratios are widely disparate due to the diversity of the calculation methods, which are usually not justified. Thus, inappropriate comparisons of these results can easily produce incorrect conclusions. The aim of this review is to select, through the literature, basic methodological requirements commonly agreed on for accurate trough-to-peak ratio assessment, and to apply them to the ABPM data on indapamide, a diuretic related to the thiazides. Six methodological requirements commonly agreed on at this time are the following: 1. study design: placebo-controlled study with a placebo run-in period; 2. patient selection: compliance with the study protocol, record obtained before and after treatment for each patient; 3. population analysis: whole and responder population; 4. quality control of the records; 5. placebo effect subtraction; 6. group and individual calculation with the indication of median values. Given that no trough-to-peak ratio has yet been calculated according to these requirements, especially for a diuretic, the above methodological points were taken into account for the calculation of the trough-to-peak ratio of indapamide, from a placebo-controlled dose-finding study involving 285 patients. *Arch Mal Cœur.* 1996, Servier International N° spécial, août 1996: 2-12.

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Blood pressure is conventionally measured using clinical sphygmomanometry; it has also been prognostically validated as the reference method [1]. Other methods, such as ambulatory blood pressure monitoring (ABPM) and self-measurement at home, have broken new ground and enhanced precision, with particular regard to the assessment of antihypertensive therapy. Technical improvements over the last 5 years, combined with instrumental validation, have transformed ABPM into an authentic clinical tool [2]. A parallel development was the 1988 Food and Drug Administration (FDA) recommendation of a new arithmetic index, the trough-to-peak ratio, for monitoring antihypertensive drug activity (recommended minimal value: 50%) [3]. The trough-to-peak ratio describes the relationship between antihypertensive effect at the end of the dosing interval (trough) and maximal effect (peak) by simple arithmetic division, expressed as a percentage. The trough-to-peak ratio is a pharmacological tool used to identify an adversely excessive peak due to the administration of an unnecessarily high dose and/or to identify an inappropriate dosing interval [4]. However, the FDA gave no detailed recommendation as to the mode of calculation, thereby raising practical problems of calculation and interpretation. ABPM is better suited than clinical sphygmomanometry to evaluate the trough-to-peak ratio, given its reproducibility and the serial measurements [5].

Indapamide, an antihypertensive diuretic, is a thiazide sulfonamide [6]. A new low-dose (1.5 mg) sustained-

release (SR) formulation has been developed to maximize the efficacy/safety ratio following international recommendations favoring low-dose antihypertensive therapy in hypertension [7, 8].

A dose-finding study using conventional sphygmomanometry showed that the antihypertensive efficacy of indapamide SR coated tablets 1.5 mg exceeded that of placebo 24 h after dosing and did not differ from that of the same formulation containing 2 mg or 2.5 mg, or from that of the immediate-release (IR) 2.5 mg formulation [9]. In addition, the lower dose reduced the incidence of hypokalemia by > 50%. The aim of the present paper is to propose a valid method of ABPM trough-to-peak ratio analysis and apply it to indapamide to supplement evaluation of the conventionally determined efficacy data.

AMBULATORY BLOOD PRESSURE MONITORING AND TROUGH-TO-PEAK RATIO

There are undeniable limitations to the conventional method of blood pressure measurement: limited reproducibility, single (as opposed to serial or repeated) measurement, a white-coat effect and a marked placebo effect. ABPM has several advantages that circumvent some of these difficulties [10, 11]. It performs and records a large number of measurements during both day and night in subjects leading normal lives; it partially eliminates the white-coat effect and shows little impact of placebo effect; it can be used to determine the activity duration and profile of an antihypertensive drug by giving a detailed description of mean blood pressure over the various phases of the 24-h period; it measures both first- and last-dose effects; it exhibits greater reproducibility of 24-h blood pressure measurements and is better suited to the calculation of trough-to-peak ratios. The current brake on its wider deployment is the lack of an international consensus on its use and interpretation, for the following reasons: absence of an international normal range, absence of prognostic data from large-scale clinical trials, absence of public health cost/benefit analysis, the constant need to include a placebo group in clinical trials, and poorer reproducibility of hourly measurements, necessitating substantial sample sizes for trough-to-peak analysis [10]. The following data are usually presented in the literature: mean diastolic blood pressure (DBP), systolic blood pressure (SBP), and heart rate (HR) over 24 h, day and night, standard deviation (SD), and the 24-h mean blood pressure profiles. These data are in fact the minimum required by the French Hypertension Society measurement group [12]. Mean values at specific periods, such as waking (getting up) and resting (going to bed), as well as other parameters reflecting blood pressure variability, are sometimes also presented [13]. The trough-to-peak ratio is also often calculated as a measure of the relationship between dose and duration of activity.

Calculation of the trough-to-peak ratio

The method of calculation is rarely discussed in detail. The trough-to-peak ratio is often calculated from the mean blood pressures published per treatment group, without giving the individual data; sometimes it is calculated from a fitted dose/plasma concentration-response curve [14]. The validity of the calculation method depends closely on the general study methodology; some key recommendations drawn from the literature and our own experience are presented below.

Study design

The crossover study is ideal in theory as the patient acts as his/her own control, but it can cause problems, in particular with respect to repeating ABPM [15]. In practice, therefore, a randomized parallel-group study over 4–6 weeks with a placebo control and placebo run-in are the minimum needed but not often achieved: durations of 2–4 weeks, no placebo, and even single dosing are sometimes seen instead. It is preferable for such a study to be conducted at an early stage of product development to validate the choice of dosage [15, 16].

