**True resistant hypertension following observed drug ingestion: a systematic evaluation**

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**Abstract**

**Aims**

Treatment resistant hypertension is common. We investigated what proportion of such patients resulted from poor drug adherence.

**Methods**

In 102 patients with uncontrolled BP, baseline BP measurements were followed by observed ingestion of their usual medications. BP was measured every 10 minutes, for up to 6 hours, followed by 24 hour ambulatory monitoring (ABPM). Further readings were obtained at a follow- up clinic.

**Results**

Median BPs were 170/91 mmHg at referral, 153/84 mmHg prior to, and 142/79 mmHg after, drug ingestion. Median daytime ABPM over the following 24 hours was 142/80 mmHg. Median BP at final follow-up clinic visit was 147/79 mmHg. The cumulative number of patients achieving a goal of <140/90 mmHg in clinic or <135/85 mmHg mean on ABPM was 57 (56%), with a further 9 (9%) controlled at the final follow up clinic visit. Thus 65% of patients achieved a systolic BP < 140 mmHg at any point immediately prior to, or after, drug ingestion; the residual 35% were considered true resistant hypertensives.

**Conclusion**

Among patients with suspected resistant hypertension, a minority were truly treatment resistant following observed drug ingestion and BP monitoring.

**Introduction**

High blood pressure (BP) is a major cause of cardiovascular disease, accounting for approximately two thirds of all strokes and half of all heart disease.1  Whilst effective pharmacotherapy has been available for the last few decades, control is not achieved in a significant proportion of treated patients. Recent reports from the Health Survey for England show that, of those on treatment, about 63% will achieve blood pressures of <140/90 mmHg.2 Although some of the remaining patients may have white coat hypertension, unrecognised secondary causes, or be sub-optimally treated, a proportion remain with so-called resistant hypertension even after specialist investigation and treatment.

True resistant hypertensive patients are defined as those who fail to achieve BP <140/90 mmHg whilst receiving 3 or more antihypertensive drugs, in maximal or best tolerated doses, one of which should be a diuretic, after exclusion of secondary causes of hypertension. The precise prevalence of resistant hypertension is uncertain but is estimated to be up to 30%,3 and consequently both the American Heart Association4 and the National Institute for Health and Clinical Excellence5 suggest that there is a need for further research into the condition.

Given that hypertension is the greatest single contributor to the risk of cardiovascular morbidity and mortality,6,7  it is perhaps not surprising that poorly controlled BP is associated with a more than two-fold increase in cardiovascular morbidity over a relatively short observation period of 4 years, when compared with controlled patients.8

The results of an earlier evaluation of data from our own clinic suggest that poor drug adherence is a major contributor to apparent drug resistant hypertension,9 although individual patients often deny non-adherence. We have now extended our initial observations to include over 100 patients with apparently resistant hypertension who were referred for observed drug ingestion and prolonged BP measurement to evaluate adherence with therapy.

**Methods**

Patients with uncontrolled hypertension referred by family practitioners, hospital physicians and cardiologists to the Peart-Rose Hypertension Clinic at St Mary Hospital underwent comprehensive investigations to eliminate secondary causes of hypertension. Where appropriate, antihypertensive drug doses were adjusted and additional drugs added according to guidelines to try and achieve BP control to <140/90 mmHg. All drugs were administered once daily except for a very small number of patients who were receiving doxazosin, standard formulation, twice daily

(n=4). All other patients on doxazosin, receiving either the standard formulation or the XL formulation were taking the drug once daily. 134 patients whose BP remained uncontrolled, after drug revision, were referred for an assessment of adherence in a specialist nurse-led clinic where drugs were administered under direct observation, and the patients’ BPs were recorded for up to 30 hours (up to 6 hours in clinic followed by 24 hour ambulatory BP monitoring [ABPM]). All patients asserted regular adherence with their medications and, of those with prior ambulatory or home BP records, >90% had no evidence or minimal evidence of a white coat response.

