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ARTÍCULO ORIGINAL

Drug treatment of hypertension: compliance and adverse reactions in a cohort of hypertensive patients in a primary care setting

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ABSTRACT

Objectives. The primary was to assess the frequency of therapeutic non-compliance due to ADRs in a cohort of patients with recently diagnosed systemic hypertension. The secondary objectives were to evaluate the blood pressure control during the follow-up in the whole cohort and in patients who received non-steroidal anti-inflammatory drugs (NSAIDs). **Methods.** A cohort of 73 recently diagnosed ambulatory hypertensive patients was followed-up for 6 months. Validated questionnaires for identification of therapeutic scheme changes and ADRs were applied monthly, during each medical visit. **Results.** Family physicians selected monotherapy in 79% of patients. The frequency of therapeutic non-compliance was 44%; non-compliance secondary to ADR was 7%. Systolic and diastolic blood pressure at the beginning of the study were 140 ± 15/90 ± 15 mm Hg for the whole cohort. At the end of the study the figures were 130 ± 11/85 ± 6 ($p < 0.001$). Patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) had higher blood pressure levels than the groups of patients not receiving such kind of drugs (134 ± 10 vs. 128 ± 8 mm Hg, $p = 0.025$ and 88 ± 7 *vs.* 83 ± 5 mm Hg, $p = 0.05$). **Conclusions.** The drugs used in the present study as monotherapy are considered acceptable choices for hypertension treatment. The frequency of therapeutic non-compliance was within the limits reported in the literature and the frequency of therapeutic non-compliance secondary to ADRs in this cohort was lower than that reported in the literature. Higher blood pressure was found in the group of patients receiving NSAIDs.

Tratamiento farmacológico antihipertensivo: Cumplimiento y reacciones adversas en una cohorte de pacientes hipertensos en atención primaria

RESUMEN

Objetivos. *El objetivo primario fue evaluar la frecuencia de falta de cumplimiento terapéutico debido a la presencia de reacciones adversas a medicamentos (RAMs) con el uso de antihipertensivos; los objetivos secundarios fueron evaluar el control de la presión arterial durante el seguimiento y en aquellos pacientes que recibieron fármacos antiinflamatorios no esteroideos.* ***Métodos.*** *Se integró una cohorte de 73 pacientes hipertensos de reciente diagnóstico, a los que se les vigiló durante seis meses. En cada visita médica mensual se les aplicaron cuestionarios validados, para identificar cambios en el esquema terapéutico y RAMs.* ***Resultados.*** *Los médicos familiares emplearon monoterapia en 79% de los pacientes. La falta de cumplimiento terapéutico se presentó en 44%; el incumplimiento terapéutico secundario a RAMs se observó en 7% de los casos. En todos los pacientes la presión arterial sistólica y diastólica al inicio del estudio fue 140 ± 15/90 ± 15 mm Hg y al final del estudio las cifras fueron 130 ± 11/85 ± 6 ($p < 0.001$). Los pacientes que recibieron fármacos antiinflamatorios no esteroideos (AINEs) tuvieron cifras de presión arterial más elevadas que pacientes que no recibieron este tipo de fármacos (134 ± 10* vs. *128 ± 8, $p = 0.025$ y 88 ± 7 vs. 83 ± 5 mm Hg, $p = 0.05$).* ***Conclusiones.*** *Los fármacos empleados en este estudio como monoterapia son fármacos aceptados para el tratamiento de la hipertensión. La frecuencia de falta de cumplimiento terapéutico se ubicó dentro de los límites descritos en la literatura y la falta de cumplimiento terapéutico secundario a RAMs fue menor que*

lo informado en la literatura. Se observaron cifras de presión arterial elevadas en pacientes que recibieron AINEs.

Key words. Antihypertensive drugs. Pharmacovigilance. Adverse drug reactions. Compliance. Drug utilization study.

