Research / Recherche

Compliance with medication among outpatients with uncontrolled hypertension in the Seychelles

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Owing to increasing rates of hypertension and cardiovascular-related diseases in developing countries, compliance with antihypertensive medication is of major public health importance. Few studies have reported on compliance in developing countries. We determined the compliance of 187 patients with uncontrolled hypertension in the Seychelles (Indian Ocean), by assessing the presence of a biologic marker (riboflavin) in the urine. The urine tested positive in 56% of the cases. Compliance varied from one physician to another (highest 72% versus lowest 33%, P = 0.003), improved with the level of literacy (62% versus 45%, P = 0.024), and depended on the presence or absence of diuretics in the medication (respectively, 45% versus 66%, P = 0.005). The ability of patients to report correctly the number of antihypertensive pills to be taken daily was a predictor of compliance (62% of the patients who gave appropriate answers had positive urine for the marker versus 31% for those giving inappropriate answers).

Introduction

Treatment of hypertension has been shown to reduce cardiovascular morbidity and mortality (*1*, *2*). Uncontrolled hypertension has been attributed to patients' failure to follow properly a prescribed drug regimen in approximately half the cases (*3*, *4*), thus reducing both the effectiveness and the cost-effectiveness of treatment (*5*) and leading to avoidable hospitalization (*6*) and increased rates of coronary events (*7*). Compliance with treatment is therefore important since hypertensive patients are often asymptomatic and medication is required over a long period. Few studies have examined compliance with antihypertensive treatment in developing countries, although the appropriate management of hypertension is an economically affordable means to control cardiovascular diseases in countries with limited resources (*8*), where hypertension is becoming a major health problem (*9–11*). Currently, in the adult population of the Seychelles (Indian Ocean) the prevalence of high blood pressure is 32%; one third of hypertensives are receiving medication and only half of these have their blood pressure under control (*11*, *12*). To investigate the extent of compliance among patients with medically treated hypertension we chose riboflavin (vitamin B2), a natural and non-teratogenic constituent of the diet (*13*), as a marker and relatively accurate indicator of compliance (*14–17*).

Patients and methods

The study was carried out towards the end of 1993 with the patients of ten doctors in 7 general outpatient clinics, out of the 15 which provide ambulatory medical care in the Seychelles. Participation was solicited and obtained from 223 consecutive patients with uncontrolled hypertension, none of whom was taking vitamin supplement preparations. Uncontrolled hypertension was defined as a diastolic blood pressure ≥90 mmHg despite medication. Patients with a

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diastolic blood pressure >115 mmHg required immediate and intensive treatment, and for this reason were not included in the study. The protocol was approved by the Ministry of Health of the Seychelles. Medical consultation and medication were free of charge, as for all inhabitants of the Seychelles. At the time of the first visit (No. 1), the study patients received riboflavin to be taken once every morning (1 tablet of 10 mg, Hanseler AG, Herisau, Switzerland), in addition to their usual antihypertensive medication. All participants received their medication at the pharmacy of the primary health care centre, as usual. Data about clinical characteristics, socio-demographic features, degree of literacy, health habits, history of hypertension, and duration of antihypertensive treatment were obtained by interview. Literacy was evaluated by the ability to read a local newspaper in at least one of the three national languages. Study patients were invited for a follow-up visit (No. 2) after an arbitrary period of 21±3 days. Patients were not informed that a special procedure (urinary examination) was to be performed on visit No. 2.

At the time of visit No. 2, the blood pressure was measured and patients were asked about the number of antihypertensive pills taken daily, which was compared with the treatment prescribed by the doctor. Results were "concordant" when the daily number of pills prescribed and taken were similar, or else "non-concordant". Compliance with medication was estimated by testing for the presence of metabolites of riboflavin in the urine, which was collected at the time of visit No. 2. This test was carried out by the treating doctors, after special training using an UV light source according to the method described by Jones (*18*). Patients were excluded from the study if visit No. 2 was not within the 21±3-day period or not between 9 a.m. and 2 p.m. or if they were hospitalized in the interval, or had made an extra visit and had the treatment changed. Rates of compliance within categories of variables were compared using the chi-squared and trend tests. Logistic regression analyses were performed to examine the relation of compliance to independant variables, including demographic, educational, lifestyle, and clinical characteristics.