These patients were instructed to omit their morning medications and to arrive in the clinic between 9.00 and 10.00am. Baseline BP was recorded using standardised techniques with an automated monitor (Welch Allyn or Dynamap) or, in patients with atrial fibrillation, a manual sphygmomanometer. Drugs were then administered under supervision and careful direct observation by a specialist nurse, after which BPs were recorded at 10 minute intervals for 2-6 hours. The initial administration usually consisted of giving 2 drugs (typically a calcium channel blocker and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker), with additional medications (e.g., diuretics, beta-blockers, alpha-blockers) administered at intervals over the ensuing 4-6 hours depending on the BP response. In order to avoid precipitous falls in BP in patients who had hitherto been poorly compliant, those patients prescribed high doses of the alpha blocker, doxazosin, received a maximum dose of 4mg of the long acting formulation. At the end of the within-clinic observation period, most patients were fitted with an ABPM device (Spacelabs 90207). Patients were informed of the findings of the study. Many were returned to their referring physicians for further management. A number of patients were reviewed on a subsequent occasion (on average 3-6 months following the observed drug ingestion), at which time conventional clinic blood pressure readings were obtained.

**Results**

Of the 134 patients with uncontrolled hypertension referred for observed drug ingestion, 32 were excluded for reasons including not meeting the criteria for resistant hypertension, having already taken their medication on the day of attendance or lack of referral BP data (Figure 1). Table 1 shows the demographics of the remaining 102 patients included in these analyses. They were 58% female, of varying ethnicity and had a mean age of 58 years. The median number of drugs taken at referral for observed drug ingestion was 5 (range 3-7) which included spironolactone in 43 (42%) patients. After observed drug administration and the period of in-clinic BP monitoring, ABPM recordings were made on 87 (85.3%) patients. Of the remainder, 6 had atrial fibrillation, 4 blood pressures were too low, 3 technical failures, 2 reasons unknown.

Table 2 shows the median (range) BP values at the various time points in the study. Baseline BPs on the day of observed drug ingestion were substantially lower than those recorded at the time of referral and there was a further reduction after drug administration (Figure 2); this fall in BP was maintained during the subsequent ABPM recording.

In 26 of the 102 patients (25.5%) included in the analyses, the baseline systolic BP (SBP) had fallen to <140 mmHg even prior to drug administration; 25 (24.5%) had BP <140/90 mmHg. Of the 97 patients with readings available following observed drug ingestion 45 (46.4%) had SBPs <140 mmHg and 44.3% had BP <140/90 mmHg. Median daytime ambulatory SBP was <140 mmHg in 46% of these patients who underwent ABPM. BP measurements from subsequent clinic follow-up appointments are available for 73 patients (in most cases between 3 and 6 months after the observed drug ingestion); the median of the most recent clinic readings has been taken as the final clinic reading. BP readings show a return to higher levels in approximately half the patients, but a further fall in the remainder.

Overall, a total of 66 (65%) out of 102 patients had SBP controlled to <140 mmHg at some time point after referral for observed drug ingestion (either immediately prior to or after observed drug ingestion, on subsequent daytime ABPM or at the final clinic appointment). This we believe is likely to reflect previous poor adherence in these patients. The residual patients (36, 35%) may be considered truly resistant but represent a minority of those originally referred. Of those patients controlled at some point following drug ingestion, there were fewer Asians and slightly more whites than predicted from the baseline demographics (table 3).

**Discussion**

One of the commonest reasons for referral to a specialist hypertension clinic is poorly controlled hypertension. Initially, many patients referred to our clinic were deemed to require further alteration of treatment and it was only after continued poor BP control following such modification that patients were eligible for an assessment of adherence by BP monitoring after observed drug ingestion. In this study we have demonstrated that BP is controlled in the majority of these patients when they are observed to take their medications, suggesting that non-adherence is a significant cause of apparent resistant hypertension.