Palabras clave. *Fármacos antihipertensivos. Farmacovigilancia. Reacciones adversas a medicamentos. Cumplimiento y estudio de utilización de medicamentos.*

INTRODUCTION

Systemic hypertension is a risk factor for cardiovascular disorders, and renal damage. Clinical trials have demonstrated that an adequate use of antihypertensive drugs is associated with a reduction of stroke and coronary artery disease mortality.[1] It has also been demonstrated that most of the antihypertensive drugs have similar efficacy regarding blood pressure reduction; therefore, when a pharmacologic treatment for hypertension is initiated, the associated medical disorders, as well as adverse drug reactions (ADRs) and cost should be taken into account for choosing the optimal treatment.[2]

In spite of the availability of antihypertensive drugs with demonstrated efficacy, the risks for stroke or cardiovascular death have not shown the expected reductions, which may be partly explained by therapeutic non-compliance.[2] There are reports that 16 to 50% of the recently diagnosed hypertensive patients abandon the treatment within the first year. Additionally, a significant proportion of patients that continue on treatment after one year withdraw one or more doses by routine.[2] By the fifth year, 54% of the patients have abandoned the treatment.[3] A study from Spain showed that less than 50% of the treated hypertensive patients achieved good blood pressure control,[4] and other studies from the same country have reported therapeutic non-compliance in 40-71% of the hypertensive patients.[5] In Mexico, there is few information regarding ADRs. The National Survey of Hypertension (Re-encuesta Nacional de Hipertensión Arterial RENAHTA), carried out in 2003-2004, reported that from 52% of people suffering hypertension and receiving medication, only 20% could mention the name of such medication.[6] In patients receiving antihypertensive treatment, some symptoms are considered as ADRs and lead to treatment withdrawal, but they are rather aggravated by the therapeutic non-compliance itself. An example of this is headache. The symptom may be a secondary effect of certain antihypertensive drugs, but it also may be a consequence of high blood pressure.[2] ADRs in adult patients accounted for 1-3% of the office visits in a primary health care center in Spain.[7] Usually the ADRs associated with antihypertensive treatment are mild, self-limited, and easily controllable; thus, they are not considered as important primary care or public health problem. Nevertheless, the physicians should carefully discuss with the patients the profile of ADRs that they may experience, and the risks associated with the lack of an appropriate antihypertensive treatment.[8] Several reports from different settings have indicated that the cause of drug withdrawal in up to 30% of hypertensive patients was non-tolerable ADRs.[3]

The Mexican Institute of Social Security (IMSS) is the largest health care system in Mexico, and it is a public system that provides care to forty million people and fourteen thousand family physicians staff its primary care services. Hypertension is one of the most frequent causes of visit at primary care; at this level of care, there is an essential list of antihypertensive drugs, that includes thiazide diuretics, β-Blockers, ACE inhibitors, Calcium channel blockers-non-dihydropyridines, Calcium channel blockers-dihydropyridines, α_1-Blockers, Central α_2-Agonists, and other centrally acting drugs.

The primary objective of the present study was to assess the frequency of therapeutic non-compliance due to ADRs in a cohort of patients with recently diagnosed systemic hypertension. The secondary objectives were to evaluate the blood pressure control during the follow-up in the whole cohort and in patients who received non-steroidal anti-inflammatory drugs (NSAIDs).

PATIENTS AND METHODS

A cohort of 73 recently diagnosed hypertensive patients from a family medicine clinic belonging to IMSS in Mexico City were followed-up for 6 months. Clinical records were reviewed to identify patients diagnosed by the family physician as suffering high blood pressure, and receiving antihypertensive therapy; patients with a diagnosis of secondary hypertension registered at the clinical record were excluded.

All the patients were diagnosed as being hypertensive within 6 months before the recruitment. To be eligible, the patients should have the same medication prescription since the beginning of the antihypertensive therapy. Patients who underwent

major changes in their therapy were not included, as well as patients physically or mentally unable to respond to the interview and patients who did not accept to participate in the study.

A convenience sampling was done.