Population analyzed

Pre- and post-treatment recordings must be available for each patient to enable each trough-to-peak ratio to be calculated on an individual basis in patients acting as their own controls. This is not always the case: individual values are often grouped, and analyzed in terms of all pre- vs all post-treatment data. Analysis of the entire study population should be supplemented by the analysis of subgroups, eg, patients who are responders or hypertensives in ABPM terms; this is informative, as nonresponders cause overestimation of the trough-to-peak ratio due to the absence of peak effect [15, 17-20], while 25% to 30% of the patients included in the studies according to World Health Organization criteria have normal or only slightly raised ABPM data [1]. Selection-inclusion and treatment response blood pressure criteria should be defined on the basis of ABPM data.

Blood pressure measurement

When blood pressure is measured using conventional sphygmomanometry, this should preferably be repeated in a research unit under standardized conditions [21-24] rather than during a visit at a predetermined time of "peak effect" [25-27]. ABPM must be favored over conventional sphygmomanometry and the following details given: type of device (compliance with British Hypertension Society [BHS] and/or American Association for the Advancement of Medical Instrumentation [AAMI] criteria), the conditions under which ABPM is performed (standardization of recording times, number of measurements, duration of recording, time of dosing etc), and the type of data quality control [1, 28].

Data processing

The selection of the data for analysis must be described (nature and percentage of aberrant values discarded, processing of missing data, percentage of cor-

rect measurements required, etc). Smoothing of the curve is generally necessary to avoid incorrectly identifying an accident of blood pressure variability as an efficacy peak. Data should be averaged over time blocks of 1–2 h (from measurements made at 15- or 30-min intervals), as longer periods artificially flatten the profile, causing overestimation of the trough-to-peak ratio by effacing the peak effect [20, 29-31].

Identification of the peak effect

The ABPM data should be scanned for peak effect in the first 6–8 h after dosing excluding the first 2 h, to eliminate a possible white-coat effect [32]. For this interval to be accurately determined, the exact time of dosing must be noted with respect to commencement of recording. No attempt should be made to identify peak effect from the overall 24-h data, as is sometimes done, since the longer the search period, the greater the probability of artefactual peaks.

Identification of the trough effect

Identifying the residual effect at the end of the dosing interval raises fewer difficulties as the trough occurs by definition at 24 h in the case of a once-daily drug. To retain its full significance, trough effect should be measured in the last hour (or last 2 h at most), and as far as possible in patients who are both awake and up. Sometimes it is measured in the last 2–4 h of the dosing interval; however, the longer the interval, the more the ratio is likely to be underestimated due to the presence of lower values at the end of the night [33].

Method of trough-to-peak ratio calculation

The general formula is shown below and the result expressed as a percentage [24]:

$$\frac{\Delta \text{ (placebo-treatment) in trough DBP (or SBP)}}{\Delta \text{ (placebo-treatment) in peak DBP (or SBP)}} \times 100\ (\%)$$

The formula is usually applied using two methods [15-17, 20, 31, 34-41]:

– either group calculation from mean blood pressure values in a group of patients: trough and peak effects are identified on the mean pressure curve, and the group trough-to-peak ratio calculated by simple arithmetical division;

– or calculation from the individual blood pressure values: individual ratios are calculated from the individual trough and peak effects, together with the median (non-Gaussian distribution) and an index of variability (confidence interval of the median or quartiles) [18]. It should also be stated whether the data include individual trough-to-peak ratio values equal to 0, < 1, or > 0 [36].

Subtraction of placebo effect - the sole methodological guideline issued by the FDA - is a frequently used expression but the method involved is not clearly described:

– individual trough-to-peak ratio: only a crossover study makes it possible to subtract placebo blood pressure from treatment blood pressure within the same patient; in practice, as parallel-group designs are more common, it is the placebo run-in blood pressure which is subtracted;

– group trough-to-peak ratio: the calculation can be performed in different ways [19]: the placebo effect should be considered as subtracted from the outset by the very fact of subtracting the placebo run-in blood pressures, in which case no further procedure is necessary. It is not then also necessary to subtract the placebo effect found in the placebo group, particularly in that the study design is not usually crossover.

Trough-to-peak ratio of diastolic and systolic blood pressure

The trough-to-peak ratio should be calculated for diastolic and systolic blood pressure since the latter is recognized as an independent cardiovascular risk factor.

Main trough-to-peak ratio results

Published values are highly variable and even contradictory between studies, within the same class of drug, the same drug, and even the same formulation of that drug. This is readily explained by the diversity of study designs, modes of blood pressure recording, methods of calculation, dosages, and pharmacokinetics (half-life, linearity).

Many converting enzyme inhibitors [43], calcium antagonists [44, 45], and beta-blockers [46] may have an acceptable trough-to-peak ratio on single dosing; however, methodologically sound studies are required to confirm the hypothesis in each case. Dose may affect the trough-to-peak ratio of drugs with nonlinear pharmacokinetics, eg, converting enzyme inhibitors or beta-blockers [34, 43, 47], in contrast to calcium antagonists with linear pharmacokinetics [47]. There has been little investigation of diuretic trough-to-peak ratios, except for a recent study whose methodology did not comply with the requirements enunciated above [48].

In conclusion, the diversity of the methods used without clearly established justification highlights a real need to standardize calculation of the trough-to-peak ratio. We propose that the following minimum rules apply:

– a controlled study vs placebo preceded by a placebo run-in;

– protocol-compliant patients with pre- and post-treatment data;

– analysis of the whole study population and responder subgroup;

– data quality control;

– explicit subtraction of the placebo effect;

– calculation of both group and individual (plus median) trough-to-peak ratios.

There have been few trough-to-peak ratio studies of antihypertensives complying with the above guidelines to date, and fewer still with antihypertensive diuretics [15, 37, 42].

