

Inequalities in prescription of hydrochlorothiazide for diabetic hypertensive patients in Colombia⁽¹⁾

Desigualdades en la prescripción de hidroclorotiazida en pacientes hipertensos diabéticos en Colombia

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ABSTRACT

Objective Evaluating differences in the suitable prescription of thiazides in hypertense patients, according to affiliation regime.

Materials and methods This was an analytical cross-sectional study. The database from a previous study was used regarding two groups of hypertense patients (subsidised regime and contributory regime) who had attended out-patient consultation between 01-09-2007 and 29-02-2008. Ideal therapy was evaluated in both groups. Univariate and multivariate analysis was carried out.

Results 136 patients (contributory: 41.9 %; subsidised: 58.1 %). Subsidised regime patients were older (mean=68.8±10) than those from the contributory regime (mean=64.1±11.1) (t-test, p=0.0110). Prescribing antihypertensive drugs was ideal in 49/136 of the patients (36.0 %). Ideal prescription accounted for 24/79 (30 %) of the patients in the subsidised regime and 25/57 (43.8 %) in the contributory one (OR=1.79; 95 % CI:0.88-3.64). Older people (aged ≥ 65yo) were at risk of receiving a non-ideal prescription (OR=2.12; 95 % CI:1.02-4.38) whilst this was not so in the subsidised regime (OR=1.62; 95 % CI:0.78-3.35).

Conclusions Ideal prescription of antihypertensive drugs was low in the population being studied. There were differences regarding age ideal prescription but not concerning affiliation regime. It is suggested that a longitudinal study be carried out in the future.

Key Words: Thiazide, health service, clinical protocol (source: MeSH, NLM).

¹ Adaptado de la ponencia presentada por los autores en la 5th International Conference de la International Society for Equity on Health, realizada en Creta, Grecia, Junio 9-11 de 2009.

RESUMEN

Objetivo Evaluar las diferencias en la adecuada prescripción de tiazidas en pacientes hipertensos, según régimen de afiliación.

Materiales y métodos Estudio de corte transversal analítico. Se utilizó la base de datos de un estudio previo, dos grupos de pacientes hipertensos: régimen subsidiado y régimen contributivo que asistieron a consulta externa entre el 01-09-2007 y el 29-02-2008. Se evaluó terapia ideal en los dos grupos. Se realizó análisis univariado y multivariado.

Resultados Se estudiaron 136 pacientes (contributivo: 41,9 %; subsidiado: 58,1 %). Los pacientes

del régimen subsidiado fueron mayores (promedio= 68,8±10) que los del contributivo (promedio=64,1±11.1) (t-test, p=0,0110). La prescripción de antihipertensivos fue ideal en 49/136 (36,0 %). En el régimen subsidiado la prescripción fue ideal en 24/79 (30 %) y en el contributivo en 25/57 (43,8 %) (OR: 1,79 IC95 % (0,88-3,64)). La edad ≥65 años fue riesgo de prescripción no ideal (OR: 2.12, IC95 % (1,02-4,38)), mientras que no lo fue estar en el régimen subsidiado (OR=1,62, IC95 % (0,78-3,35)).

Conclusiones La prescripción ideal de antihipertensivos es baja. Hay diferencias en la edad, en la prescripción ideal, mas no por régimen de afiliación. Se sugiere un estudio longitudinal en el futuro

Palabras Clave: Tiazidas, servicios de salud, protocolos clínicos (*fuentes Decs, BIREME*).

Arterial hypertension (AHT) is one of the most prevalent chronic pathologies around the world, affecting a large number of people and is associated with significantly increased risk of morbidity and mortality caused by cardiovascular events (1,2). The objective of both pharmacological and non-pharmacological therapeutic approaches to this entity is to reduce such complications' incidence. Several treatment recommendations and guidelines are thus available (3-5)

Five large groups of antihypertensive medicaments are used in AHT treatment: angiotensin converter enzyme inhibitors (ACEI), angiotensin-II receptor antagonists (ARA-II) or blockers, diuretic drugs (especially hydrochlorothiazide (HCTZ), a first-line diuretic drug which belongs to the thiazide class), calcium antagonists (CaA) and beta blockers (BB). These medicaments have been shown to be effective in reducing arterial pressure (AP) (this being a non-fatal acute coronary event), cerebrovascular attack, cardiac failure and reducing the risk of death from cardiovascular causes (6,7). However, suitable control of AP is particularly difficult, especially in cases where AHT and type 2 diabetes mellitus (DM2) coexist, very frequently leading to comorbidity in hypertense patients.