Therapeutic non-compliance was assessed by specific interrogatory and by pill-count. Non-compliance was considered to be present when one or more questions of a validated questionnaire[5] received affirmative responses. The clinical chart was reviewed in order to complete the information.

Non-compliance secondary to ADRs was defined as a discontinuation of the antihypertensive treatment due to the presence of a drug-related clinical manifestation, as reported by the patient, irrespective of the discontinuation duration or of the number of suspended doses.

Before the cohort was assembled, a pharmacoepidemiological committee was integrated. The committee included five members (two internists, two pharmacologists, and one family physician), who determined the appropriateness of the treatment, ADRs due to medication (antihypertensive) and classified the event according to its severity by using the algorithm of Karch and Lasagna.[9] Appropriateness of treatment was defined as compliance of validated clinical guidelines based on The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria.[10] All family physicians working at the clinic received an educative program of pharmacovigilance, in order to update them for identification and report of probable ADRs.

During the first sixth months of the year 2000, the patients were selected and recruited by their treating primary care physicians or by a trained nurse who identified and invited them to participate in the waiting room of the primary care facility. Patients were interviewed by the nurse, who filled a questionnaire about family history, evolution of the illness, co-morbidity, and the complete treatment received since the beginning of the therapy until the last medical visit. During the 6-months follow-up, after each monthly visit to family physician, the nurse interviewed to the patients and registered their blood pressure, weight, antihypertensive drugs and dosages, other received drugs (particularly non-steroidal anti-inflammatory drugs [NSAIDs]), and relevant clinical data. The day prior to the visit, the patients were reminded by telephone to bring their remaining pills. Immediately after the medical visit, the patients were interviewed by a nurse who asked them in an open way about symptoms suggestive of ADRs during the last 30 days. The interviewer did not mention or suggested any specific symptom, but only asked the patients if they experienced any symptom that they attributed to a drug during that period. If a suspected ADR was present, the patients' actions, such as medical advice request, treatment suspension, self-medication, or others, were recorded.

Patients were classified in one of the four following groups, according to the antihypertensive prescription that they received during the follow-up: 1) Patients who continued with the therapeutic scheme during the entire follow-up; 2) modification of the therapeutic doses during the follow-up; 3) and those with permanent discontinuation of medication.

ETHICS

The study protocol was approved by the Institutional Review Board. Primary care physicians were invited to voluntarily participate in the study. An oral consent of the patients to participate in the study was obtained; patients were informed about the follow-up characteristics and the planed procedures, but the objective of the study was not disclosed. During the study, when mild ADRs were identified by the committee, the attending physician was contacted and informed, and a recommendation for modifying the treatment was done. As defined in the study protocol, in case of moderate to severe ADR, the patients should be found for immediate treatment, but moderate or severe ADRs did not occur during the study.

STATISTICS

Frequencies and percentages were calculated for each antihypertensive therapeutic scheme, ADRs, non-compliance, causes of non-compliance, and drug–drug interactions. Blood pressure level was compared among the 4 described groups by ANOVA and Tukey's post-hoc test. Additionally, the blood pressure level of patients receiving NSAIDs was compared with that of patients who did not receive NSAIDs by Student's t test. A two-tailed p value ≤ 0.05 was considered as statistically significant.

RESULTS

Table 1 shows some clinical and demographic characteristics of the 73 patients included in the cohort.

At the beginning of the follow-up 58 patients (79%) received monotherapy and only 15 (21%) received a combination of antihypertensive drugs (see table 2). At the end of the study the number of patients receiving a single drug dropped to 45 (62%), and the number of patients receiving combined treatment increased to 20 (27%); 8 patients (11%) suspended the therapy definitively.

The prescribed drug combinations (see table 3) were considered as appropriate in 86.6% of the patients at the beginning, and in 80% at the end of the study; in 4 cases there was not indication (heart failure) for such therapeutic scheme: a combination of a beta-blocker and an ACE-inhibitor (2 patients) and a combination of four drugs including a beta-blocker, an ACE-inhibitor, a calcium channel antagonist, and chlorthalidone (2 patients).