INDAPAMIDE'S TROUGH-TO-PEAK RATIO

The new sustained-release (SR) formulation of indapamide 1.5 mg was validated in a dose-finding study using conventional sphygmomanometry 24 h after dosing [9], which showed antihypertensive efficacy greater than placebo and similar to that achieved both with higher dosages of the same formulation and the 2.5-mg immediate-release (IR) formulation; the lower dose SR formulation also reduced the incidence of hypokalemia (< 3.4 mmol/L) by > 50%, thereby optimizing the efficacy/safety ratio. The aim of the present study was to apply a valid method of trough-to-peak ratio analysis to the indapamide ABPM data to supplement assessment of the efficacy data obtained by conventional sphygmomanometry. However, the analysis of the ABPM data is purely descriptive as the selection criterion and primary outcome measure were determined using conventional sphygmomanometry in compliance with WHO criteria.

The protocol and conventional sphygmomanometry efficacy results have already been published elsewhere [9].

Study design

This was a European placebo-controlled dose-finding study randomized into parallel groups comprising a 1-month-placebo run-in followed by double-blind once-daily dosing with placebo, indapamide IR 2.5 mg, or indapamide SR 1.5, 2, or 2.5 mg for 2 months.

Patients

The inclusion criteria were age 18 to 70 years and mild-to-moderate hypertension (supine diastolic blood pressure: ≥ 95– ≤ 114 mm Hg).

Blood pressure measurement

In addition to conventional sphygmomanometry, all patients underwent 24-h ABPM on the last day of the run-in (M0) and last day of active treatment (M2). Two devices were used: SL 90207 (Spacelabs) and Diasys 200 R (Novacor), with the same device being used for both recordings in each patient. All patients were fitted with the device between 08:00 and 10:00 h, 24 h after the last dose, during a day of normal activity. Dosing was performed after fitting; the device was removed by the investigator 24 h later, the following morning, before the next dose. The devices were programmed to record blood pressure every 15 min from 06:00 to 22:00 h and every 30 min from 22:00 to 06:00 h.

Selection of data for analysis

The data were selected using the following quality control guidelines: compliance with device fitting times (08:00–10:00 h), 24-h recording, elimination of aberrant values (DBP > SBP, DBP < 40 mm Hg or > 140 mm Hg, SBP < 50 mm Hg or > 240 mm Hg) except if clinically justified, elimination of recordings containing < 80% of validated measurements, absence of > 1 averaging interval.

Statistical analysis

The ABPM data were secondary efficacy measures: variation in diastolic and systolic blood pressure over 24 h, during the day (07:00–22:00 h) and during the night (22:00–07:00 h). Analysis of covariance vs inclusion blood pressure was performed using SAS software in patients with both pre- and posttreatment data as required by the protocol.

Calculation of trough-to-peak ratio

Calculation was based on the methodology described above: data averaging in 2-h blocks, calculation of both group and individual trough-to-peak ratios, subtraction of run-in placebo effect, calculation of ratios in the overall population and in the responder and hypertensive subgroups (in terms of ABPM), peak effect defined as the maximal decrease in daytime blood pressure, excluding the first 2 h after fitting the recording device, ie, the 2–13 h post-fitting interval, or 10:00–21:00 h assuming fitting at 08:00 h, trough effect defined as the value at 23:00–24:00 h after dosing, ratios calculated separately for diastolic and systolic blood pressure.

Results

Patients before and after treatment for 2 months

Of the 285 patients, 266 completed the 2 months of the study in compliance with the protocol (two patients were included in error and there were 17 drop-outs, for reasons previously described elsewhere) [9].

Following data quality control, 109 patients were selected for analysis. Their characteristics are shown in table I. Mean ambulatory 24 h, daytime (07:00–22:00 h) and nocturnal (22:00–07:00 h) blood pressures and heart rate at inclusion and after treatment for 2 months are shown in table II, together with the rates of responses (defined as a reduction in daytime DBP > 5 mm Hg or in daytime SBP > 7 mm Hg). Mean blood pressure differed between treatment groups at inclusion; in particular, blood pressure was lowest in the indapamide SR 1.5 mg group. Analysis of covariance taking the baseline blood pressure imbalance into account showed that the reduction in DBP with indapamide SR 1.5 mg differed significantly from that on placebo, but not from that on indapamide IR 2.5 mg, except in nocturnal DBP. The reduction in SBP on indapamide SR 1.5 mg differed significantly from placebo except in nocturnal and 24-h SBP. The variation

TABLE I – DEMOGRAPHIC CHARACTERISTICS

	P	IR 2.5	SR 1.5	SR 2	SR 2.5
Patients analyzed (included) (n)	19 (53)	28 (54)	21 (52)	22 (49)	19 (58)
Age (years) (SD)	52.5 (9.0)	53.9 (8.7)	56.6 (10.1)	52.3 (12.3)	53.1 (8.4)
Sex (n) (men)	13 (68.4)	16 (57)	13 (61.9)	13 (59.1)	9 (47.4)
Body weight (kg) (SD)	71.6 (14.5)	69.1 (11.7)	75.7 (15)	74 (14.1)	72.5 (9.3)
Previous HT treatment [n (%)]	11 (57.9)	19 (67.9)	11 (52.4)	10 (45.5)	12 (63.2)
Duration of HT (years) (SD)	3.4 (3.6)	3 (3.3)	1.7 (1.8)	4 (6.6)	5.5 (4.9)
Casual DBP (mm Hg) (SD)	101.2 (4.9)	101.7 (5.2)	100.8 (4.1)	101.6 (5.3)	101.6 (4.7)
Casual SBP (mm Hg) (SD)	162.6 (15.4)	162.9 (15.3)	161.9 (14.7)	164.7 (15.0)	159.6 (18.8)
HT at inclusion (ABPM criteria) [n (%)]	15 (79)	19 (68)	17 (8)	17 (77)	12 (63)

P: placebo; IR 2.5: indapamide 2.5 mg immediate-release tablets; SR 1.5: indapamide 1.5 mg sustained-release coated tablets; SR 2: indapamide 2 mg sustained-release coated tablets; SR 2.5: indapamide 2.5 mg sustained-release coated tablets; HT: hypertension; SD: standard deviation; casual DBP: supine diastolic blood pressure at inclusion using conventional sphygmomanometry; casual SBP: supine systolic blood pressure at inclusion using conventional sphygmomanometry; ABPM: ambulatory blood pressure monitoring; ABPM criteria of hypertension: 24-h DBP > 87 mm Hg or 24-h SBP < 139 mm Hg.

in heart rate with indapamide SR and IR did not differ from that with placebo in any period. The mean reductions in DBP and SBP are shown per period and treatment group in figure 1. Pre- and posttreatment 24-h blood pressure profiles in the three treatment groups: placebo, indapamide SR 1.5 mg, and indapamide IR 2.5 mg are shown in figure 2.