The fall in BP from the time of referral for observed drug ingestion to the baseline readings immediately prior to drug administration is best explained by poorly adherent patients deciding to take some or all of their tablets when understanding the nature of the procedure to be embarked upon, although regression to the mean could also have contributed to this fall. Of those whose BP fell on ABPM monitoring after observed drug ingestion (compared with BPs measured immediately before and after ingestion), a white coat effect could have contributed in a minority although the likelihood of significant white coat hypertension had been reduced by prior investigation in most patients; the observed BP reduction probably reflects the delayed onset of action of drugs (particularly long-acting ones) administered under observation. On average, there was a substantial BP reduction following referral for observed drug ingestion with 46% of the 102 patients included in these analyses achieving an SBP <140mmHg by the end of the period of observation after drug ingestion. For those patients with available BP readings at subsequent clinic visits, BP returned to higher levels in a substantial number of patients (best explained by a return to poor adherence) but a further fall in others (possibly reflecting improved adherence following careful discussion of the results with individual patients). Overall, therefore, a total of 66 out of 102 (65%) patients had SBP controlled to <140 mmHg at some time point after referral for observed drug ingestion. Many ethnic groups were represented amongst this hypertensive population. Although the differences are small there was some evidence that there were more whites and fewer Asian patients who obtained blood pressure control, perhaps implying that there may be some ethnic differences in adherence to drug therapy in this group of patients.

The implications of these findings are substantial. There remains high residual morbidity and mortality from cardiovascular complications of hypertension in uncontrolled patients.8 The economic consequences of uncontrolled hypertension, the increased frequency of visits to general practitioners, referrals to specialists and further (often unwarranted) investigations consume substantial resources and funding in an already economically challenged healthcare system. Improvement in adherence to antihypertensive drugs, in general, could lead to health care savings in the UK in excess of £390 million per year.10

Recently there was enthusiasm for treatment of patients with apparent drug resistant hypertension with renal sympathetic denervation,11 following early promising results.12 In light of our results, and another small study that demonstrated no benefit of renal denervation on BP in resistant hypertension when medicines adherence was properly taken into account by witnessed antihypertensive drug taking,13 it is highly likely that many patients in these trials were non-adherent to their medications and changes in adherence behaviour following the intervention may have contributed to the initial favourable results, which have not been borne out in subsequent investigations.14 The issue of medicine adherence is being addressed in ongoing trials of the technique but in the meantime there is a moratorium on the procedure outside the context of clinical trials in the UK.15

 The more general issue of poor adherence deserves more extensive study than possible in this report. The prevalence of poor adherence in many medical disorders is high and the health care consequences of treatment failure are considerable, both in terms of financial costs and residual morbidity and mortality. Triggers for poor adherence include inadequate patient education and lack of understanding, regimen complexity, the stigma of multiple drug therapy, denial and other poorly understood psychological reasons.

**Limitations of this study**

Referral of patients for observed drug ingestion necessitated an explanation to the patients as to the nature of the procedure; this clearly may have had an impact on patients’ adherence with drug treatment between referral and observed drug ingestion. Nevertheless, the majority still had high baseline BP readings on the day of observed drug ingestion and we endeavoured to mimic usual drug administration during the procedure.

Our findings are likely to have underestimated the prevalence of non-adherence because the maximal benefits of many drugs (particularly those which are long-acting) are not seen for several days or weeks following initiation and therefore their full effect may not have been observed in the relatively short observation period (up to 30 hours) in this study.

Less than one third of the patients in this study were taking spironolactone. We have previously shown in an extensive study that spironolactone is extremely effective in poorly controlled hypertensives,16 and this has recently been confirmed in a randomised controlled trial.17 More patients might have been controlled if spironolactone had been included routinely in patients’ drug regimens; however, in many patients this had previously had been tried but withdrawn because of intolerance.