Therapeutic non-compliance was recorded in 32 patients (43.8%) but only in 5 of them, it was due to the occurrence of an ADR. When the group of non-compliant patients was compared with the group of compliance, no differences in sociodemographic variables (age, sex or literacy), treatment (duration of antihypertensive treatment, type of medication prescribed, number of ADRs, potential interactions), and blood pressure level were found.

Twelve patients temporarily discontinued the antihypertensive treatment because they did not get their medication (the pharmacy was short of supplies). Nine of them resumed the original therapeutic scheme, two modified the original scheme, and

Table 1. Clinical and demographic characteristics of the studied patients

	n	%
Sex	73	
Female	48	66
Male	25	34
Age years Mean ± Standard deviation	56 ± 12	
Civil status		
Married	33	45
Single	40	55
Literacy		
None	10	14
Elementary school or high school	42	58
Tobacco consumption*	11	15
Alcohol consumption**	29	40
Coexisting diseases registered on clinical record		
Diabetes type 2	5	16
Peptic disease	5	16
Peripheral venous insufficiency	4	13
Osteoarthritis	3	9
Migraine	2	6
Dyslipidaemia > 200 mg/dL total cholesterol, or > 150 mg/dL triglycerides	2	6
Ischaemic heart disease	1	3
Other	10	31
Days from diagnosis Median (min-max)	34	1-179

* Tobacco consumption was considered as positive if the patient consumed one or more cigarettes per day.

** Alcohol consumption was considered as positive if the patient consumed ≥ 60 mL of distilled beverages or ≥ 200 mL of fermented beverages per day.

Table 2. Medication prescription to patients at the beginning and the end of the study.

Drugs used	Beginning of the study n=73 n (%)	End of the study n=73 n (%)
Captopril	38 (52)	29 (40)
Drug combinations*	15 (21)	20 (27)
Metoprolol	7 (10)	4 (6)
Chlorthalidone	6 (8)	3 (4)
Enalapril	4 (6)	4 (6)
Propranolol	1 (1)	2 (3)
Verapamil	1 (1)	1 (1)
Nifedipine	1 (1)	1 (1)
α-methyldopa	0 (0)	1 (1)
No drugs	0 (0)	8 (11)

* Specific drug combinations are shown in table 3.

Table 3. Drug combinations prescribed at the beginning and the end of the study.

Combinations of drugs	Beginning of the study n	End of the study n
• Captopril + chlorthalidone	7	9
• Enalapril+ chlorthalidone	4	2
• Captopril + metoprolol*	2	2
• Nifedipine + chlorthalidone	1	1
• Captopril + nifedipine	1	1
• Enalapril + nifedipine	0	1
• Metoprolol + chlorthalidone	0	1
• Captopril + hydrochlorothiazide	0	1
• Captopril + chlorthalidone + metoprolol + nifedipine*	0	1
• Captopril + chlorthalidone + metoprolol + verapamil*	0	1
Total	15	20

Values shown are absolute frequencies. * Non-recommended combinations.

one permanently discontinued the treatment. These 12 patients were taking captopril (8 patients), chlorthalidone (2) and metoprolol (2).

Table 4 shows the classification of patients according to levels of blood pressure and type of treatment. At the beginning of the study, 20.5% was controlled, from optimal to normal high, while at the end, this percentage improved to more than fifty percent. Regarding type of treatment, combination of medication did not increased from baseline to final evaluation. At the end of the study, 46 patients (63%) remained with monotherapy, and 20 (43.5%) were in bad control of hypertension.

Table 5 shows the 21 ADRs detected during the six months of the follow up. All the ADRs were related only to five different drugs. Thirteen out of 21 ADRs were attributed to an ACE inhibitor (captopril [11] or enalapril [2]). All the suspected ADRs were identified by the nurses during the interview after the medical visit, but only 4 of them were detected and reported by the attending physicians during the medical visit. All the ADRs were classified as mild. According to the Karch and Lasagna algorithm,[9] 20 ADRs were classified as "probably-related" and one as "doubtfully-related" to the suspected drug.

