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Summary table

What is known about topic	• Poor adherence is a well-recognised cause of apparently resistant hypertension. • Accurately measuring patient adherence has historically been very challenging. • Urine analysis by high-performance liquid chromatography-tandem mass spectrometry has recently become routinely available as a method of screening for non-adherence.
What this study adds	• The most common reasons for non-adherence were adverse effects of medication and forgetfulness. • Adherence rates for thiazide/thiazide-like diuretics and spironolactone were lower than for other classes of antihypertensive drug. • Approximately one third of non-adherent patients disputed their results. Further research on the effect this assay may have on the patient-clinician relationship is warranted.

Abstract

Poor adherence with pharmacotherapy is well recognised as one of the main barriers to achieving satisfactory blood pressure control, although accurately measuring patient adherence has historically been very challenging. Urine analysis by high-performance liquid chromatography-tandem mass spectrometry has recently become routinely available as a method of screening for non-adherence. In addition to measuring rates of adherence in hypertensive patients, this study aimed to investigate the reasons for non-adherence given by patients and how patients react when they are informed of their results. This was a retrospective observational study looking at results from the routine use of this assay in a specialist hypertension clinic in Birmingham, UK, in patients with uncontrolled hypertension and those under consideration for renal denervation. Out of the 131 patients analysed, only 67 (51%) were taking all their medications as prescribed. Forty-three patients (33%) were taking some of their medications, whilst 21 patients (16%) were completely non-adherent. The most common reasons cited for non-adherence were adverse effects of medication and forgetfulness. Adherence rates for thiazide/thiazide-like diuretics and spironolactone were lower than for other classes of antihypertensive drug. Despite the objective nature and high sensitivity of the test, 36% of non-adherent patients disputed the results. A minority of patients did not attend follow-up. Further research investigating the implications of a ‘non-adherence’ result on the patient-clinician relationship is required.

Introduction

Although effective and well-tolerated once-daily antihypertensive medications are widely available, poor adherence with recommended treatments continues to be one of the main barriers to satisfactory blood pressure (BP) control (1, 2). A recent meta-analysis of data on more than 376,000 patients from 20 studies assessing drug adherence for seven preventative drug classes (including five antihypertensive drug classes), found that the mean adherence over all studies was only 57% after a median of two years (3). A longitudinal study by Vrijens *et al* using a database of over 4700 patients prescribed once a day antihypertensive medication from 21 phase IV clinical studies, demonstrated that by the end of one year, almost half of the patients had stopped taking their antihypertensive medication (4).

Measurement of patient adherence has historically been very challenging, and as a result, suboptimal adherence to a prescribed drug regimen often goes unrecognised in everyday clinical practice. One of the main problems with measuring behaviours such as adherence is that the act of measurement itself can have some bearing on the behaviour, the so-called Hawthorne effect. If patients are aware their medication-taking is being monitored, this in itself can stimulate adherence (5). Consequently, patients underreport non-adherence and also take medication immediately prior to testing or clinic appointments, so-called ‘white coat adherence’ (6). Conversely, clinical judgement alone is believed to overestimate the rate of non-adherence to antihypertensive medication (7).

Adherence can be measured directly or indirectly. Direct measurement involves either observing ingestion of the drug or by detecting its presence in plasma or urine. Indirect measures assume ingestion based on proxy-evidence such as self-reporting or number of dosages removed from a container (5). Traditional methods of measuring adherence (computerised records of prescription pharmacy refills, pill counts, questionnaires, patients' diaries) are inexpensive but have severe limitations and have been shown to overestimate it (8). Electronic monitoring methods such as the medication event monitoring system (MEMS; AARDEX Group, Ltd, Sion, Switzerland) have been regarded as the gold standard for monitoring adherence in clinical trials, because of their automaticity and precision of timing when patients take or omit doses. Although MEMS is based on an indirect measurement, it has been extensively validated and used in drug trials since 1988, including several studies conducted in the field of hypertension (8). Biochemical methods of testing can detect whether a drug has been ingested but until recently have been considered relatively costly. They are highly sensitive but cannot provide any information on when doses were taken or omitted and are affected by the white coat adherence phenomenon. Urine analysis by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) has recently come to the fore as a useful method of screening for non-adherence in hypertensive patients (9). A group at the University of Leicester in the United Kingdom were among the first to develop this test that is able to screen for 52 of the most commonly prescribed antihypertensive drugs or their metabolites using a random urine sample. The test is inexpensive and we have been using this test in routine clinical practice in the hypertension clinic at University Hospitals Birmingham NHS Foundation Trust since November 2013. Studies published to date making use of such an assay to measure adherence rates have not

looked at the reasons for non-adherence or whether adherence rates change on subsequent testing. How patients react when they are informed of their results and what explanations they give for not taking their medications are two of the questions we hoped to answer with this retrospective observational study. Subsequent work will aim to investigate the potential implications this assay can have on medication taking behaviour and on the patient-clinician relationship.

