Editorial

Dried Blood Spot to Screen for Antihypertensive Medications and to Asses Treatment Adherence

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Despite the multiplicity of national and international initiatives encouraging the detection and management of subjects with an elevated blood pressure (BP), hypertension awareness, treatment, and control remain insufficient worldwide. Indeed, among patients receiving antihypertensive medications, target BP is achieved at best in half of them in the United States,[1] and results are unfortunately much lower in low/middle-income countries.[2] Besides the common problems of drug availability and therapeutic inertia, which result in an inadequate management of many hypertensive patients, poor adherence to prescribed medications has been identified as a frequent cause of uncontrolled hypertension resulting in poor cardiovascular outcomes.[3] Therefore, most recent guidelines have put a strong emphasis on detecting and supporting drug adherence to improve BP control and have provided some clues on how to consider modifiable determinants of adherence.[4] Today, patients with a poor adherence remain largely unrecognized for several reasons. One of them, regularly notified by treating physicians, is the absence of a reliable, easy-to-use, and cheap tool enabling to detect patients who do not take their treatments as prescribed. In addition, as adherence is highly variable within the course of therapies, physicians should also be able to test it repeatedly at reasonable costs as a support for their therapeutic interventions.

In this issue of *Hypertension*, Peeters et al[5,6] present data on a new method developed to monitor drug adherence easily using dried blood spot (DBS) sampling and analysis of 8 antihypertensive drugs and 4 active metabolites using ultra-high performance liquid chromatography–tandem mass spectrometry. They conducted this single center-study in 135 hypertensive patients in whom drug concentrations were measured simultaneously using the DBS approach and on plasma samples. They also evaluated pharmacokinetic parameters and the impact of various clinical parameters responsible for the intra- and interpatient variability of plasma drug levels. To that purpose, a broad range of trough levels was sampled up to around 40 hours after drug intake. Results show that DBS could detect drug levels of the chosen compounds within a median time of 25 hours after the last reported drug intake. The lower levels of detection and quantification were higher in DBS compared with plasma; hence DBS is less sensitive for measuring trough levels of antihypertensive drugs. However, in several cases, DBS concentrations were actually higher than those measured in plasma at trough, probably because DBS measured drug concentrations in the whole blood including cells. When DBS results were negative, plasma values were generally negative. Data show that the determination of hydrocholorothiazide remains more problematic than that of blockers of the renin-angiotensin system or calcium channel blockers. Few false negative values were observed with DBS, which could be explained by the time between intake and sampling. The variability of trough drug levels was very high in this patient group. The main determinants of this variability were age, weight, and sex and as expected, the time between intake and sampling and the dose of the drugs. Authors conclude that DBS may be a suitable method to detect poor adherence in hypertension although the method still needs to be ameliorated and validated for larger groups of patients with controlled or uncontrolled hypertension. In this respect, a large clinical trial is ongoing in patients with resistant hypertension, in which this new method will be used to monitor drug adherence (trialregister.nl; NTR6914).

The ability to screen for the presence of antihypertensive drug using the DBS sampling method can be of great clinical value because of its simplicity and its possible application not only in hypertension centers but also in physicians' offices. In fact, the DBS idea is not entirely new. Yvar Bang published the concept of measuring substances on a dried blood matrix in 1913, and R. Guthrie used this approach successfully later on to screen for phenylketonuria. Since then, the method has improved considerably mainly through the development of analytical methods such as liquid chromatography and mass spectrometry.[7] Today, >120 biomarkers and drugs are measurable using DBS sampling including some antihypertensive drugs.[7] Though seemingly unsophisticated, the DBS methodology is nevertheless facing several analytical pitfalls that must be taken into account to ensure the adequacy of the results as reviewed by Zakaria et al.[7] The establishment of reference intervals or decision limits appears to be essential for DBS analytes.[7] For the screening of drug adherence, it might be sufficient to detect if the drug is present or absent of the blood sample as it is done today with urine samples. However, the method should not generate too many false negative results to avoid accusing inappropriately patients of nonadherence. The data presented by Peeters et al[5] seem somehow reassuring in this respect. The quantitative interpretation of DBS-measured blood concentrations is much more difficult