Antihypertensives were prescribed concomitantly with another drug with well – known potential drug–drug interaction risk in 31 patients (42.5% of the study sample). The most frequently prescribed combination of this kind was an ACE inhibitor with a NSAID (24 patients); in up to 13 of them captopril was prescribed with diclofenac.

Systolic and diastolic blood pressure at the beginning of the study was 140 ± 15 / 90 ± 15 mm Hg (mean ± standard deviation [SD]) respectively, for the whole cohort. At the end of the study the figures were 130 ± 11 / 85 ± 6. The differences were statistically significative ($p < 0.001$). When classified in subgroups according to the treatment, patients who continued with the therapeutic scheme during the entire follow-up (n = 45), those with modification of the therapeutic doses during the follow-up (n = 20), and those with permanent discontinuation of medication (n = 8), showed similar blood pressure levels during the study (129 ± 13 / 84 ± 6, 134 ± 9 / 87 ± 7 and 128 ± 8 / 85 ± 6 mm Hg, n.s.) (mean ± SD systolic and diastolic blood pressure). Patients receiving NSAIDs (n = 28; 38.3%) had significantly higher blood pressure than patients not receiving such kind of drugs (n = 45; 61.7%) (134 ± 10 mm Hg versus 128 ± 8 mm Hg, p= 0.025 and 88 ± 7 mm Hg versus 83 ± 5 mm Hg; p = 0.05).

Table 4. Classification of patients according to control of hypertension and type of treatment.

Classification	Beginning of the study n (%)	End of the study n (%)
Optimal (< 120/ < 80 mm Hg)		
Monotherapy	0	2 (2.73)
Combined therapy	1 (1.36)	2 (2.73)
Without treatment	0	1 (1.36)
Normal (120-129/80-84 mm Hg)		
Monotherapy	3 (4.10)	13 (17.80)
Combined therapy	1 (1.36)	3 (4.10)
Without treatment	0	5 (6.84)
Normal High (130-139/85-89 mm Hg)		
Monotherapy	8 (10.95)	11 (15.06)
Combined therapy	2 (2.73)	1 (1.36)
Without treatment	0	1 (1.36)
Stage 1 (140-159/90-99 mm Hg)		
Monotherapy	35 (47.94)	15 (20.54)
Combined therapy	4 (5.47)	6 (8.21)
Without treatment	0	2 (2.73)
Stage 2 (160-179/100-109 mm Hg)		
Monotherapy	10 (13.69)	4 (5.47)
Combined therapy	4 (5.47)	4 (5.47)
Without treatment	0	0
Stage 3 (180 or +/110 or + mm Hg)		
Monotherapy	3 (4.10)	1 (1.36)
Combined therapy	2 (2.73)	1 (1.36)
Without treatment	0	1 (1.36)
TOTAL	73	73

Table 5. ADRs detected during the study.

Drug	ADR	n
Captopril	Somnolence	3
	Cough	2
	Dizziness	2
	Headache	2
	Anxiety	1
	Fatigue	1
Enalapril	Cough	1
	Paresthesia	1
Metoprolol	Confusion	1
	Nervousness	1
	Somnolence	1
Verapamil	Headache	1
	Fatigue	1
Nifedipine	Dizziness	1
	Headache	1
	Paresthesia	1

DISCUSSION

In the present study, the proportions of patients receiving 1 and 2 antihypertensive drugs were similar, but the proportion of patients receiving more than 2 drugs (11%) was more than two-fold higher as compared with a recent study that included a sample of more than 5,000 hypertensive patients.[11] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend the addition of a second drug from a different class when a single drug fails to achieve the goal of control of blood pressure. The initial recommendation drug is thiazide diuretics, but is known that most of patients will need combination of medication to control blood pressure.[12] However, it is interesting to highlight that up to 16% of the patients receiving a combination of drugs after 6 months of follow-up in the present study, received a non-recommended combination in the literature.[11,13]