Materials and Methods

This was a retrospective observational study looking at results from the routine use of urine adherence testing in the hypertension clinic at University Hospitals Birmingham NHS Foundation Trust, which receives referrals from primary and secondary care physicians in the West Midlands for investigation and management of patients with uncontrolled hypertension. Following consultation with a hypertension specialist, patients were asked to provide a urine sample for analysis. Patients included all those being worked-up for consideration of renal denervation and those with uncontrolled and apparently ‘resistant’ hypertension in whom non-adherence needed to be excluded. By definition, patients with resistant hypertension included those with BP that was not controlled to target, that is, a clinic systolic BP of greater than 140 mmHg and/or diastolic BP greater than 90 mmHg, despite treatment with at least three antihypertensive medications (usually including a diuretic). Following explanation that their urine would be tested for the presence of their prescribed blood pressure medicines, patients were asked to provide a random urine sample for analysis. Prior to attending clinic, patients were not given any warning about this test in order to exclude white coat adherence. Patients provided verbal consent and none

refused. Samples were frozen at minus 20°C and sent to University Hospitals of Leicester NHS Trust pathology department for analysis. Samples were analysed using HPLC-MS/MS for the presence of antihypertensive drugs or their metabolites. The technique has been described in detail elsewhere (9). Data on all patients undergoing the test during a two year period between November 2013 and November 2015 was collected retrospectively from electronic patient records. This included 131 patients in total. Data collected included: basic demographics, the names of prescribed antihypertensive medications, the reason for the test being carried out, and the medications detected in the urine sample. Data on the response of the patient when informed of the results and the reasons given by the patient for non-adherence (when applicable) were obtained from electronic clinic letters. Because this information was collected retrospectively, some information was lacking in a minority of patients.

Results

One-hundred-and-thirty-one urine samples from 131 patients were analysed. The median number of antihypertensive drugs prescribed was 4 (IQR 3-5; mean 4.14); the median number of drugs detected in the urine was 3 (IQR 1-4; mean 2.76) (Figure 1).

In five cases, when furosemide was the only drug not detected in the urine, it was deemed not to be clinically significant by the investigators due to its short half-life, and these five patients were considered to be adherent. Only 67 patients out of the 131 (51%) were taking all their medications as prescribed (‘adherent’); 43 patients (33%) were taking some of their prescribed medications and therefore deemed ‘partially adherent’ with their treatment; 21 patients (16%) were not taking any of their

medications and were categorised as ‘completely non-adherent’ (Figure 2). Out of 122 patients with uncontrolled hypertension prescribed 3 or more drugs (including a diuretic in 106 cases), only 55 (45%) were completely adherent with prescribed medications and could be deemed truly ‘resistant’.

When patients were separated into ‘new referrals’ and ‘follow-up’ categories, a significant difference in adherence was observed: adherent 38% versus 59%; partially adherent 38% versus 30%; non-adherent 25% versus 11%; Kendall’s tau-b 0.219, p= 0.009.

From the 64 patients categorised as partially or completely non-adherent, six patients did not attend follow-up after providing the urine sample. When the remaining 58 patients were presented with their results, 25 admitted to non-adherence (43%), whilst 21 denied non-adherence (36%) and disputed the result according to documentation in electronic clinic letters (Table 1). Twelve patients (21%) neither denied nor admitted it and it was unclear as to the reasons for non-adherence. The reaction was not known in the non-attenders.

Out of the 25 patients who admitted non-adherence, the most common reason cited in the clinic letter was adverse effects of medication (9 patients; 36%), closely followed by forgetfulness (8 patients; 32%); in 6 cases there was no documented reason given. Other explanations included running out of medication, misunderstanding instructions, prescription cost and apathy (Table 2).

In the 12 cases where non-adherence was neither admitted nor denied, a language barrier was felt to be the main factor behind non-adherence in six cases (lack of English was noted in the clinic letters). In five cases there was no documentation of patient reaction in the notes, and in one case a carer had been administering the medication.

