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Mixed models showed no need for initial response monitoring after starting antihypertensive therapy

Katy J.L. Bell[a,*], Andrew Hayen[a], Petra Macaskill[a], Jonathan C. Craig[a,b], Bruce C. Neal[c], Les Irwig[a]

[a]*School of Public Health, The University of Sydney, New South Wales, Australia*
[b]*Department of Nephrology, The Children's Hospital at Westmead, New South Wales, Australia*
[c]*The George Institute for International Health, Royal Prince Alfred Hospital, The University of Sydney, New South Wales, Australia*

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Abstract

Objective: To demonstrate how mixed models may be used to estimate treatment effects, and inform decisions on the need for monitoring initial response.

Study Design and Setting: Mixed models were used to analyze data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which examined the effects of perindopril and indapamide in 6,105 patients at high risk of a cerebrovascular event.

Results: The mean effect of perindopril was to lower blood pressure (BP) (systolic/diastolic) by 6/3 mmHg. The mean effects of perindopril/indapamide varied according to baseline BP, and lowering of BP ranged from 9/5 to 14/5 mmHg (for individuals with a baseline systolic BP <140 and >150 mmHg, respectively). We found no variation in the effects of treatment on BP for either perindopril alone or in combination with indapamide. The effects of treatment on the individual can be predicted from the mean effect of treatment for the group (perindopril) or baseline systolic BP subgroup (perindopril/indapamide).

Conclusion: Monitoring initial treatment response is unnecessary for antihypertensives similar to those examined in this study. To address this issue for other therapies, we suggest that trials should report estimates of treatment effects from mixed models, and the CONSORT statement should be expanded to include this item.

Keywords: Blood pressure; Vascular diseases; Chronic disease; Randomized controlled trial; Linear models; Statistical models

Introduction

Clinical care commonly involves monitoring patients with chronic disease. Although monitoring is used in nearly every chronic disease, it is uncertain whether monitoring does more good than harm, and valid methods remain poorly defined. Monitoring may be divided into the following phases: pretreatment, initial response, maintenance, reestablish control and posttreatment [1]. Initial response monitoring uses repeated measurements soon after a new therapy is started to check if a patient's response is within a range that maximizes the benefits while minimizing the harms. Monitoring initial response to drug treatment may be done using patient-centered outcomes, intermediate outcomes, or adherence measures [2]. In this article, we limit our discussion to initial response monitoring of intermediate outcomes.

Intermediate outcomes (such as blood pressure [BP] and cholesterol) are usually used for initial response monitoring in patients with chronic conditions. These outcomes are used to predict patient-relevant, long-term endpoints, like a patient's risk of stroke or myocardial infarction. These "hard" endpoints are unsuitable for monitoring purposes, as they may occur many years after the patient is first diagnosed, be irreversible, or carry a substantial mortality risk. The intermediate outcomes are often responsive to therapy, and by using therapy to alter the value of an intermediate outcome early on in the disease process, the clinician hopes to change the patient's risk of developing later clinically important outcomes.

An intermediate outcome should only be considered for monitoring if a change in this outcome is known to predict the effect of treatment on the risk of the clinical outcome. Such evidence usually comes from population-level meta-analyses of randomized controlled trials, where change in

* Corresponding author. School of Public Health, Edward Ford Building A27, The University of Sydney, Camperdown, New South Wales 2006, Australia. Tel.: +61293515994; fax: +61293515049.
E-mail address: katyb@health.usyd.edu.au (K.J.L. Bell).

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intermediate outcome is related to change in risk of clinical outcome for patients on active treatment relative to those on placebo. However, although the population average treatment effect on an intermediate outcome may predict the population average treatment effect on the risk of a clinical outcome, the intermediate outcome might not be useful for monitoring the treatment effect in an individual. Measurement variation can cause random change in the intermediate outcome in an individual. Failure to recognize nontreatment-related variation in the intermediate may lead clinicians to make inappropriate changes to therapy, or conversely, to delay taking action when they should intervene [3].

Because of the potential for misinterpretation of changes observed in the intermediate outcome within an individual, unnecessary initial response monitoring is best avoided. Population data from randomized trials can be used to decide when initial response monitoring is unnecessary for the individual. For instance, monitoring is unnecessary (and best avoided) if the treatment effect on the intermediate outcome is the same for everyone. However, monitoring may be necessary if the treatment effect on the intermediate outcome differs between individuals. In this case, the need for monitoring will usually depend on the probability of meeting defined treatment targets. If there is a high probability that a patient will meet a predetermined target level with treatment, then there will be no need for monitoring. Conversely, if there is uncertainty whether the patient will meet the target level, then initial response monitoring will be needed.

Much of the variation observed between patients on treatment may be explained by pretreatment differences between patients, short-term variability, and measurement error [4]. Temporal variation in an intermediate outcome in the placebo arm of a randomized trial represents variation from all nontreatment sources. This variation includes within-person measurement variability, attributed to both measurement error and short-term biological fluctuations. It also includes between-person variation in baseline level of the intermediate outcome and change in the intermediate outcome over time; this variation may arise because of differences in underlying physiology and the effect of cointerventions besides the trial medication (these cointerventions may be nonpharmacological, such as diet and exercise, or may be other nontrial medications). If there is no variation in the treatment effect between patients, then the variability in the treated group should be equivalent to that in the placebo group. Analysis of the difference in variability between placebo and active treatment groups provides insight into whether the treatment effect differs between individuals. The main sources of variability in randomized controlled trials are summarized in Table 1 (adapted from Ref. [4]).

A common example of initial response monitoring is BP monitoring after starting a new antihypertensive agent. Individuals are started on antihypertensive treatment if they are judged to be at increased risk of a vascular event. A recent population-based prospective study found 1.8% of an English population suffered one or more vascular events over a 3-year period, with a steep increase in risk with increasing age [5]. The proportion of individuals at increased risk of a vascular event (for whom antihypertensives are prescribed) is considerably greater than this, and will grow further as populations age. As nearly all individuals commenced on antihypertensive treatment are monitored for their initial response, there are a large number of individuals having potentially unnecessary initial response monitoring of BP.

Table 1
Sources of variation in measured outcomes in randomized controlled trials

Source	Description
Between treatments	Variation caused by average effect of treatment
Between patients	Variation caused by differences between patients unrelated to treatment
Within patients	Variation caused by measurement variability
Between patients in treatment effect	Variation caused by differences between patients in effect of treatment

Adapted from [4].

In this article, we use data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [6], a randomized trial of perindopril and indapamide in patients at high risk of stroke, to demonstrate how mixed models may be used to inform decisions on initial response monitoring. Monitoring questions potentially answered by this trial include: Should we monitor BP after starting perindopril in patients at high risk of a vascular event? Should we monitor after starting perindopril and indapamide together?

Methods

Study design and population

We analyzed data from PROGRESS [6]. This trial evaluated the effects of perindopril alone compared with single placebo, or perindopril together with indapamide compared with double placebo on the risk of stroke in 6,105 high-risk patients. The decision on whether patients would be allocated to single therapy (single placebo or perindopril) or dual therapy (double placebo or perindopril/indapamide) was decided on clinical grounds before randomization; for this reason, single therapy and dual therapy groups are considered separately.

Outcome measures

We fitted mixed models using systolic and diastolic BP as outcomes. Measurements were made to the nearest 2 mmHg, with a standard mercury sphygmomanometer.