Calculation of indapamide trough-to-peak ratios

Group vs individual trough-to-peak ratios

The DBP peak effect was - 8.4 mm Hg on indapamide IR 2.5 mg and - 9.5 mm Hg on indapamide SR 1.5 mg, with troughs of - 8.2 mm Hg and - 8.1 mm Hg, respectively, giving group trough-to-peak ratios of 98% and 85%. DBP and SBP values in the other groups are shown in table III. DBP individual trough-to-peak ratios were 60% (median) on indapamide IR 2.5 mg (1st and last quartiles: 18%, 111%) and 60% on indapamide SR 1.5 mg (16%, 89%). Median SBP and DBP values in the five treatment groups are shown in figure 3a.

Overall population vs responders and hypertensives (ambulatory vs conventional blood pressure measurement)

DBP individual trough-to-peak ratios in responders in terms of ABPM (reduction in daytime DBP > 5 mm Hg or in daytime SBP > 7 mm Hg) were 60% (IR 2.5 mg) and 55% (SR 1.5 mg) (Figure 3a). In responders in terms of conventional blood pressure

TABLE II – ABPM DATA BEFORE AND AFTER TREATMENT FOR 2 MONTHS

	P (n = 19)		IR 2.5 (n = 28)		SR 1.5 (n = 21)		SR 2 (n = 22)		SR 2.5 (n = 19)	
	M0	M2	M0	M2	M0	M2	M0	M2	M0	M2
DBP mm Hg (SD)										
24 h	93.4 (6.7)	91.3 (8.5)	91.3 (11.9)	83.1 (7.8)	89.1 (8.6)	83.8 (9.7)	93.2 (9.9)	84.5 (9)	91.7 (9.8)	85.8 (9.5)
D	97.7 (8)	94.7 (9.2)	94.7 (12)	87.1 (8.6)	93.5 (8.6)	86.5 (10)	96.8 (10.1)	87.7 (9.7)	94.6 (10.5)	89.2 (9.5)
N	79 (8.4)	79.1 (11.4)	80.4 (12.8)	70.0 (8.5)	76.1 (9.4	73.8 (10.4)	81 (9.3)	74.3 (7.7)	82.2 (10.1)	74.8 (9.5)
SBP mm Hg (SD)										
24 h	144.9 (13.8)	140 (13.9)	143.3 (16.3)	129.2 (11.8)	142.3 (10.8)	131.9 (11.3)	145.1 (15.6)	132 (14.5)	144.2 (12.5)	134.3 (13.3)
D	150.2 (14.3)	143.8 (13.7)	147.2 (16.8)	133.5 (12.3)	147.5 (11)	135.2 (12)	148.7 (15.8)	135.5 (15.3)	147.7 (12.5)	138 (13.3)
N	128.1 (16.7)	126.7 (8.7)	130.5 (17.3)	115.7 (13.6)	126.6 (12.8)	121.4 (12.2)	133.7 (16.2)	121.8 (12.8)	133.5 (15)	122.2 (12.9)
Responders (ABPM criteria) [n (%)]	8 (42)		22 (79)		16 (76)		19 (86)		8 (42)	
Heart rate (bpm) (SD)										
24 h	78.5 (10.2)	79 (10)	77 (9.7)	78.8 (9.4)	74.0 (7.9)	75.6 (8.7)	76.9 (6.1)	79.3 (5.8)	76.5 (10.3)	80.1 (8.6)
D	81.2 (10.8)	81.7 (10.9)	80.2 (10.2)	82.6 (10.1)	76.2 (8.5)	78.0 (8.8)	80.2 (7)	82.8 (6.7)	79.2 (10.7)	83.5 (8.8)
N	69.6 (9.3)	69.9 (8.9)	66.6 (8.9)	66.6 (8.2)	66.7 (6.9)	68.0 (10)	67.0 (5.6)	68.5 (6.1)	67.1 (9.7)	67.9 (8.8)

P: placebo; IR 2.5: indapamide 2.5 mg immediate-release tablets; SR 1.5: indapamide 1.5 mg sustained-release coated tablets; SR 2: indapamide 2 mg sustained-release coated tablets; SR 2.5: indapamide 2.5 mg sustained-release coated tablets; M0: inclusion visit; M2: end of study visit after treatment for 2 months; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; D: day; N: night; ABPM criteria of response: reduction in daytime DBP ≥ 5 mm Hg or in daytime SBP ≥ 7 mm Hg.