Data from the detection rates with the most commonly prescribed classes of antihypertensive drugs were analysed, which can be seen in Table 3. Adherence rates for thiazide/thiazide-like diuretics, including indapamide, bendroflumethiazide and hydrochlorothiazide (53.95%) and the aldosterone antagonist spironolactone (47.83%) were lower than for other classes of antihypertensive drug.

We also analysed adherence rates according to the number of antihypertensive drugs prescribed (Figure 3). There was a trend towards decreasing adherence rates with the higher number of drugs prescribed, although this did not reach statistical significance ($p=0.115$) because the vast majority of patients were prescribed between three and five antihypertensive drugs (109 out of 131, 83%) and similar rates of adherence (approximately 50%) were observed in those patients.

Discussion

Direct measurement of adherence in hypertensive patients by urine analysis using HP LC-MS/MS is a highly effective method of establishing whether patients are taking their blood pressure medications as prescribed. In the study by Tomaszewski *et al* making use of this method to analyse the urine of hypertensive patients at a specialist

hypertension clinic in Leicester, 25% of the 208 patients who underwent screening were found to be partially or completely non-adherent (9). However, they included all new referrals and follow-up patients. In our routine clinical practice, we are more selective in whom we test as the assay is mainly used to investigate for non-adherence in those most likely to be non-adherent i.e. those with uncontrolled hypertension apparently refractory to drug treatment. In this retrospective observational study, overall, we found that approximately half of the patients were taking their medications as prescribed (51%). Patients were not given any prior warning about the test, reducing the likelihood of the white coat adherence phenomenon confounding the results, a strength of this study. This study confirms that poor adherence with prescribed treatment remains one of the most important causes of failing to achieve target blood pressure. A significant proportion of patients were not taking any of their antihypertensive medications (16%). This is a high figure due to the selectivity of patients in whom the test is used as a screening method and does not reflect the true prevalence of complete non-adherence in the clinic. The most extreme case included one patient who was referred to the clinic having been prescribed ten antihypertensive medications under the care of a cardiologist, none of which were detected in his urine. When analysing only the patients with uncontrolled hypertension prescribed three or more drugs (usually including a diuretic), 55% were found to be partially or completely non-adherent. This finding is very similar to a previous study using a similar methodology, which found approximately half (53%) of patients with apparent resistant hypertension were non-adherent (10). In light of this finding, our view is that urine adherence testing should become routine when managing patients with apparent resistant hypertension because patients with true resistance warrant meticulous investigation for secondary causes. Such investigations are expensive, time-

consuming and potentially involve radiation exposure. In patients with confirmed poor adherence, such tests may be completely unnecessary and the focus can be shifted towards optimising adherence.

Previous studies using urine analysis to measure adherence have not looked at how such patients react when they are informed of the results, or the reasons given for not taking their medications. It was noted from the present study that when informed of the results of their urine tests, patients acted in different ways. Despite the objective nature of the test, and explanation to the patient of its high sensitivity, about 30% of non-adherent patients denied that they were not taking their medications. Whether this represents a refusal to admit the truth, a false negative test result or simply a misunderstanding is not known. However, anecdotal evidence suggests that even when patients disputed the result, they were usually open to the suggestion of starting treatment afresh with a single BP agent, indicating that there was actually an issue with the number of medications they were prescribed. When a patient did admit to non-adherence, treatment could then be tailored to that particular individual with an emphasis on ways to improve adherence. It is important not to appear judgemental in this situation. Good relationships between healthcare providers and their patients are essential for good adherence. Some of the most important attributes that have previously been shown to be determinants of adherence in patients include an empathetic and non-judgemental attitude, ready availability and good quality of communication (11).

A multitude of different factors have been shown to contribute to poor adherence. Two important features specific to hypertension include the asymptomatic and

lifelong nature of the disease itself. In keeping with this, the most common explanations given for non-adherence in the present study were adverse effects and forgetfulness. Memory and recall are well-known obstacles to good adherence. Simply forgetting to take the medicine at the right time, or poor recall of prescription instructions are both common (5). A study in 1979 by Anderson *et al* showed that patients could recall less than 50% of prescription instructions (12), and memory performance has subsequently been found to correlate with reduced adherence across a number of chronic diseases (13). There are other well-recognised issues relating to the drug therapy of hypertension, including drug tolerability, treatment duration, drug costs and complexity of the treatment regimen (11, 14). Regimen complexity is an important cause of non-adherence. Number of doses per day has been shown in a systematic review to be inversely related to adherence; adherence was significantly higher for once-daily compared with multiple-daily dosing (15). Because regimen complexity is a barrier that tends to reduce adherence, use of once-daily long-acting substances can improve adherence (15). However, the pharmacokinetics of a twice-daily dosing regimen actually confers better maintenance of drug action despite a higher percentage of omitted doses (8). A Cochrane review on interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings showed that simplification of dosing regimens increased adherence in seven out of nine studies (16), although only one study reported an increase in adherence together with a reduction in blood pressure (17). Fixed-dose combinations have been frequently proposed as a strategy for improving adherence in patients with cardiovascular disease. There are obvious advantages in reducing the pill burden but drawbacks too. For example, missing one dose means several drugs are omitted, doses cannot be easily titrated, combinations are fixed and they are more expensive. In the