Results

A total of 223 consecutive patients were enrolled in the study, and 36 had to be excluded, mainly because of non-attendance at visit No. 2. The main characteristics of the remaining 187 patients are summarized in Table 1. The urine tested positive in 104 subjects (compliance rate, 56%). Compliant patients had a mean diastolic blood pressure during visit No. 2 of 96 mmHg, compared with 100 mmHg for the others ($P = 0.05$); the blood pressure had been similar in the two groups during visit No. 1 (102 vs. 104 mmHg in compliant and non-compliant patients, respectively).

Table 1: **Numbers of individuals with positive and negative urine tests for riboflavin within categories of selected characteristics**

Characteristics	Urine negative (n = 83)	Urine positive (n = 104)	P^a
Sex:			
Females	59	70 (54)[b]	
Males	24	34 (59)	0.579
Age (years):			
<50	26	28 (52)	
50–65	40	57 (59)	
>65	17	19 (53)	0.665
Literate:			
Yes	45	73 (62)	
No	38	31 (45)	0.024
Smoking:			
No	67	91 (58)	
Yes (≥1 cigarette/day)	16	13 (45)	0.203
Alcohol:			
No	52	72 (58)	
Yes (≥1 drink/day)	31	32 (51)	0.344
Duration of therapy:			
<5 years	41	46 (53)	
>5 years	42	58 (58)	0.482
Number of tablets/day:			
<4	34	46 (58)	
4–6	31	35 (53)	
>6	18	23 (56)	0.786
Reported vs. prescribed number of pills/days:			
Non-concordant	27	12 (31)	
Concordant	56	92 (62)	<0.001
Doctor:			
Other	53	64 (55)	
No. 3	12	31 (72)	
No. 7	18	9 (33)	0.006

[a] Chi-squared tests were calculated to assess the difference in proportion of riboflavin positive and negative urine tests among subcategories of the characteristics listed in column 1.
[b] Figures in parentheses are percentages within each category.

Compliance according to demographic, educational, lifestyle, and clinical characteristics. Tables 1 and 2 show that compliance varied among the different physicians ($P = 0.006$), and was associated with literacy ($P = 0.024$) and the ability to report correctly the number of antihypertensive pills taken daily

Table 2: **Univariate and multivariate relations between compliance with medication and selected characteristics**

Characteristics	Univariate		Multivariate[b]	
	OR[a]	95% CI	OR[a]	95% CI
Sex:				
Females	1		1	
Males	1.19	0.64–2.24	1.97	0.78–4.99
Age (years):				
<50	1		1	
50–65	1.32	0.67–2.60	1.81	0.78–4.18
>65	1.04	0.44–2.44	1.82	0.63–5.27
Literate:				
Yes	1		1	
No	0.50	0.27–0.92	0.64	0.29–1.42
Smoking:				
No	1		1	
Yes (≥1 cigarette/day)	0.60	0.27–1.33	0.52	0.18–1.55
Alcohol:				
No	1		1	
Yes (≥1 drink/day)	0.75	0.40–1.38	0.92	0.39–2.17
Duration of therapy:				
<5 years	1		1	
>5 years	1.23	0.69–2.20	1.31	0.65–2.65
Number of tablets/day:				
<4	1		1	
4–6	0.83	0.43–1.62	0.91	0.41–2.00
>6	0.94	0.44–2.03	1.19	0.46–3.06
Reported vs. prescribed number of pills/days:				
Non-concordant	1		1	
Concordant	3.70	1.73–7.91	3.57	1.53–8.30
Doctor:				
Other	1		1	
No. 3	2.14	0.99–4.60	1.56	0.62–3.92
No. 7	0.41	0.17–1.00	0.48	0.17–1.34

[a] An odds ratio (OR) above 1 means better compliance.
[b] Multivariate analysis includes all the variables listed as well as use of diuretics.

(P <0.001). Estimates of odds ratios were different for patients with appropriate reporting of their antihypertensive treatment compared to patients with inappropriate reporting, and these estimates were similar in univariate and multivariate analyses. None of the other relationships was significant in the multivariate analyses, but the point estimates of the two significant univariate correlates (literacy and doctors) were similar in multivariate analyses. Variables previously demonstrated as being predictive of adherence to medical regimens, i.e., age (*19*), number of daily tablets (*20–22*), as well as other variables, like sex, smoking and drinking habits, and the duration of therapy, were not related to compliance in this study.

