Wildener’s principle: pre-treatment value determines post-treatment response

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Introduction

Over more than half a century numerous studies have documented that pre-treatment blood pressure (BP) is a determinant of the anti-hypertensive response.1-4 This has been shown for systolic and diastolic BP, acute and long-term response, monotherapy and combination therapy, and for office BP as well as for 24 h ambulatory BP. The first observation along that line was perhaps made by Freis et al who, in 1958, in a very careful in-patient study reported a decrease in BP with chlorothiazide in every single hypertensive patient whereas in 15 normotensive subjects followed under exactly similar dietary and hospital control conditions, no reduction in BP occurred.10 This phenomenon that the pre-treatment level determines to a large extent the change per se, that is, the principle of initial value (German: Ausgangswertgesetz) was first described by Josef Wilder in 1931 who proposed that the ‘direction of initial value high’ vs. low’ was a determinant of the response of body function to any agent.11,12

Hypothesis and validity

In 1976, Dixon and Johnson put forward the hypothesis that ‘the magnitude of the fall in blood-pressure in response to an antihypertensive drug depends on the level of the pretreatment pressure, and there is a direct relationship between the two in that the higher the pretreatment pressure the greater the fall in pressure in response to treatment’.13 Subsequent testing of this hypothesis in 42 published small studies in a total of 971 patients with 23 anti-hypertensive drug regimens revealed that in clinical practice ‘most of the regimens failed to show ideal behavior’ but that the ‘hypothesis of relating pre-treatment BP to the subsequent fall in BP provided a useful method for assessing the effectiveness and variability of patient-responses to treatment’.14 Law et al., by doing a meta-analysis of 354 randomized double-blind, placebo-controlled trials of thiazides, β blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers, showed that the relation between the pre-treatment level and the fall in blood pressure (BP) was well fitted by a straight line.15 If pre-treatment BP was 10 mmHg higher, the reduction in BP with one drug at standard dose increased on average by 1.0 (95% confidence interval 0.7–1.2) mmHg systolic and 1.1 (0.8–1.4) mmHg diastolic.15

Generalization

The observation that the pre-treatment value is a determinant of the post-treatment response is by no means restricted to hypertensive cardiovascular disease. A similar phenomenon has been observed for the therapeutic response of heart rate,16 haemoglobin A1c,17,18 total cholesterol, LDL and HDL cholesterol19,20 and body mass index after LAP-BAND placement.21 It likely applies to most therapeutic responses that can be graded. The greater the baseline risk (up to a certain degree), the greater the magnitude of benefit from a therapy. Particularly, illustrative are the heart rate data with ivabradine (Figure 1) showing regardless of the dose employed an almost identical pattern of response entirely depending on pre-treatment values.16 The decrease in heart rate is very pronounced in patients with a resting heart rate >90, but below a pre-treatment heart rate of 60 the negative chronotropic effect of ivabradine seems to vanish. However, generalizations of Wilder’s principle should be done cautiously. Berntson et al. showed that manipulations, which are known to be largely of autonomic origin, yielded larger effects than did manipulations having significant non-autonomic components.22 Wilder himself stated that beyond a certain medium range there was an increasing tendency toward absent and even toward reversed (paradoxic) responses.12

Wildener’s principle and regression to the mean

Regression to the mean is defined as the phenomenon that an extreme variable of an individual on first measurement will tend to be closer to the mean on its second measurement. Thus, it is a purely statistical phenomenon that can be observed with any clinical

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parameter such as BP, heart rate, BMI, cholesterol, etc. With regression to the mean, the correction can be upward or downward. In contrast, Wilder’s principle states that the mean response in a population depends on the mean pre-treatment value. In other words, the higher is the mean BP in a patient population at baseline the greater will be the decrease in BP with anti-hypertensive therapy. Thus, in RCT’s regression to the mean is dealt with by design, and by the observed treatment effect in the placebo group, while the principle of initial value is not affected by study design.

Implications

Little surprise that pharma has used these and other data for marketing purposes. The simple fact that response to a drug is more marked when pre-treatment levels are high and gradually diminishes as pre-treatment levels become lower seems to attest to its safety and efficacy. Such a drug has been touted to be ‘intelligent’ in that it lowers the endpoint progressively better the more it has been out of the normal range.

Although described decades ago, it remains uncertain whether the Wilder’s principle of initial value represents a real biological phenomenon or simply a statistical artefact. From a clinical perspective, Wilder’s principle of initial value is an important concept, since it predicts that in the patients with the most severe abnormality or disease, that is, the ones with the highest BP the fall in BP will be greater with the same medication than in those with less severe hypertension. If the effect were similar (i.e. if the fall in BP were independent of pre-treatment level), we would encounter many more clinical complications related to hypotension with anti-hypertensive treatment.

Practical applications

This would indicate that we have to take the pre-treatment level into account when comparing efficacy of various interventions in clinical trials. This issue becomes particularly relevant when anti-hypertensive response is assessed by two different methods in the same patient population such as for instance by office BP and by 24 h ambulatory BP. Average office BP measurements have been reported to be between 6/3 and 10/5 mmHg >24-h BP. Thus Wilder’s principle would predict a lesser fall after any intervention with ambulatory BP than with clinic BP measurements. Indeed, in patients who had a baseline systolic BP of 160 mmHg or more in the recent multicentre, prospective, randomized SIMPLICITY 2 BP trial, renal denervation lowered office BP by 33/11 mmHg after

Figure 1 Baseline heart rate and heart rate response to three different doses of Ivabradine.
first glance, the discrepancy between the two therapeutic responses in the same patients seems to represent a clinical conundrum as is obvious from the controversy elicited by the publication of SIMPLICY 2. A very similar discrepancy between office BP response and ambulatory BP response to renal denervation was recently reported from 10 European centers. However, had Wilder’s principle been taken into account and had the authors expressed their results as a scatter plot related to the pre-treatment BP level for both clinic and ambulatory BP, most if not all controversy could have been averted. Indeed, as recently shown by Ott et al., once white coat- or pseudo-resistant hypertension had been excluded and pre-treatment BP levels were similar by office and by ambulatory measurements, no difference in the anti-hypertensive response after renal denervation was observed. Most illuminating in this context is the thorough meta-analysis by Mancia and Parati showing that treatment-induced reduction in BP in general was smaller for the 24-h average than for the office BP. However, when we examine stratum in which pre-treatment BPs were similar, that is, 150–159 mmHg, the decreases in office and 24 h ambulatory BP were equally similar (Figure 2). This would indicate that the disparate decreases in office and ambulatory BP recordings were predominantly related to uneven pre-treatment levels. Of note, as Parati et al. have suggested, attenuating sympathetic activity by renal denervation may reduce BP responsiveness to external stimuli and BP variability. Thus, renal denervation would tend to reduce any white coat effect in otherwise controlled patients (Figure 3).

Wilder’s principle has been with us for >8 decades and by and large has been ignored. Time has come to recognize it and to take it into consideration whenever appropriate.

Conflict of interest: none declared.

References


Figure 2 Office and 24-h ambulatory blood pressure, pre-treatment values, and anti-hypertensive response. Data from Mancia and Parati.28

Figure 3 Average reduction in blood pressure (adjusted for the change in the placebo group; with 95% confidence intervals) according to the usual pre-treatment blood pressure, from the results of 354 randomized trials, with the best fitting line. Data from Law et al.15

6 months, whereas the corresponding fall in ambulatory BP was a mere 10/5 mmHg.24 Pre-treatment BP levels were 178/96 for office and 146/86 mmHg for ambulatory values, respectively. At a