Two or more antihypertensive drugs are necessary in up to 80 % of cases, a diuretic usually being included for ensuring that the recommended AP is achieved (i.e. <130/80 mmHg) (8). Less than 50 % of hypertense patients receive treatment in practice and less than 30 % of these are suitably controlled (9). Suitable treatment of AP in patients suffering from DM2 must therefore be considered as being a priority. The correct prescription of antihypertensive drugs and the rational use of them in combination are thus fundamental for ensuring a satisfactory result, given by controlling AP and really reducing cardiovascular risk. Consequently, using one or more vasodilator antihypertensive agents in combination with thiazide diuretics (TD) represents the ideal therapeutic option (3-5). A good part of the evidence concerning TDs comes from studies such as the antihypertensive and lipid-lowering treatment to prevent heart attack (ALLHAT) and systolic hypertension in the elderly programme (SHEP) (7,9) where it has been concluded that they should be drugs of choice as first-line antihypertensive therapy. This has been because they have been demonstrated to safely reduce the incidence of all major cardiovascular events in currently-recommended doses; clinical benefit has also been produced in spite of minimum increases in glucaemia and serum lipoprotein levels (7,10). TD efficacy in AHT treatment is based on a double effect as they are long-term hypotensor drugs, due their arterial vasodilator action and to their diuretic effect and reduced intravascular plasma volume. TDs also reduce the sodium-dependent pressor response; such response is a common phenomenon as a result of one or more vasodilators being used when they are prescribed for long periods of time in the absence of a diuretic.

The current panorama regarding AHT treatment reveals that TD are being underused; the formulation of several groups of antihypertensive vasodilator drugs is opted for in most cases, meaning that additional hypotensor effects are not produced but adverse effects and costs certainly do become increased (ineffective polypharmacy) (11). The concepts of efficacy, safety and convenience rationalise the amount and possible combinations of antihypertensive drugs; by contrast, their availability under the Benefits Plan (BP) and in the market for several pharmacological groups and their respective molecules leads to the unlimited prescription of combinations without the pertinent recommendations being taken into account (3,4,8). Effective pharmacological groups should be prescribed which have been shown to be able to reduce cardiovascular morbidity and mortality as well as reduce arterial pressure in controlled studies and that they can provide total coverage in line with the standards laid down by different Colombian General Health Social Security System (GHSSS) regimes (11,12). As TDs represent an effective element in treating AHT, access to such medicament should be equitable. Health system affiliation in Colombia depends on one's ability to pay. It is considered

that all people residing in Colombia are affiliated to the contributory or the subsidised regime within the GHSSS, as well as those who are temporally affiliated, according to that laid down in Decree 806/1998 (10,11,13). The health promotion entities (HPE) in each regime are responsible for complying with health insurance's undelegable functions. Entities administering the subsidised regime are called subsidised regime HPE and must cover their patients' according to the BP (10).

The fact that there is low prescription of ideal therapy in patients having such indication should call attention to the topic of equity in health (bearing both GHSSS affiliation regimes in mind as determining factors) which could be defined as being the lack of systematic differences in health (or in their greater social determinants) between groups having different levels of social advantage/disadvantage (14). A definition could also be used proposing that equity implies evaluating inequality from a concept of social justice. According to this, all analysis of inequity in health must contemplate "social determinants of health" as part of identifying the "causes of the causes" and in producing inequities as the centre of their analysis and recommendations. It must always be born in mind that such evaluation has policy implications in both daily decision-making and public policy (15). In the case of this study it was expected that there would be differences in ideal prescription of antihypertensive medicaments in diabetic patients between contributory or subsidised GHSSS affiliation regimes. The lack of uniformity in treating arterial hypertension thus led to trying to identify routes for inequity (adding the Colombian health model's different socio-demographic contexts) by means of exploring the differences in prescribing TD according to the type of GHSSS affiliation. Inequities were detected in health service provision, this being suitable prescription of TD in terms of this study.

MATERIALS AND METHODS

Study type and design: Analytical cross-sectional study. A previous study's database was used covering two populations of hypertense patients: one from the subsidised health regime and the other from the contributory regime. The data concerned patients attending external consultation control between the 1st September 2007 and the 29th February 2008.

