Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study

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Abstract

Objectives To prospectively compare compliance with treatment in patients with hypertension responsive to treatment versus patients with treatment resistant hypertension.

Design Prospective case-control study.

Setting Outpatient department in a large city hospital in Switzerland, providing primary, secondary, and tertiary care.

Participants 110 consecutive medical outpatients with hypertension and taking stable treatment with at least two antihypertensive drugs for at least four weeks.

Main outcome measures Treatment compliance assessed with MEMS devices; blood pressure determined by 12 hour daytime ambulatory monitoring (pressure $<135/85$ mm Hg in patients aged ≤ 60 years and $<155/90$ mm Hg in patients aged >60 indicated hypertension responsive to treatment).

Results Complete data were available for 103 patients, of whom 86 took $\geq 80\%$ of their prescribed doses ("compliant") and 17 took $<80\%$ ("non-compliant"). Of the 49 patients with treatment resistant hypertension, 40 (82%) were compliant, while 46 (85%) of the 54 patients responsive to treatment were compliant.

Conclusion Non-compliance with treatment was not more prevalent in patients with treatment resistant hypertension than in treatment responsive patients.

Introduction

Potent and well tolerated drugs are available for controlling blood pressure in most patients with hypertension. In some patients, however, normal blood pressures cannot be achieved even after prolonged treatment.[1 2] Such patients have treatment resistant hypertension, which, according to one definition, is persistent high blood pressure ($>140/90$ mm Hg for patients aged ≤ 60 years or $>160/90$ mm Hg for those aged >60) in spite of treatment for a sufficient duration with at least two appropriate antihypertensive drugs.[2 3] Various explanations have been given for treatment resistant hypertension. These include secondary hypertension, endogenous resistance to treatment, and, foremost, non-compliance with antihypertensive drug regimens.[3]

Non-compliance with treatment is thought to be common in patients with treatment resistant hypertension. In one study only 20-30% of patients with arterial hypertension had their condition controlled.[4 5] This deficit in treatment response was partially explained by the observation that only two thirds of patients were taking their drugs correctly and as prescribed.[4 5] In another study only 15% of hypertensive patients strictly followed their drug regimen a year after diagnosis, and up to half had stopped taking any treatment.[6] Non-compliance is especially common when a complex antihypertensive drug regimen is prescribed or when a patient has poor knowledge, understanding, and perception of hypertension.[7–10] It is usual to consider patients to be sufficiently compliant with their treatment when they take $\geq 80\%$ of their prescribed antihypertensive drugs.[11 12]

The extent of non-compliance is difficult to gauge in patients with arterial hypertension. Different methods for estimating compliance have been used—such as self reported compliance, pill counts, and measurements of drug concentrations in serum or urine or of low dose chemical markers in plasma and urine.[13 14] Pill boxes that electronically record every opening (medical event monitoring systems (MEMS)) have substantially improved the assessment of compliance and have been used successfully in various clinical trials in arterial hypertension[12 14–17] and other conditions. Interestingly, electronic monitoring of compliance has not yet been reported for patients with treatment resistant hypertension. This is surprising considering the belief that treatment resistance is commonly due to non-compliance. To our knowledge no published prospective studies specifically compare drug compliance in unselected patients with treatment resistant hypertension with that in patients with treatment responsive hypertension.

We therefore conducted such a study to better understand the magnitude and role of non-compliance in treatment resistance. To better assess the true response to treatment and the change of response due to monitoring with MEMS devices, we measured patients' ambulatory blood pressure before and after monitoring their compliance.

Participants and methods

Participants

The medical outpatient department of the University Hospital offers primary, secondary, and tertiary care for the population of the city of Basle. About 5000 new patients have been seen and about 20 000 patient visits have occurred each year over the past five years. About 75% of patients are primary care patients. A hypertension clinic is associated with the outpatient department.