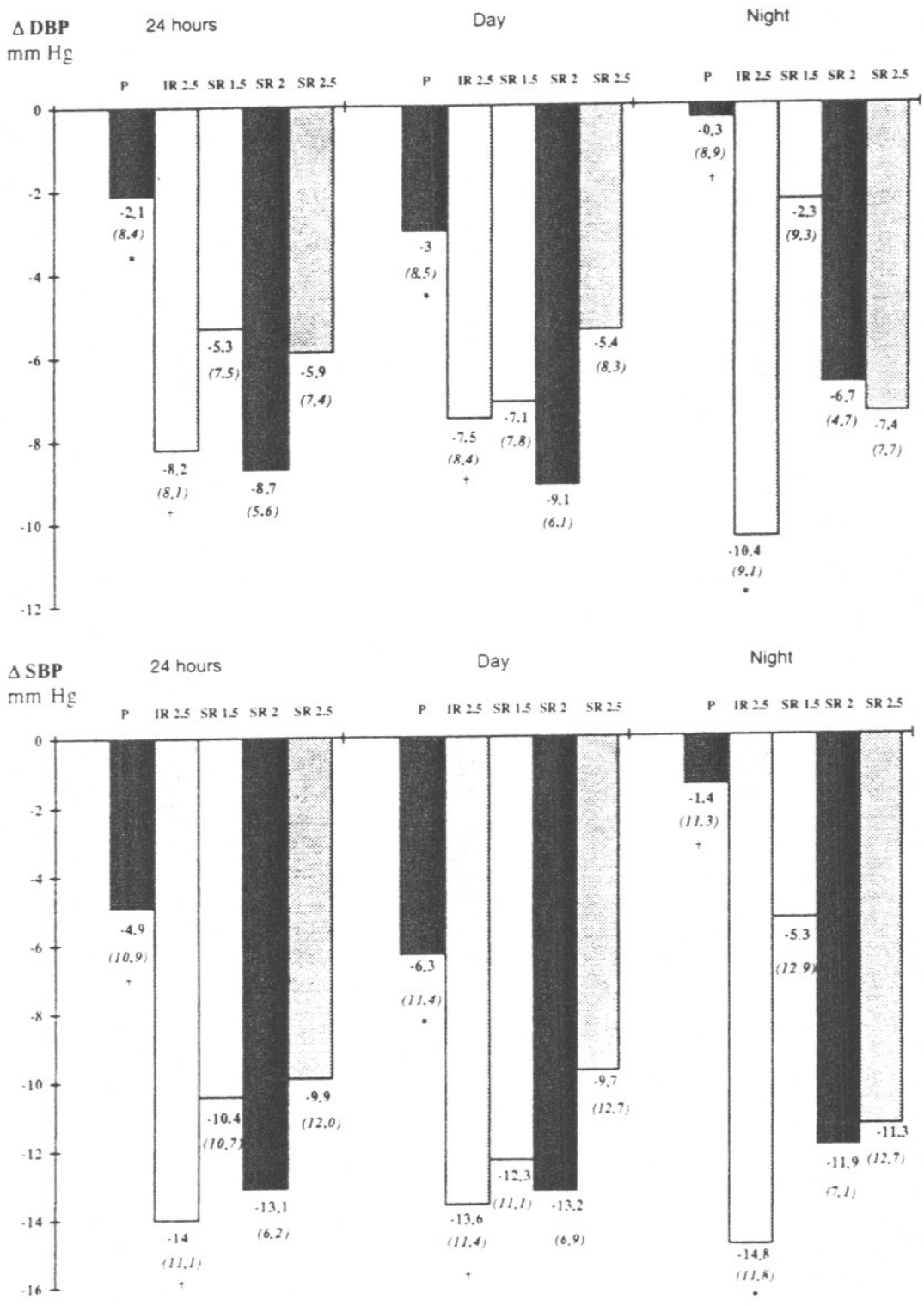

FIG. 1 – Mean systolic and diastolic blood pressure reduction. (P: placebo; IR 2.5: indapamide 2.5 mg immediate-release tablets; SR 1.5: indapamide 1.5mg sustained-release coated tablets; SR 2: indapamide 2 mg sustained-release coated tablets; SR 2.5 : indapamide 2.5 mg sustained-release coated tablets; SD: standard deviation; Δ DBP: mean reduction in diastolic blood pressure after treatment for 2 months; Δ SBP: mean reduction in systolic blood pressure after treatment for 2 months; †: P · 0.05 SR 1.5 mg vs placebo or vs IR 2.5 mg; * : P · 0.05: SR 1.5 mg vs placebo or vs IR 2.5 mg).