**Strengths of the study**

This is the first systematic observation to investigate the impact of observed drug ingestion on BP responses in patients with apparent resistant hypertension. Our previous pilot study 9 only included a small number of patients and it was felt important to extend the observations with greater numbers to arrive at a robust conclusion. Our observations will hopefully dissuade physicians from referring patients for extensive investigations and invasive treatments without a detailed assessment of medicines adherence, including observed drug ingestion.

The availability of sensitive assays for antihypertensive drugs and their metabolites in urine has only become available recently and we have no observations in these reported patients. However, our recent clinical experience shows that approximately 50% of patients with apparent resistant hypertension, when urine tested for all prescribed drugs, have either no drug or metabolite present, or test positive for a fraction of the prescribed drugs. These independent findings strongly support our current observations and the conclusions drawn from their findings.

**Conclusions**

Among patients with apparent resistant hypertension, the majority achieve control when observed to take their usual medications suggesting that non-adherence is a major cause of poor BP control. Further study is required into the psychological and other factors leading to poor adherence. Patients and their physicians need to be educated and innovative solutions to the problem need to be sought.

**Conflict of interest**

The authors have no conflicts of interest to report.

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**Table 1.** Characteristics of study population

|  |  |
| --- | --- |
|  | **Total (n=102)** |
| Age, years, mean (range)  | 57.8 (20-87) |
| Female, n (%)  | 56 (54.9%) |
| Ethnicity, n (%) |  |
|  White | 23 (22.6%) |
|  Black | 45 (44.1%) |
|  Asian | 23 (22.5%) |
|  Missing | 11 (10.8%) |
| Number of BP drugs at referral for observed drug ingestion, median (range) | 5 (3-7) |

 Drug classes

 Calcium channel blockers 98 (96%)

 Angiotensin converting enzyme inhibitors

 or Angiotensin receptor blockers 97 (95%)

 Diuretics-thiazide or thiazide like 85 (83%)

 Beta-blockers 49 (48%)

 Doxazosin 50 (49%)

 Spironolactone 32 (31%)

 Other 4 (4%)

**Table 2.** Median (range) of blood pressures (mmHg) and heart rate (bpm) at different time-points during the study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time-point** | **n** | **SBP** | **DBP** | **Heart rate** |
| **Referral from clinic for observed drug ingestion** | 102 | 171.5 (143,223) | 91 (57, 128) | 78 (49, 139) |
|  |  |  |  |  |
| **Baseline, prior to drug administration** | 102 | 153 (105, 221) | 84 (52, 131) | 75 (42, 130) |
| **After drug administration** | 97 | 142 (87, 200) | 79 (55, 122) | 67 (39.97) |
|  |  |  |  |  |
| **ABPM day-time** | 87 | 142 (96, 207) | 80 (52,113 | 71 (47,108) |
| **ABPM night-time** | 84 | 128 (89, 193) | 70 (49.109) | 67 (10,91) |
|  |  |  |  |  |
| **Final clinic visit** | 73 | 147 (115, 212) | 79 (51, 119) | 78.5 (46, 137) |
|  |  |  |  |  |

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; ABPM, ambulatory blood pressure monitoring; bpm, beats per minute.

Paired t-tests on within-subject **mean** differences:

|  |  |  |
| --- | --- | --- |
| **Comparisons** | **SBP** | **DBP** |
| Referral vs Baseline | p<0.0001 | p<0.0001 |
| Baseline vs Post drug administration | p<0.0001 | p<0.0001 |
| Baseline vs Daytime ABPM | p<0.0001 | p=0.003 |
| Post drug administration vs Final clinic visit | p=0.07 | p=0.53 |

**Table 3**

Ethnicity of patients controlled or not controlled at some time point during the study and follow up.

 **Controlled (n) Not controlled (n)**

White 17 6

Black 31 14

Asian 12 11

Unknown 6 5

**Figure Legend**

**Figure 1** - Study profile

**Figure 2** - Distribution of blood pressures (median, interquartile range and maximum and minimum values excluding outliers) at various time points during the study. SBP = systolic blood pressure, DBP = diastolic blood pressure. Statistical comparisons shown in Table 2