Information from this database was debugged so that only data was used regarding patients who had TD in their treatment schemes. All clinical histories from subsidised regime (Subs) health providing institutions (HPI) were analysed. STALCAL software (EPI-info, version 6.0) was used for calculating a representative sample in contributory regime (Contr) HPI.

The information was collected by using a form containing epidemiological variables and others related to antihypertensive treatment (drug, dose, AP).

Each patient's ideal therapy was classified for this investigation as follows:

- Ideal: when criteria regarding efficacy, safety and pharmacokinetic convenience were complied with; and
- Non-ideal: when the combination was contraindicated, had problems of synergy and/or was not recommended. The interns involved in this project (NC, CG, AP) made the evaluation.

The number of antihypertensive drugs prescribed was taken as an ordinal variable; its values ranged from 1 to 4, 1 being monotherapy, 2 therapy dual and so on, successively.

Statistical analysis

The relationship between affiliation regime and non-ideal prescription of antihypertensive drugs was subjected to univariate and multivariate analysis.

Data was tabulated in Excel (version 2007). The Shapiro Wilk's test was used as variable normality test; the variables had normal distribution which is why parametric statistics were then used. Categorical variables were presented in terms of frequency and percentage. Quantitative variables were presented as averages with their respective means of dispersion. The Chi square test (X²) was used for calculating bivariate analysis for associating categorical variables. Differences between means and the Student t-test were used for calculating the quantitative variables. <0.05 was considered as being significant for all analysis and data was estimated with 95% confidence intervals. The effect of confusion given by age was evaluated for people older than 65. STATA statistical software (version 10.1) was used for analysing data.

The Project was approved by the Universidad Nacional de Colombia's Medicine Faculty's Ethics Committee. It has been considered as being research involving no risk according to Ministry of Health article 11/Resolution 008430/1993.

RESULTS

Fifty-seven patients (41.9 %) were included in the study from the contributory regime and 79 (58.1 %) from the subsidised regime. There were age differences

in the two groups of patients, this being discreetly greater in the subsidised (mean=68.8+/-10yo) than the contributory regime (mean=64.1+/-11.1yo) (Student T test= -2.5775, p=0.0110). There was a greater prevalence of subjects aged 65 or more in the subsidised regime group (52/79, p=65.8 %) than in the contributory regime group (29/57, 50.88 %); these differences were not statistically significant (Chi2=3.07, p=0.08).

Antihypertensive drug prescription was ideal in 49/136 (36.0 %). Regarding GHSSS affiliation regime, prescription was ideal in 24/79 (30 %) of subsidised regime patients and in 25/57 (43.8 %) from the contributory regime. Such difference (13.8 %) between both regimes was not statistically significant (OR=1.79; 95 % CI:0.88-3.64), although it was clinically different.

Table 1. Ideal prescription and its relationship to the number of medicaments prescribed for patients from contributory and subsidised regimes

Number of antihypertensive drugs prescribed	Ideal	Ideal	Ideal	Total
	Both groups	Subsidised regime	Contributory regime	(Ideal and non-ideal)
	n (%)*	n (%)*	n (%)*	n (%)
1	5 (10.20)	3 (12.5)	2 (8)	6 (4.41)
2	40 (81.63)	21 (87.5)	19 (76)	70 (51.47)
3	4 (8.16)	0 (0)	4 (16)	42 (30.88)
4	0 (0)	0 (0)	0	15 (11.03)
Total	49 (100)	24 (100)	(100)	136 (100)

Chi2=25.8, p=0.001

Table 2. Medicaments being most prescribed in ideal and non-ideal therapy

Type of therapy	Frequency	%
Ideal therapy		
ACEI + HCTZ	42	30.88
HCTZ	6	4.41
HCTZ + ARA II	5	3.68
ACEI + HCTZ + CaA DHP	4	2.94
HCTZ + CaA DHP	3	2.21
Non-ideal therapy		
HCTZ + CaA no DHP	17	12.50
ACEI + HCTZ + BB	14	10.29
ACEI + HCTZ + CaA no DHP	14	10.29
HCTZ + BB	3	2.21
HCTZ + ACEI + CaA DHP + BB	3	2.21

Note: angiotensin converter enzyme inhibitors (ACEI), hydrochlorothiazide (HCTZ), angiotensin II receptor antagonist (ARA II), dihydropyridine calcium-antagonists (CaA DHP), non-dihydropyridine calcium-antagonists (CaA no-DHP) and beta blocker (BB).