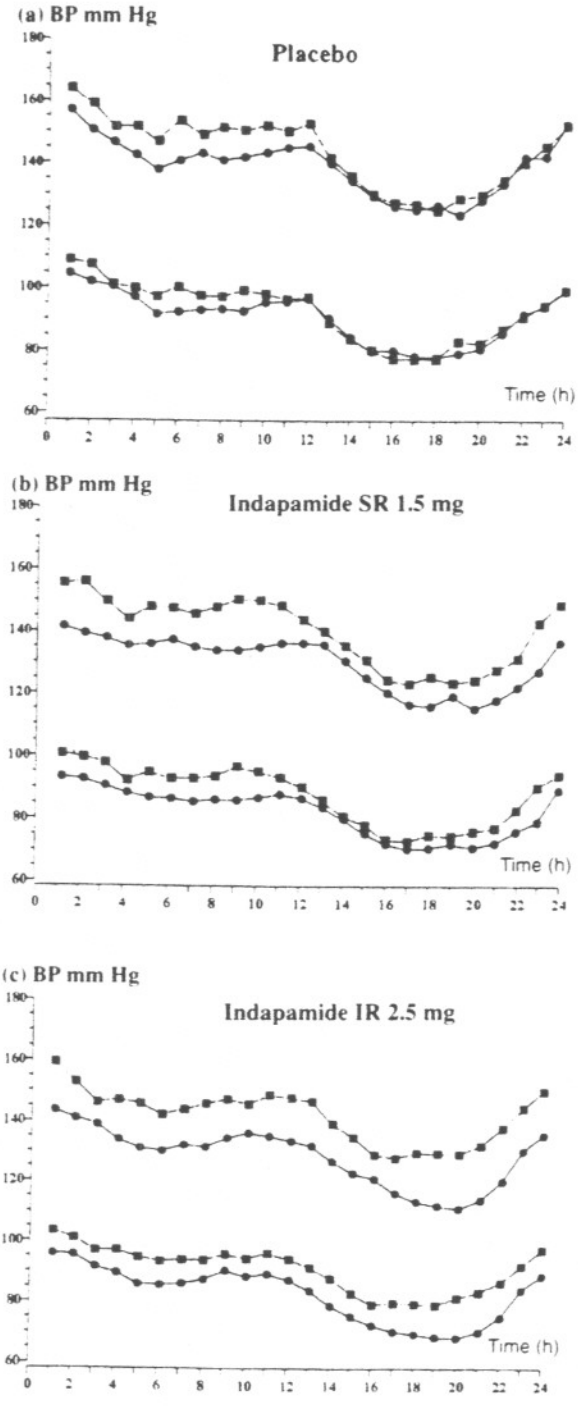

Fig. 2 – Chronogram of systolic and diastolic blood pressure (SBP, DBP) before and after treatment for 2 months. (a: placebo; b: indapamide SR 1.5 mg; c: indapamide IR 2.5 mg; SBP: systolic blood pressure; DBP: diastolic blood pressure; ■: averaged hourly values at inclusion; ●: averaged hourly values after treatment for 2 months).

criteria (DBP ≤ 90 mm Hg or decrease in DBP ≥ 10 mm Hg), median DBP individual trough-to-peak ratios were 82% (IR 2.5 mg) and 60% (SR 1.5 mg); the respective SBP ratios were 74% and 53%. In patients hypertensive in terms of ABPM (24 h DBP > 87 mm Hg or 24 h SBP > 139 mm Hg), median DBP individual trough-to-peak ratios were 41% (IR 2.5 mg) and 60% (SR 1.5 mg) (figure 3a).

DISCUSSION

ABPM provides a description of the antihypertensive effects of different doses of a drug and their duration and profile of activity in phase II trials. There is no question as yet of ABPM data replacing conventionally acquired data; as the latter have been validated in terms of their prognostic significance, they remain the gold standard for determining the minimal active dose of an antihypertensive drug [1]. The 1.5 mg dose of indapamide SR was itself validated through the use of conventional sphygmomanometry [9]. The purpose of analyzing the ABPM data was that of descriptive validation.

Methodology

The analysis of the ABPM data complied with the following stringent criteria: the study was conducted at an early stage of product development [16]; both design and duration were appropriate for assessing the full efficacy of the study drug; the data were quality-controlled in compliance with a number of explicit guidelines; the recording devices were officially approved (the Spacelabs SL 90207 device met BHS and AAMI criteria for DBP and SBP; the Novacor Diasys 200 R device met AAMI criteria for DBP and SBP and BHS criteria for SBP) [28]. Patients who were hypertensive in ABPM terms were identified using the criteria in the meta-analysis by Staessen et al [31]. The criteria of treatment response and calculation of individual trough-to-peak ratios complied with current criteria [15-17, 20, 31, 34-42].

Limitations

The study has a number of limitations. Patient selection-inclusion criteria were based on data obtained by conventional sphygmomanometry rather than by ABPM. Data control resulted in the rejection of > 50% of patients from the analysis. Though the time of fitting of the recording device was documented, and though investigators were required to administer treatment immediately after fitting, time of dosing was not itself documented [49], but simply equated by extrapolation to the time of fitting. The times of going to bed, waking up, and getting up were not documented. The data were scanned for peak effect over a long interval, 2–13 h after dosing (daytime), which may have led individual trough-to-peak ratios to be underestimated; the 2–8 h post-dosing interval might have been more appropriate [38]. Individual trough to peak ratios of 0, ⁻ 0, or · 100 were includ-

TABLE III – TROUGH-TO-PEAK RATIO CALCULATED IN GROUPS (PLACEBO RUN-IN EFFECT SUBTRACTED)

	Placebo (n = 19)	IR 2.5 mg (n = 28)	SR 1.5 mg (n = 21)	SR 2 mg (n = 22)	SR 2.5 mg (n = 19)
DBP					
. peak effect (mm Hg)	−6.8	−8.4	−9.5	−11	−8.4
. time of peak (2-h block)	4-5	4-5	8-9	6-7	8-9
. trough effect (mm Hg)	−0.4	−8.2	−8.1	−7.9	−5.9
. TPRg (%)	6	98	85	72	70
SBP					
. peak effect (mm Hg)	−11.0	−14.0	−16.0	−14.5	-10.9
. time of peak (2-h block)	4-5	10-11	8-9	2-3	8-9
. trough effect (mm Hg)	−1.5	−14.5	−14.2	-11.0	-12.8
. TPRg (%)	14	104	89	76	117

P: placebo; IR 2.5: indapamide 2.5 mg immediate-release tablets; SR 1.5: indapamide 1.5 mg sustained-release coated tablets; SR 2: indapamide 2 mg sustained-release coated tablets; SR 2.5: indapamide 2.5 mg sustained-release coated tablets; DBP: diastolic blood pressure; SBP: systolic blood pressure; TPRg: group trough-to-peak ratio calculated from group mean blood pressures.