It has been documented that fixed-dose combinations usage avoids irrational combinations.[11] The drugs used in the present study as monotherapy are considered acceptable choices for hypertension treatment;[14] however, the proportion of patients receiving monotherapy at the end of the study was higher than 50%, whereas it is accepted that monotherapy allows good control for only 30-50% of the patients.[15] The high proportion of patients receiving monotherapy and remained in bad blood pressure control at the end of the study, reinforce the relevance of using combined drugs when monotherapy is not enough in achieving the goal.[12]

Non-compliance is related to many factors, and definition of an appropriate cut-point is very difficult, because clinical outcomes are related to multiple variables and not only to the antihypertensive treatment itself. Our decision to classify as non-compliance secondary to ADR those cases in which some of the drugs were discontinued, even transitorily, allowed us to identify certain patients' misconducts that may potentially affect the results of the therapy. We were expecting that with the use of these strict criteria our proportion of patients with non-compliance would be higher than that reported in the literature,[16] but this did not occur; it is possible that closely monitoring during the follow-up, and the short period of observation accounted for the low frequency of ADR-related non-compliance (5 out of 73 patients; 7%) seen in the present study. The trend for treatment abandon after longer follow-up periods was not assessed, but it may be important as suggested by other studies.[3] An important finding in this study was the temporarily treatment discontinuation in 12 patients (16% of the study sample) due to lack of drugs.

Another finding of the present study is the low rate of ADRs identification by the physicians. They only reported 4 of the 21 ADRs identified by the research nurse. Some authors have reported similar results; in a study of hospitalized patients, the physicians failed to detect and report 57% of the patients whose admission cause was an ADR to drugs;[17] moreover, in the same study there was an association between the severity of the ADR and the probability of detection, and mild and moderate ADRs were under-recognized. Another report showed that 68% of the physicians had suspected one or more ADRs, but they did not report them, particularly because the ADR was very well known or mild, thus reporting it was not worthy; 25% of the physicians in the same study never had diagnosed an ADR, and 30% of them did not know how to report them.[18] The issue regarding who should be responsible for detecting and reporting the ADR to antihypertensive drugs remains controversial.[18] In developing countries where the healthcare institutions have limited personnel and resources, this responsibility usually corresponds to the physicians, instead pharmacists. This was the case of the clinical setting in which our study was carried out.

In the present study only mild ADRs were observed. In addition, most ADRs were observed in patients treated with captopril, a drug with a well-known toxicity profile. Although there have been reported that side effects attributed to antihypertensives drugs do not represent an important problem in primary care, or public health problems,[7] this idea is controversial.[19]

About one third of the patients in this study were taking NSAIDs; this point is important because, patients that receiving NSAIDs had significantly higher blood pressure levels than patients who did not receive this kind of drugs; this finding has been previously reported.[20,21] The mechanism by which these drugs increase blood pressure and interfere with antihypertensive drugs is not fully understood, but it has been reported that they may reduce the efficacy of beta-blockers, diuretics, and ACE inhibitors because of inhibition of the prostaglandin metabolic pathway, enhancing vasoconstriction.[20]

Since the beneficial effect of a strict blood pressure control has been widely demonstrated, opportune detection of therapeutic non-compliance, use of inappropriate drug combinations or potential drug-drug interactions (e.g., antihypertensive –

NSAIDs) should be a priority for the healthcare team, in order to identify potential failures in drug treatment. This is especially important in chronic asymptomatic health conditions such as hypertension, in which lack of control can cause severe complications.

In conclusion, the results of this study underscore the importance of implementing actions directed to strengthen the appropriate utilization of drugs and the guidelines' adherence, as well as the reinforcement of the pharmacovigilance program in primary care settings. Additionally, it is necessary to consider the convenience of designing education programs for the patients, in order to improve compliance and the identification of possible ADRs; for these programs, the role of the primary care nurse is relevant, as part of the health care team supporting the physician's recommendations and helping in the follow-up of patients with chronic diseases.

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