All patients seen in the department during May to December 1997 were systematically and prospectively screened for inclusion into our study, irrespective of the reason for their visit. For each patient visit, a questionnaire was filled in by the treating residents about whether the patient had hypertension, as defined below, and, if so, the number of antihypertensive drugs being taken. We systematically pursued any missing questionnaires. Patients were defined as having arterial hypertension if their clinic blood pressure was $>140/90$ mm Hg if aged ≤ 60 years or $>160/90$ mm Hg if aged >60 or if they were taking antihypertensive drugs and had a history of arterial hypertension.[1] Patients were eligible for the study if they had primary hypertension and had been following a stable treatment regimen of between two and four drugs for at least a month.

In addition, a committee of senior residents and a study nurse identified any patients known to be hypertensive who were treated in the outpatient department during the screening period in order to check the efficiency of the screening procedure. After we had obtained eligible patients' written informed consent, we conducted a careful clinical evaluation, medical history, and chart review.

Blood pressure measurement

We measured clinic blood pressure and 24 hour ambulatory blood pressure using validated devices (Profilomat, SpaceLabs 90207, Novacor DIASYS 200).[18] For the initial measure of ambulatory blood pressure, carried out before we monitored patients' compliance with treatment, blood pressure and heart rate were recorded every 20 minutes in daytime (8 am to 7 59 pm) and every 40 minutes during night time (8 pm to 7 59 am). At the end of the study we again measured patients' clinic and ambulatory blood pressure. The second measure of ambulatory blood pressure, using the same device fitted to the same arm as for the first, recorded only daytime values except for patients whose mean night time blood pressure in the initial measure was less than 10% lower than their initial daytime mean. In these patients both daytime and night time recordings were made.

We considered ambulatory blood pressure to be within the normal range if the mean daytime systolic blood pressure was <135 mm Hg and the diastolic pressure <85 mm Hg.[1] Patients whose daytime mean blood pressure at the start of the study was in the normal range were defined as responsive to treatment (control group), while those with blood pressure above the normal range were defined as non-responsive, in accord with a well published working definition.[3]

Monitoring compliance with treatment

Using a medical event monitoring system (MEMS, Aardex, Switzerland), we monitored patients' drug compliance over four weeks. Two of each patient's antihypertensive drugs were packaged and labelled by study staff in the outpatient department into two containers that allowed electronic recording of cap openings and closures. At the end of the observation period, information on each patient's compliance for the two drugs was generated by the device (MEMS-4 Communicator 3804-00, Quick Read version 2.0, Aardex). We then calculated the mean percentage of prescribed doses removed from the MEMS devices and considered patients whose values were $\geq 80\%$ as "compliant."

Statistical analysis

We entered all data into a spreadsheet (Excel, Microsoft, Redmond, USA) and calculated group means and standard deviations. We calculated differences between responsive and non-responsive patients by use of Fisher's exact test on a 2×2 table for proportions and Student's t test for group means. We performed statistical analyses using EpiInfo version 6.0 (Centers for Disease Control, Atlanta, USA) or Statview version 5.0 (SAS Institute, Cary NY, USA). We made power calculations with GB-Stat 6.0 (Dynamic Microsystems, Silver Spring MD, USA) and cross checked our results using a nomogram calculating the sample size based on the standardised difference.[19]

Results

From May 1997 to November 1997, we recruited 110 patients into the study. Five patients were lost to follow up (one with acute myocardial infarction, one lost to follow up, and three who did not tolerate ambulatory blood pressure monitoring). Two further patients refused the second measurement of ambulatory blood pressure at the end of the study and had lost their MEMS devices. Complete outcome assessment was therefore available for 103 patients, on whom all further calculations are based. Table 1 shows their characteristics.