UMPIRE randomised controlled trial, use of a fixed dose combination of aspirin, simvastatin and two blood pressure lowering drugs did result in improved adherence compared with the usual care group (86% vs 65%; relative risk of being adherent, 1.33 95% CI, 1.26-1.41; p <0.001), but this did not translate into a reduction in cardiovascular events or serious adverse events (18). Although the effect of dosing frequency on adherence was not analysed in our study, we were able to establish a trend towards decreasing adherence rates with the higher number of drugs prescribed. This did not reach statistical significance (p=0.115) because most patients in our study were prescribed 3-5 antihypertensive drugs, with only a minority of patients prescribed fewer than three antihypertensive drugs or greater than five. Our study did show that new referrals were less likely to be fully adherent and more likely to be completely non-adherent to their medications than follow-up patients. Reasons for the better rates of adherence shown in the follow-up patients are multifactorial but likely to be significantly contributed to by the closer attention to adherence these patients receive in the hypertension clinic.

Patients' beliefs and perceptions are also very important when it comes to adherence. Studies involving patients with a wide range of medical conditions have found that high rates of non-adherence are related to doubts about personal need for medication and concerns about potential side effects (5, 19, 20). Beliefs about the illness, perceptions of pharmaceuticals, expectations and experiences of symptoms all influence patients' behaviour with regard to medicine taking (5). These beliefs may change over time. Patients often 'test' their need for the medication by altering the dose or taking a 'drug holiday' and monitoring the effects (21). Such drug holidays may or may not be detected with urine testing, depending on the timing of events.

Although the urine test can be affected by white coat adherence, it is unlikely that any of the patients were aware of the test when it was first performed, prior to attending the clinic. Subsequent testing may be affected by this phenomenon as patients became wise to the test and this is an area that offers the opportunity for further research.

When looking at the most commonly prescribed classes of antihypertensive drugs, adherence rates for thiazide/thiazide-like diuretics (53.95%) and the aldosterone antagonist spironolactone (47.83%) were substantially lower than for other classes of antihypertensive drugs, which were all around 70%. This observation is consistent with a large observational study which showed that patients initiating treatment with angiotensin receptor blockers had a dramatically lower likelihood of early non-persistence (stopping the medication) compared with patients initiated on diuretics (22). Diuretics are highly effective antihypertensive drugs and patients with resistant hypertension often benefit from intensification of diuretic therapy, including the addition of an aldosterone antagonist. However, adverse effects may lead to non-adherence so it is important to encourage patients to be open and honest if they are experiencing intolerable side effects. Direct questioning about commonly experienced adverse effects are encouraged and substitutions made if an issue is highlighted.

In our clinic, no patients have so far refused to have the test performed. However, six patients who were found to be non-adherent did not attend their follow-up appointment, and speculatively, this could be because they feared the doctor’s response or felt guilty about not taking their tablets. The test may have been the reason for the patient not attending but this is not known and it was only a small minority of patients. Further research is required into what implications this assay

might have on the patient-clinician relationship and we intend to explore this in subsequent projects using quantitative and qualitative methodologies.

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Conflicts of Interest

There are no conflicts of interest.

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Figure legends

Figure 1: Box-and-whisker plot comparing the median number of antihypertensive medications prescribed with the median number detected in the urine in this group of patients with uncontrolled hypertension.

Figure 2: Pie-chart showing percentage of patients in this cohort who were adherent, partially adherent, and completely non-adherent with their antihypertensive medication.

Table 1: Table showing non-adherent patients' reactions when presented with their urine test results.

Table 2: Table showing patients' explanations for non-adherence.

Table 3: Adherence rates with the seven most commonly prescribed antihypertensive drug classes in the clinic. ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

Figure 3: Graph showing percentage of patients who were fully adherent according to the number of antihypertensive drugs they were prescribed.