Compliance according to medications. Table 3 shows the utilization of different antihypertensive medications. The use of diuretics, the most common treatment, was associated with a lower compliance in univariate analysis (P = 0.005); although not more significant statistically, the point estimate of the effect was unchanged in multivariate analysis. Other types of antihypertensive medications were not related to a significant modification of compliance, but better compliance was observed with β-adrenergic blockers.

Predictive value for compliance. Table 4 shows that appropriate reporting back of treatment modalities, together with full compliance on self-reporting, had a 73% positive predictive value for compliance as indicated by a positive test for riboflavin. The positive predictive value decreased to 62% when concordant reporting back was considered alone.

Discussion

This study showed 56% compliance with treatment in a population of uncontrolled hypertensive patients in the Seychelles. This result accords with previous studies in developed countries on compliance with treatment of a chronic disease like hypertension (*4, 23–25*). However, there are few studies on compliance in developing countries (*26*), despite its major public health importance. Developing countries face increasing rates of chronic diseases, notably hypertension and cardiovascular-related diseases (*9–11*). With poor compliance the efficiency of treatment is lower, thereby increasing the rate of uncontrolled hypertension (*27*). Urine testing for the tracer, riboflavin, is an immediate and valid measure of the patient's compliance on the day the specimen was collected (*17*). The procedure is simple, requires no expensive equipment (*28, 29*) and is well adapted to clinical research in a developing country (*29*). Owing to the short half-life, this method only confirms ingestion of the drug during the previous few hours, and gives no information on the dynamics of compliance. For this reason the importance of an overestimation on the day of the control visit, as compared to the usual compliance ("toothbrush" effect), cannot be assessed (*21, 30, 31*). Furthermore, the exclusion of patients for non-attendance at the clinic presumably eliminates mainly patients with low adherence, thus leading to overestimation of compliance and emphasizing the importance of the phenomenon of non-adherence.

Table 3: **Univariate and multivariate relations between compliance and type of medication**

Characteristics	No. of patients	Univariate		Multivariate[b]	
		OR[a]	95% CI	OR[a]	95% CI
Angiotensin-converting enzyme inhibitors:					
No	146	1		1	
Yes	41 (22)[c]	1.03	0.51–2.07	0.99	0.45–2.19
Central-adrenergic inhibitors:					
No	113	1		1	
Yes	74 (40)	0.57	0.32–1.04	1.98	0.58–6.77
β-adrenergic blockers:					
No	125	1		1	
Yes	62 (33)	1.57	0.84–2.93	2.33	1.11–4.87
Calcium entry blockers:					
No	149	1		1	
Yes	38 (20)	1.12	0.54–2.32	1.51	0.65–3.48
Hydralazine hydrochloride:					
No	155	1		1	
Yes	32 (17)	1.20	0.55–2.62	1.59	0.64–3.92
Diuretics:					
No	96	1		1	
Yes	91 (49)	0.43	0.24–0.78	0.53	0.26–1.10

[a] An odds ratio above 1 means better compliance.
[b] Multivariate analysis included variables mentioned in Table 1.
[c] Figures in parentheses are percentages.

In agreement with the findings of previous studies on the importance of the doctor–patient relationship for compliance (*32, 33*), substantial differences in levels of compliance were found among patients followed by different doctors. This difference may be related to the selection of patients in different primary health care centres. Literacy is probably an important determinant in the clinician–patient relationship for adequate understanding of all aspects of this chronic and asymptomatic disease as well as of treatment modalities. In this study, a better rate of compliance was found among literate patients.

Table 4: **Compliance estimates by testing for metabolites of riboflavin in the urine vs. appropriate reporting back of treatment modalities and full compliance on self-reporting**

	Urine positive (n = 104)	Urine negative (n = 83)	Total
Appropriate reporting back and full compliance:			
Yes	60	22	82
No	44	61	105
Total	104	83	187

Sensitivity = 58%, specificity = 73%, positive predictive value = 73%, negative predictive value = 58%

Because most previous studies were done in developed countries where illiteracy is less prominent, no data were available on this issue. The use of diuretics was associated with a lower compliance, possibly due to side-effects. But false negative results, due to dilution of the urinary metabolite of riboflavin, cannot be excluded, although not previously reported in the literature.