Response to antihypertensive treatment

Measurements of clinic blood pressure at the start of the study identified 43 patients who were responsive to antihypertensive treatment and 62 who were non-responsive. With the initial ambulatory blood pressure monitoring, we reclassified 12 of the non-responsive

Table 1 Characteristics of 103 hypertensive patients by their compliance* with antihypertensive treatment. Values are numbers (percentages) unless stated otherwise

Characteristic	All patients (n=103)	Compliant (n=86)	Non-compliant (n=17)
Mean (SD) age (years)	61.9 (11.3)	61.8 (10.8)	60.9 (13.6)
Male to female ratio	1.2	1.4	1.8
Mean (SD) body mass index (kg/m^2)	27.0 (4.0)	29.2 (4.5)	27.4 (4.4)
Tobacco smoker	19 (18)	16 (19)	3 (18)
Family history of hypertension	68 (66)	60 (70)	8 (47)
Diabetes	11 (11)	10 (12)	1 (6)
Hyperlipidaemia	32 (31)	27 (31)	5 (29)
Drink alcohol (>3 units/day)†	6 (6)	5 (6)	1 (6)

*Patients compliant if $\geq 80\%$ of prescribed doses taken correctly.
†1 unit defined as one standard drink.

Table 2 Characteristics of 103 hypertensive patients by their responsiveness* to antihypertensive treatment. Values are numbers (percentages) unless stated otherwise

Characteristic	Responsive (n=54)	Non-responsive (n=49)
Compliant with treatment†	46 (85)	40 (82)
Percentage of doses taken:		
Mean (SD)	91 (19)	88 (18)
Median (range)	98 (11-100)	96 (11-100)
Mean (SD) age (years)	65 (10.4)	62 (9.5)
Male to female ratio	0.67	0.72
Mean (SD) body mass index (kg/m^2)	26.6 (4.5)	27.0 (3.5)
Tobacco smoker	10 (19)	9 (18)
Drink alcohol (>3 units/day)‡	3 (6)	3 (6)
Family history of hypertension	32 (59)	36 (73)
Diabetes	8 (15)	3 (6)
Hyperlipidaemia	19 (35)	13 (27)

*Patients responsive to treatment if 12 hour ambulatory blood pressure <135/85 mm Hg if aged ⩽60 or <155/90 mm Hg if aged >60.
†Patients compliant if ⩾80% of prescribed doses taken correctly.
‡1 unit defined as one standard drink.

patients as responsive (Fisher's exact test of numbers of responsive and non-responsive patients as assessed by clinic blood pressure versus ambulatory blood pressure; P = 0.127). Based on the results of ambulatory blood pressure, we classified 55 patients as responsive (control group) and 50 as non-responsive. Thus, about half of our patients taking two to four antihypertensive drugs fulfilled the criteria for treatment resistance.[3]

Compliance with treatment

The mean percentage of prescribed doses removed from the MEMS devices was 89% (SD 22%, range 11-100%). Of our 103 patients, 86 had a compliance ⩾80% and were classified as compliant, whereas 17 had a compliance <80% and were classified as non-compliant. There were no differences between compliant and non-compliant patients in their baseline characteristics, including duration and extent of hypertension, medical history, family history of hypertension, and alcohol intake (table 1).

We found no significant difference between patients responsive to antihypertensive treatment and those who were non-responsive in the percentage of prescribed doses removed from the MEMS devices (table 2): 40/49 (82%) of non-responsive patients were compliant, compared with 46/54 (85%) of responsive patients (Fisher's exact test P = 0.33). We also found no difference between responsive and non-responsive patients in the mean percentage of prescribed doses removed from the MEMS devices (91% (SD 19%) *v* 88% (18%), Student's *t* test P > 0.2). Our data suggest that poor compliance with antihypertensive treatment was not more prevalent in treatment resistant patients than in treatment responsive patients.

To assess whether factors known to influence compliance[3] could also be identified in our study population, we investigated the influence of the dosing regimen on compliance,[20] for which our study was sufficiently powered. Compliance dropped significantly from 93% (SD 16%) with a once daily dosing regimen (used for 160 drugs) to 77% (33%) for a twice daily dosing regimen (28 drugs) (Student's *t* test P < 0.005). These data suggest that frequent and evening doses lead to omitted doses (that is, to non-compliance), in line with results from other studies.[20]

Effect of monitoring compliance

To determine whether the use of the MEMS devices led to improved compliance and therefore to better blood pressure control, we measured blood pressure again at the end of the study. We found no significant change in 12 hour ambulatory blood pressure: systolic and diastolic pressures were 140.5 (SD 16.1) and 85.52 (10.8) mm Hg at the start of the study and 137.0 (14.4) and 82.5 (10.8) mm Hg at the end of the study. We also found no significant change in clinic blood pressure (data not shown).

