A Novel Measurement Index for Antihypertensive Medication Burden and Its Use

To the Editor:

With the widespread use of blood pressure medications, it has become extremely difficult to assess the effects of elevated blood pressure on physiological and pathological phenomena without the confounding effects of antihypertensives. In both observational studies and randomized clinical trials, attempts to account for the antihypertensive effects have ranged from overly simplified dichotomous measures (either on or not on treatment) to tedious formulas that, in most instances, cannot be calculated in the population studied. Here, we propose a novel yet simple measurement index that not only takes into consideration whether an individual is on treatment but also accounts for the number and doses of each antihypertensive medication taken. We are suggesting that this measure maybe superior to the dichotomous measure and can be used to prospectively assess changes in blood pressure treatment. The developed measure was used in an ongoing trial, the Antihypertensive and Vascular, Endothelial, and Cognitive Function, to evaluate the burden of antihypertensive treatment before and after the intervention. The Antihypertensive and Vascular, Endothelial, and Cognitive Function Trial is a double-blind, randomized clinical trial examining the cognitive effects of antihypertensive medications among older adults with mild cognitive impairment. As part of the research protocol, participants were tapered off their usual antihypertensive medications and started on one of the study medications (lisinopril, candesartan, or hydrochlorothiazide; step 2: nifedipine XL; and step 3: metoprolol). This new measure of the antihypertensive load was used to monitor the drug burden of the participants during different phases of the trial. We define the antihypertensive load as the sum of the ratio of the current daily dosage divided by the maximum recommended daily dosage for each medication. The maximum daily dosage of each agent as indicated for hypertension was obtained from the drug database. A similar but more complex drug burden index has been indicated for hypertension was obtained from the drug database.

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\text{Antihypertensive load} = \sum_{\text{antihypertensive medications}} \frac{\text{prescribed daily dosage}}{\text{maximum daily dosage}}
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Using this antihypertensive load index, we are monitoring the drug burden of the participants and evaluating whether achieving blood pressure control is associated with increased antihypertensive burden during the study period. So far we have enrolled and randomized 34 individuals, 26 of whom were receiving antihypertensives (mean age: 70 years; 65% women; 27% blacks; antihypertensive load: 0.60±0.09; controlled to below 140/90 mm Hg [58%]). Overall, the antihypertensive load decreased in our sample to 0.55±0.13, although we achieved a 100% control rate. Of particular interest, among the 15 participants who were controlled when they entered the study, their load significantly decreased from 0.50 to 0.25 (Mann-Whitney test \(P=0.034\)), although they remained controlled. In comparison, using the dichotomous measure (treated or not) or the number of antihypertensives, we were unable to detect a difference from before to after the study entry (median: 1 before and after; \(P=0.125\)). These data suggest that an easy-to-calculate yet refined index of antihypertensive therapy may be superior to the widely used traditional dichotomous variable to adjust for an antihypertensive effect in the study population. There are inherent limitations to the antihypertensive load. Assumptions were made with respect to the dose-response linearity of antihypertensive medications. For many commonly used classes of antihypertensive agents, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, \(\beta\)-blockers, and calcium-channel blockers, dose-response linearity does hold well. This index also does not account for interindividual and intraindividual pharmacodynamic variability. The antihypertensive load index is not designed to be an exact numeric measure of the pharmacokinetic or dynamic characteristics of medications but rather a simple yet useful measure that accounts for the variety of medications, doses, and regimens that are currently in use in the population at large. Our ability to achieve 100% control in our small sample is relatively unusual. The exclusion of those on \(>2\) antihypertensives may have lead to a selection bias toward individuals with “easier-to-control” hypertension. This measure may be superior to the dichotomous measure used widely in adjusting for antihypertensive medications in epidemiological and experimental studies. We have found in our trial, the Antihypertensive and Vascular, Endothelial, and Cognitive Function Trial, that such an index is useful in fine tuning the antihypertensive measurements that we were not able to detect using other traditional measures. Because of the small sample size, the use of this measure needs further confirmation.

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