In this study, appropriate reporting back on medication was predictive of a significant increase in compliance with the medical regimen. Patients who were more knowledgeable about their treatment were 3.6 times more likely to be compliant that those who were less aware, even after adjusting for other putative determinants of compliance. Questioning patients about their treatment can therefore give useful and simple information to identify compliant patients (*19, 34*). However, the positive and negative predictive values of an appropriate reporting back of treatment modalities on the actual compliance rate, as estimated by a positive test for riboflavin in urine, were not very high (73% and 58%, respectively) so that accurate reporting of medication cannot be used alone as a surrogate test.

In conclusion, a 56% rate compliance with antihypertensive treatment was found in a population of uncontrolled hypertensive patients in a developing

country. This figure is probably an overestimate in view of the method used and the exclusion of non-attenders. These findings emphasize the need to improve the quality and efficiency of medical treatment, including improved cooperation between patients and doctors. This issue is of major public health importance in view of the rate of uncontrolled hypertension related to poor compliance (*27*). The resulting higher morbidity and mortality, associated with poor utilization of medication and funds, are a correctable problem in countries with limited resources (*30*).

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Résumé

Observance du traitement chez des patients ambulatoires présentant une hypertension non contrôlée aux Seychelles

Dans les pays en développement, où l'on observe une augmentation des taux d'hypertension et des maladies cardio-vasculaires, l'observance du traitement par antihypertenseurs est d'une importance primordiale du point de vue de la santé publique. Rares sont les publications consacrées à l'observance du traitement dans ces pays. La présente étude avait pour objectifs de déterminer le taux d'observance du traitement chez des patients présentant une hypertension artérielle non contrôlée et consultant un centre de soins de santé primaires dans un pays en développement, et d'évaluer les facteurs influant sur l'observance.

Au total, 223 patients présentant une hypertension artérielle non contrôlée (tension diastolique ≥90 mmHg et <115 mmHg) vus consécutivement dans 7 centres de soins de santé primaires aux Seychelles ont été suivis par un médecin parmi les 10 médecins participant à l'étude. L'étude a été réalisée vers la fin de l'année 1993. Le taux d'observance du traitement par antihypertenseurs a été mesuré indirectement par la présence d'un métabolite urinaire de la riboflavine, trois semaines après l'addition de riboflavine aux médicaments antihypertenseurs pris quotidiennement. Après exclusion de 36 patients, essentiellement en raison de leur absence aux visites de suivi, 187 patients ont été étudiés. Les tests urinaires étaient positifs dans 56% des cas. Ce taux est probablement surestimé, du fait de la méthode utilisée pour évaluer l'observance et de l'exclusion des patients perdus de vue. Il variait d'un médecin à l'autre (de 72% à 33%, p = 0,003), s'améliorait avec le niveau d'alphabétisation du patient (62% contre 45%, p = 0,024) et dépendait de la présence ou de l'absence de diurétiques dans le traitement (45% contre 66%, p = 0,005).

Une analyse multivariée, incluant à la fois ces variables et des paramètres démographiques, n'a pas modifié sensiblement ces résultats. L'aptitude des patients à indiquer correctement le nombre de pilules d'antihypertenseurs à prendre chaque jour était un facteur prédictif de l'observance (62% des patients ayant donné une réponse correcte avaient un test urinaire positif pour le marqueur contre 31% pour ceux qui donnaient une réponse erronée, p<0,001). Ces résultats soulignent la nécessité d'améliorer la qualité et l'efficience du traitement médical, y compris au niveau de la coopération patient-médecin. Cette question est d'une importance primordiale du point de vue de la santé publique étant donné le taux élevé d'hypertension artérielle non contrôlée due à la non-observance du traitement. La morbidité et la mortalité élevées qui en résultent, ainsi que la mauvaise utilisation des médicaments et des ressources financières, sont des problèmes qui peuvent être corrigés dans les pays ne disposant que de ressources limitées.

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