The number of antihypertensive drugs prescribed was similar for both subsidised regime patients (Me=2; 95 % CI:2-3) and those from the contributory regime (Me=2; 2-3 95 % CI) (Mann Whitney= 1.42, p=0.15). However, a tendency was observed regarding a greater number of medicaments being prescribed for patients affiliated to the contributory regime (Table 1).

Table 1 shows that dual therapy had the highest prescription percentage, followed by three-drug therapy. However, only 4/42 (9.5 %) of all patients prescribed 3 medicaments and who belonged to the contributory regime had an ideal prescription regime. The same happened with the 15 patients receiving 4 medicaments belonging to the contributory regime who had a non-ideal prescription regime. 30/70 (42.8 %) of patients receiving dual therapy had a prescription which was not ideal.

Table 3. Subjects whose arterial tension (TA) was controlled (for both groups, whether receiving ideal therapy or not)

Control T.A	Affiliation regime and ideal therapy					
	Contributory			Subsidised		
	Ideal	Ideal	Total	Ideal	Ideal	Total
	No	Yes		No	Yes	
NO	25 (56.82)	19 (43.18)	44 (100)	42 (67.74)	20 (32.26)	62 (100)
SI	7 (53.85)	6 (46.15)	13 (100)	12 (70.59)	5 (29.41)	17 (100)
Total	32 (56.14)	25 (43.86)	57 (100)	54 (68.35)	25 (31.65)	79 (100)

Chi= 0.0360 p=0.850 Chi2= 0.0500 p=0.823

Chi= 0.0360 p=0.850; Chi2= 0.0500 p=0.823

Table 2 presents the medicaments which were prescribed with greater frequency during ideal and non-ideal therapy. Arterial pressure was controlled in 30/136 (22.05 %) for both groups, being similar for people in both the contributory (13/57, 22.8 %) and subsidised regime (17/79, 21.5 %). Control was greater for contributory regime patients having an ideal prescription than those from the subsidised regime (by 16.74 %), even though such difference was not statistically significant (Table 3).

Table 4. Multivariate analysis of the relationship between ideal therapy, affiliation regime and age

Variable	OR	Std. Err.	z	P>z	95% Conf. Interval (Inf-Sup)	
Subsidised regime	1.6241	.6012	1.31	0.190	0.7861	3.3555
Age>=65	2.1217	.7857	2.03	0.042	1.0267	4.3845

Note: Logistic regression n=136, LR chi2(2)=6.75, Prob > chi2=0.0342, Log likelihood = -85.512149; Pseudo R2=0.0380

Multivariate analysis revealed that the effect of age was a more explicative variable for ideal prescription than affiliation regime in people aged over 65 when considering the effect of age as potential confusion variable for explaining the relationship between suitable prescription and affiliation regime (Table 4).

DISCUSSION

As already mentioned, the data for the sample used in this study was taken from a database compiled during a previous study by Cano et al, (9). There were differences in age amongst subjects from the two affiliation regimes. Such result could be explained by the different socio-demographic contexts in the health model used in this study, concentrating on a non-contributing third-age population from the subsidised regime. Given the controversy regarding AHT therapy in people aged over 80, it is worth noting that there was an upper age limit of 87 in the contributory regime and 94 in the subsidised one, showing these patients' ever increasing presence in clinical practice (16).

Total hydrochlorothiazide (HCTZ) prescription prevalence was 30.6 % (27 -34.2 % 95 % CI), such figure still being far from the upper recommended limit (80 %) (6, 17,18).

The number of antihypertensive drugs was tabulated regarding the type of GHSSS affiliation for analysing the number of drugs prescribed. It was found that 95 out of every 100 hypertense patients were prescribed 2 or 3 medicaments as antihypertensive therapy (i.e. dual therapy and a combination of three drugs had priority). However, such result should be explained in the light of differences in ideal treatment arising from regime as it was shown that there was a difference between both regimes regarding ideal prescription (28 % difference between both types of prescription), there being a greater percentage of non-ideal therapy compared to ideal therapy.

The foregoing result begins to shed light on the inequity present in the suitable prescription of TD in the hypertense population, bearing in mind the data indicating that less than 50 % of hypertense people receive treatment in practice and less than 30 % of these are suitably controlled. Such figures show a lack of equitable health service distribution when it is born in mind that as TD are contained within the BP then there is no reason for not prescribing them for the people who require them (i.e. hypertense patients having no contraindication for them being administered).