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Table. Clinical Clues to Detect and to Support Drug Adherence in Uncontrolled Hypertension

Detection of poor adherence in clinical practice
Take time and talk about adherence in a nonjudgmental way. Ask patients simply and directly if they are sticking to their drug regimen: "the way we ask matters"
Eventually use a questionnaire as an adherence workup tool, for example, the Drug Adherence Work-up (DRAW) questionnaire is available at colorado.gov/pacific/sites/default/files/DC_CD_Adherence-Screening-DRAW_Million-Hearts.pdf (verified April 15, 2020)
Obtain information on prescription refills in pharmacy using e-prescriptions or e-refills or electronic monitoring (if available)
Measure drugs in biological fluids (blood and urine, if available). Consider the possibility of white coat adherence when evaluating the results
Clues to support drug adherence
Identify the patient's personal barriers and fears limiting drug adherence
Simplify drug treatment using single-pill combinations
Stop any unnecessary drug treatment potentially interfering
Collaborate with other healthcare providers (nurses and pharmacists)
Build a habit of medication taking, matching the patient's daily routine
Use reminders, week organizers, or mobile apps (with patient's agreement)
Organize social support (with patient's agreement)
Use electronic feedback (if available)
Provide positive reinforcement when patients have good adherence
Repeat adherence measurements for persistently uncontrolled hypertension

because it depends on several factors including the drug dose and the time since the last dose—a parameter that is not always very accurate.

The DBS technique also has some technical and clinical limitations. Technically, the system, as Peeters et al[5] propose it, covers only a small number of antihypertensive agents. Thus, β-blockers are not yet included in the panel, and there appears to be some difficulties with hydrochlorothiazide. Considering the large variety of antihypertensive compounds used in clinical practice, this might be considered a limiting factor, but it is correctable. A greater use of single-pill combinations as proposed by guidelines[4] may partially solve this problem, as the presence of only one component of the combination needs to be tested. Authors suggest that DBS will prevent from white coat adherence because drug levels and BP are measured simultaneously.[5] White coat adherence is a major limitation for all punctual measurements of adherence during a medical term. The major issue lies in the fact that patients anticipate the results of their BP control, and the same is true for any measurement of adherence during the consultation if patients are aware that this parameter will be verified periodically. Moreover, most patients are eager to please their physicians demonstrating that they do follow their prescriptions. Thus, white coat adherence will always be a question when interpreting adherence results based on a single measurement. In this respect, the lack of information on the dosing history, despite the fact that DBS could be repeated, will be another limitation of the technique.

Despite these limitations, screening of antihypertensive drugs with the DBS methodology remains a promising approach because it fulfills many of the desired qualities of a screening method, although one does not yet know its real cost.[5] The method is now ready to be evaluated in patients with resistant hypertension—a clinical situation in which poor adherence is very common and measuring antihypertensive drugs in urine has become the reference.[8] A comparison of the respective performance of DBS and urine testing would be of interest, and whether in the future, DBS will supersede urine testing is an open question. Rather than concentrating on resistant hypertension, other perspectives for the DBS method could be envisaged. For example, drug screening could be performed more systematically whenever physicians consider the need to add another antihypertensive drug in uncontrolled patients. Such a strategy might potentially limit the number of drug classes necessary to control BP in many patients and hence reduce the global pill burden.

A good adherence to lifestyle recommendations and to prescribed medications is a prerequisite for a successful BP control in hypertension. The Table provides some practical clues on how to detect and support drug adherence in uncontrolled hypertension. The development of new methods to screen for drug adherence in clinical practice is essential, as it will never be possible to improve adherence on a large scale without a reliable way to identify the problem. However, the recognition of a lack of adherence is only the beginning of a long journey to help patients achieving the therapeutic goals and maintaining their lifelong treatment.

Disclosures

None.

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