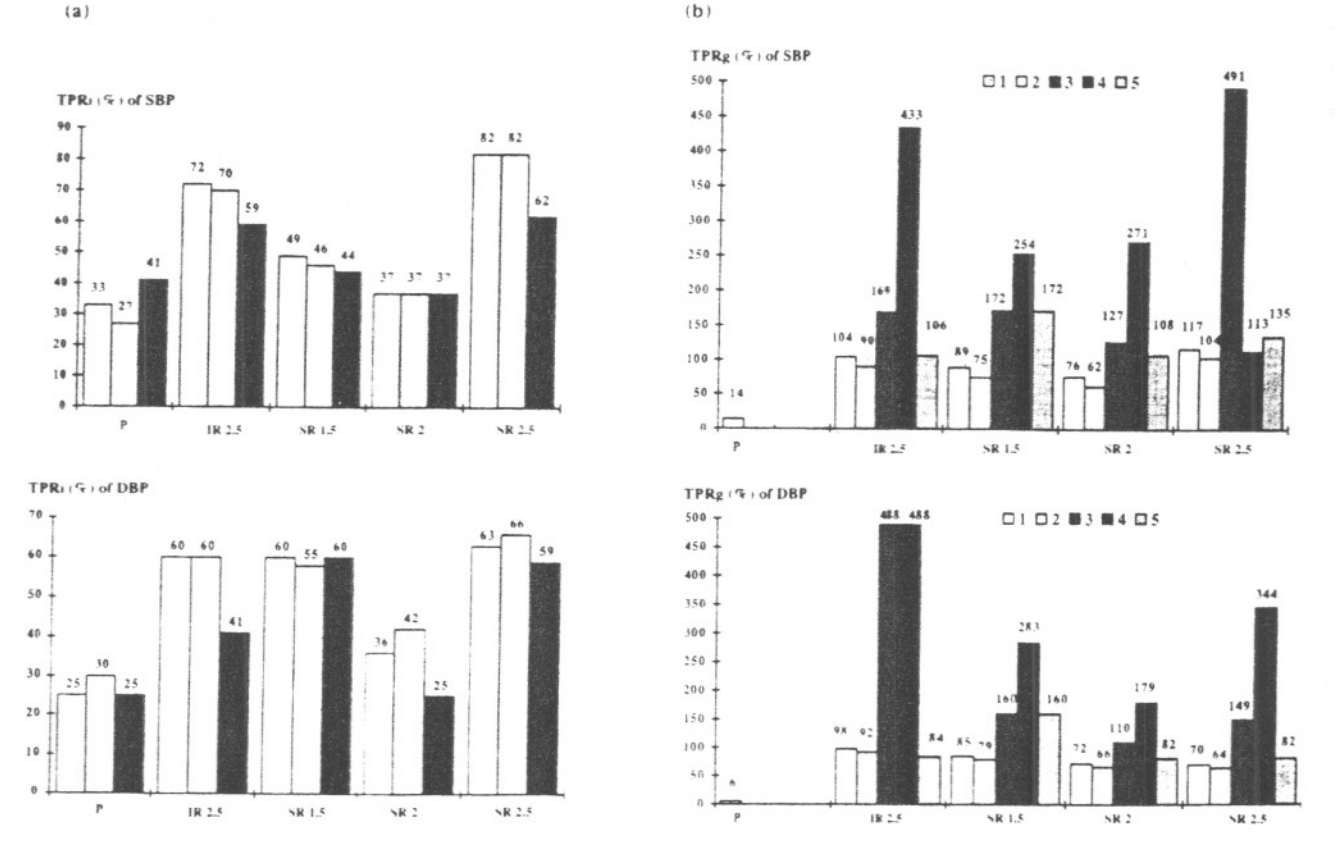

FIG. 3 – Individual and group systolic and diastolic blood pressure trough-to-peak ratios. i : individuals; g : group; P: placebo; IR 2.5: indapamide 2.5 mg immediate-release tablets; SR 1.5: indapamide 1.5 mg sustained-release coated tablets; SR 2: indapamide 2 mg sustained-release coated tablets; SR 2.5 : indapamide 2.5 mg sustained-release coated tablets; SD : standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; (a): individual trough-to-peak ratios calculated from individual values and ratios (median) [□: individual trough-to-peak ratios (median) in the overall population; □: individual trough-to-peak ratios (median) in ambulatory blood pressure measurement (ABPM) responders (reduction in daytime DBP ≥ 5 mm Hg or in daytime SBP ≥ 7 mm Hg); ■: individual trough-to-peak ratios (median) in ABPM hypertensives (24 h DBP > 87 mm Hg or 24 h SBP ≥ 139 mm Hg)]; (b): group trough-to-peak ratios calculated from mean group values using different methods (1: subtraction of the run-in placebo effect; 2: subtraction of the control placebo effect by subtracting the group trough-to-peak ratios of the placebo and treated groups; 3: control placebo effect subtracted by subtraction of mean hourly values of the placebo group at the equivalent peak and trough times in the treated group; 4: control placebo effect subtracted by subtracting the placebo group peak and trough effects from those in the treated group; 5: control placebo effect subtracted by subtracting the placebo and treatment curves, time block by time block, before calculating the trough-to-peak ratio.

ed in the calculation, leading to an increase in the variability of the results [20, 35, 49].

Having described these limitations, it should be emphasized that the analysis not only complied with currently recognized methodological requirements but was also the first such analysis undertaken with an antihypertensive diuretic.

Results

The ABPM results confirmed those of clinical sphygmomanometry: the 24-h blood pressure profiles showed that indapamide SR 1.5 mg was similar in antihypertensive efficacy to indapamide IR 2.5 mg (figure 2).

On average, 26% of patients had normal ABPM values at inclusion according to Staessen et al's reference values (table I) [31]; this percentage is within the documented range (25% to 30%). In particular, this was the case for nocturnal blood pressure in the patients randomized to indapamide SR 1.5 mg: DBP 76.1 ± 9.4 mm Hg (< 79 mm Hg) and SBP 126.6 ± 12.8 mm Hg (< 127 mm Hg).

Median individual ratios for indapamide SR 1.5 mg and indapamide IR 2.5 mg were 60% and 60% (DBP) and 49% and 72% (SBP), respectively. Group trough-to-peak ratios were 85% and 98% (DBP) and 89% and 104% (SBP), respectively, which meets FDA requirements under the most stringent calculation conditions.