Some patients would have been reclassified on the basis of the second measure of ambulatory blood pressure (14 non-responsive patients changed to responsive and eight responsive changed to non-responsive). However, such reclassification would not have altered the percentages of compliant and non-compliant patients. This suggests that compliance monitoring with MEMS devices did not improve compliance to a degree that influenced the conclusions of our study.

Discussion

We measured compliance with treatment among patients with treatment responsive hypertension and those with non-responsive hypertension. Remarkably, we were unable to confirm the common assumption that non-compliance with treatment is substantially more prevalent in patients not responsive to antihypertensive drugs. Nine out of 49 (18%) patients with non-responsive hypertension were non-compliant, compared with eight out of 54 (15%) patients who responded to treatment. Using a sample size calculation, we estimate that, in order to detect a statistically (but perhaps not clinically) significant difference (P = 0.05) between the two groups, one would have to investigate at least about 1300 patients (for power of 80%) or 1700 patients (for power of 90%) (compliance in responsive patients 91% *v* 88 % in non-responsive patients, standard deviation 19%).

We used ambulatory blood pressure monitoring to identify treatment resistant hypertension. Had we used clinic blood pressure instead, we would have substantially overestimated treatment resistance: 28% of the patients would have been falsely identified as being resistant to treatment, probably because of the "white coat" component of their hypertension.

Comparison with other studies

We used a definition of compliance (percentage of days when the correct number of doses were taken) that has been used in many recent hypertension trials.[21 22] In our study average compliance reached 89%, higher than in some other studies.[23–25] This might suggest that we were dealing with a selected group of highly compliant patients. To ascertain whether the patients in our study are similar to those in other studies, we investigated factors that are known to influence treatment compliance in hypertensive patients and for which our study was sufficiently powered. We found that the dose regimen significantly influenced compliance, being 93% with a once daily regimen compared with only 77% with a twice daily regimen—results almost identical to those in other studies.[20 26]

More recent studies of antihypertensive treatments have also found levels of compliance of about 80%.[21 22]

Even an older study of hypertensive patients attending the St Louis Veterans Affairs Medical Center found a high compliance rate with a twice daily drug regimen of 74.9% (days with 100% compliance), and only patients with a three times daily regimen had a relatively low compliance of 59.0%.[20] The patients in our study and patients treated with modern treatment regimens in general only rarely have three times daily dosing regimens. Furthermore, lower doses and newer drug classes have reduced the likelihood of side effects and may thus have improved compliance. Also, hypertension is now better recognised. We conclude that the compliance rates in our study are in line with newer studies[21 22] as well as subgroups of patients in older studies[20] who were following similar drug regimens as in our study.

Limitations of study

For most of our patients, pretreatment blood pressures could not be reliably ascertained, and patients were included because they had a history of known hypertension and were taking antihypertensive drugs.[1] However, the aim of our study was not to evaluate resistance to antihypertensive treatment, it was to assess the common assumption that patients whose hypertension is not well controlled with drugs are likely to be non-compliant. The main elements that lend validity and generalisability to our conclusion that non-compliance is not necessarily the main factor in explaining treatment resistance are (*a*) that the control group of identically recruited patients matched well with the patients resistant to treatment, (*b*) the identification of true treatment resistance by measuring ambulatory blood pressure, (*c*) the use of MEMS devices to measure compliance with two different drugs for each patient, and (*d*) the prospective design in a mainly primary care setting.

Hypertensive patients' compliance with treatment decreases over time,[23 24 27] and our study lasted only 28 days. However, the patients we recruited had been taking a stable regimen of antihypertensive drugs for at least a month, and most had been treated with antihypertensive drugs for years. We therefore assumed compliance to be stable during our study.