The effect of mode of calculation (group vs individual) was confirmed: thus group ratios exceeded individual ratios [15, 31, 37].The documented variability in individual ratios was shown by the differences between quartiles and the percentages of patients with individual ratios ⩾ 50% [18, 19, 42]. Fifty-seven percent of patients on indapamide SR 1.5 mg had a DBP trough-to-peak ratio ⩾ 50% vs 54% on indapamide IR 2.5 mg. The nonexclusion of maximum and minimum values (individual trough-to-peak ratio < 0 or > 100) may partly account for this finding [35]. Furthermore, a group trough-to-peak ratio with no indication of numerator or denominator can be misleading; eg, the SBP trough-to-peak ratio of indapamide SR 1.5 mg (89%) was lower than that of indapamide IR 2.5 mg (117%), whereas the peak and trough effects of indapamide SR 1.5 mg were greater than those of indapamide SR 2.5 mg (table III). Also, the diverse methods of placebo subtraction mean that great care should be exercised when interpreting a "placebo-subtracted" result. Some examples of placebo subtraction in calculating group trough-to-peak ratios are given in figure 3b. The methods are: (1) subtraction of the run-in placebo effect; (2) subtraction of the control placebo effect by subtracting the group trough-to-peak ratios of the placebo and treated groups; (3) control placebo effect subtracted by subtracting the mean hourly values of the placebo group at the equivalent peak and trough times in the treated group; (4) control placebo effect subtracted by subtracting the placebo group peak and trough effects from those in the treated group; (5) control placebo effect subtracted by subtracting the placebo and treatment curves, time block by time block, before calculating the trough-to-peak ratio. The trough-to-peak ratio may thus become multiplied fivefold without real clinical significance.

The trough-to-peak ratio is known to be affected by the mode of selection of the population for analysis; thus intention-to-treat analysis of the overall population, including those who are noncompliant, may underestimate the peak effect and hence overestimate the ratio [40, 50]. The ratio may also be overestimated by including nonresponders in the overall population for analysis [17-20, 31]. Results with indapamide in the responder subpopulation were similar to those in the overall population (figure 3a). In the present case, the definition of hypertensive patients and responders according to conventional rather than ABPM criteria tended to overestimate the individual trough-to-peak ratio. DBP individual trough-to-peak ratios in patients hypertensive in terms of conventional sphygmomanometry vs ABPM were: 60% vs 55% (SR 1.5 mg) and 82% vs 60% (IR 2.5 mg); the corresponding figures in responders were 60% vs 60% (SR 1.5 mg) and 60% vs 41% (IR 2.5 mg). The influence of dose on group and individual trough-to-peak ratios was not significant (SR 1.5 mg, SR 2 mg, SR 2.5 mg), as expected with drugs having linear pharmacokinetics [34, 47]. This is the case with indapamide, as with calcium antagonists such as amlodipine, nifedipine, and verapamil, and contrasts with converting enzyme inhibitors such as enalapril and cilazapril or beta-blockers such as dilevalol [43, 47].

The nature of the formulation (IR 2.5 mg vs SR 2.5 mg) did not appear significant. The plasma half-life of indapamide is approximately 20 h; the aim of the change in formulation is not to prolong a half-life that is already sufficiently long, but to obtain a plateau blood concentration profile that flattens the potentially deleterious plasma peaks.

CONCLUSION

DBP individual trough-to-peak ratios were 60% for both indapamide SR 1.5 mg and indapamide IR 2.5 mg, with first and last quartiles of 16% and 89% and 18% and 111%, respectively; the corresponding group trough-to-peak ratios were 85% and 98% respectively, after subtracting the run-in placebo effect. Thus the trough-to-peak ratios for indapamide, in the first-ever calculation under stringent conditions for an antihypertensive diuretic, confirm that indapamide SR 1.5 mg is effective over 24 h in the treatment of hypertension.

Acknowledgements. Our thanks to the study investigators. France: *B. Adam, G. Amabile, A. Archimbaud, G. Audet, J. Aurouze, B. Authier, J.F. Badina, C. Bastien, E. Bientz, J. Blaignan, J.J. Blanc, M. Bory, J. Bouchet, S. Boutelant, A. Carré, M. Chickli, D. Conte, R. Cros, M. Dullocchiot, P. Delage, G. Delhome, M. Deschamps, G.P. Desbonnets, H. Elbaz, J.M. Fabre, J.P. Fauvel, L. Feutrie, J.P. Fillastre, B. Fouabire, D. Franchomme, J. Fronville, F. Galinier, J.P. Garcia, J. Garnier, J. Gayet, P. Gosse, P. Gross, P. Guerin, J.P. Guilloux, L. Hillion, V. Hulin, J.L. Imbs, H. Isard, J.C. Jamot, J. Josse, J. Joly-Jolyot, P. Laffly, J. Landure, B. Lardy, M. Laville, P. Lefebvre, E.Y. Li, M. Lusinchi, D. Mailly, J.M. Mallion, J.Y. Manceau, P. Marnmor, J.P. Maurin, P. Mazars, D. Meric, M. Meunier, E. Moatti, L. Monthiers, A. Mouysset,*

E. Muller, S. Musso, D.T. N'Guyen, G. Petit, C. Philippe, P. Pujo, F. Reynes, D. Roccaz, Y. Roulin, M. Safar, M. Salvi, M. Sanchez, P. Souid, D. Stephan, J.L. Tommasini, C. Tzincoca, P. Zech. Belgium: *J.M. Coupez, G. Creytens, J. Verhaeghe.* Great Britain: *P. Avraamides, S. Davies, M. MacMahon, C. Mealings, M.V.J. Raj.* Italy: *E. Ambrosioni, F.V. Costa, G. Finardi, P.L. Malini, E. Marchesi, G. Perani, E. Strocchi.* Monitors: *S. Barrandon, V. Salzman (France), I. Jacobs, A. Van Dessel (Belgium), V. Hodder (Great Britain), M.G. Besse-Boffi (Italy).*

KEY WORDS: hypertension, ambulatory blood pressure monitoring, diuretic, indapamide, trough-to-peak ratio.

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