The more intensive care and the more frequent visits associated with our study might have improved compliance. Moreover, use of the MEMS devices has been found to significantly increase compliance and response to antihypertensive treatment.[27 28] We therefore measured ambulatory blood pressure at both the start and the end of the study. The average decreases in systolic and diastolic blood pressure were 3.5 mm Hg and 3 mm Hg respectively. These values did not reach statistical significance and are lower than those found in the previously mentioned studies.[27 28] Reclassification of patients as responsive versus non-responsive to treatment on the basis of our second blood pressure monitoring would not have led to different conclusions. Nevertheless, we cannot exclude the possibility that monitoring with MEMS devices improved compliance while not substantially improving blood pressure control.

Our study setting might have selected for patients who were generally more compliant than average. However, as mentioned above, compliance rates in our patients were similar to those reported other studies, most of which were conducted in Europe. Nevertheless, substantial differences may be found in different geographical and cultural settings.

Patients without a full set of data (that is, those who disposed of their MEMS devices) might be expected to be more likely to be non-compliant and were excluded from our study. However, only two patients threw away their MEMS devices.

What is already known on this topic

For many patients with arterial hypertension, blood pressure cannot be adequately controlled despite treatment with antihypertensive drugs

Patients' poor compliance with treatment is often suggested as the reason for lack of response to antihypertensive drugs

What this study adds

When treatment compliance was monitored in hypertensive patients following stable treatment regimens, no difference in compliance was found between those with treatment resistant hypertension and those responsive to treatment

Factors other than patients' compliance with treatment regimens should be examined to explain lack of response to antihypertensive drugs

Conclusions

We found that non-compliance was not associated with resistance to antihypertensive treatment. We suggest that other factors independent of a patient's willingness to adhere to a treatment regimen are more relevant in explaining treatment resistance in most patients.

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Managing demand: transfer of management of self limiting conditions from general practice to community pharmacies

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The management of patients who visit general practitioners for acute, self limiting, health problems is a widespread concern for the workload of general practitioners.[1] Although nurses and pharmacists receive government support for providing treatment for self limiting conditions,[2] patients exempt from prescription charges are not necessarily motivated, or do not have the resources, to obtain care from other sources.[3 4] This increases the workload for general practitioners in areas with high percentages of exempt patients. We examined how referring patients with self limiting conditions directly to a community pharmacist would affect general practitioners' workload.

Participants and methods

All patients seeking general practice appointments or telephone prescriptions for 12 conditions at one general medical practice were offered a consultation with a community pharmacist at one of eight community pharmacies serving that practice.[5] The pharmacists prescribed treatments from a limited formulary. Patients exempt from NHS prescription charges received medicines free of charge through one pharmacy, which they chose from the eight included in the trial. Participants were patients who obtained general practice care over a four month baseline period and those who used general practice or pharmacy services during a six month intervention period.

Once we had removed the financial disincentive to use alternative sources of primary care, we were able to assess the extent to which patients would transfer from general practice care to community pharmacy management. We measured transfer rates and reductions in general practice consultations for the 12 conditions together and individually. We also examined prescribing outcomes and reconsultation rates.

Results

Over the six months of the trial, the overall workload of the general practitioners was unaffected, but the workload for the 12 study conditions decreased ($P = 0.001$, 95% confidence interval 0.397 to −0.108). Overall, 37.8% of the combined consultations for the 12 conditions were transferred, but specific conditions had higher transfer rates—head lice, indigestion, thrush, and constipation. Patients that presented with earache, cough, and sore throat (or any combination of these) were more likely to want to consult a general practitioner (table).

Most patients (88.7%) who transferred to the pharmacy were prescribed a formulary product (table). Almost half (49.0%) of the patients who consulted a general practitioner were prescribed a drug that could have been provided from the pharmacies' limited formulary, and an eighth received prescriptions for products that could be purchased over the counter. Almost a quarter (22.6%) of general practice consultations resulted in a prescription for an antibiotic, while 10.4% patients received a prescription for a condition unrelated to the reason for the consultation. Reconsultation rates did not differ significantly between patients who consulted a general practitioner and those who consulted a pharmacist. Both groups of patients were comparable with respect to age, sex, and the number of