Regarding ideal therapy in each affiliation group, 63.97 % of all prescriptions in both groups corresponded to non-ideal therapy (36.03 % ideal prescription). According to test for independence data, prescribing TD for hypertense patients was an independent variable for affiliation to a determined GHSSS regime. Ideal prescription percentage in the Contr group (43.86 %) was greater than that for the Subs group (30.38 %) and, even though the variable dependent hypothesis was rejected, there was a clinical difference regarding what is relevant in this type of study (13.38 % in this case). It should be stressed that a population lacking the means to pay is concentrated within the subsidised regime; these people have access to health services via a state subsidy and are attended by subsidised regime-administered entities (19) where they must often resort to legal means to guarantee that they receive the health services being provided by such entities. Also, "complex bureaucracies have been created which slow down and limit the health service through cost-dependent mechanisms," (20) thereby inevitably producing inequality amongst GHSSS users.

It was found that more medicaments were prescribed in dual therapy (half of all prescriptions), followed by therapy having three or more medicaments. According to type of therapy for each combination (ideal - non-ideal), ideal prescription and non-ideal prescription was 27 % and 24 % respectively in the dual therapy group (i.e. where greater prescription occurred). If it is well-known in practice that dual therapy is more effective and safe in most cases, then applying this concept could arise from doctors' ignorance and lack of training concerning the type of dual therapy which may be suitable for each patient, as well as the influence of other factors such as pharmaceutical market pressure to favour more novel drugs than combinations with HCTZ.

There was a much greater difference regarding ideal and non-ideal therapy being prescribed in the triple therapy group, i.e. a 34 % difference in favour of non-ideal prescription. This figure is alarming as it supports foregoing statements about ideal prescription, as a relationship was seen between the number of drugs and their percentage within non-ideal therapy.

Differences regarding the number of medicaments prescribed were observed between the two regimens from the data derived from the Chi2 test according to type of regime. All results corresponded to ideal therapy being monotherapy, the prevalence of this type of prescription being very low. It should be born in mind that most patients presented complications

and/or a difficult to control disease (AHT being a chronic disease) requiring a greater number of medicaments at the ages in question.

Ideal prescription for the contributory regime had a greater prevalence in dual therapy (8 % difference in favour of the subsidised group). Non-ideal therapy corresponded to half the ideal in these two groups, a high percentage of unsuitable prescription being observed in spite of a high prevalence of ideal prescription.

There was a particular finding in the triple therapy group. It has been previously stated that there was a total of 4% ideal therapy and 38 % non-ideal therapy; total ideal therapy corresponded to contributory group patients and the greatest percentage of non-ideal therapy corresponded to the subsidised regime. It was considered that treatment with four medicaments was unsuitable due to problems regarding synergism, contraindication or not being recommended. Most total prescription was concentrated in the contributory regime; this could have been due to factors related to how doctors ascribed to these HPI had been trained, but being consistent with that said about the dual therapy. Such greater prescription could have been due to a lack of availability of medicaments in HPI services and other factors related to the quality of the service provided in these institutions, as well as the attending doctor's anxiousness for achieving treatment goals.

The ideal therapy most prescribed was the ACEI+HCTZ combination; such therapy is economic and very safe as it has a nephroprotective effect and has effective prolonged action. This was followed by HCTZ monotherapy. It was observed that most non-ideal therapy prescription concentrated on combinations of medicaments, non-DHP Ca being most prescribed. Studies directed at optimising AP control have shown the need for using an average of higher than 2.5 medicaments per patient (26-28).

Some clarifications must be made regarding the different types of medicaments in antihypertensive therapy. Low prescription of DHP CaA and ARA II was noted; by contrast, non-DHP CaA (verapamyl) were formulated for one out of every four patients, even though not being considered to be first-line medicaments. AHT is a syndrome whose treatment envisages several aspects. Some work has indicated low antihypertensive effectiveness, deterioration in glycaemia control and lipid profile, mainly in association with thiazides, in the particular case of BB (21). Then there is the inconvenience of their prescription in diabetics as they can lead to increased weight and

attenuate adrenergic manifestations in case of hypoglycaemia. Mandatory formulation of BB has thus only been recommended in diabetics when there is left ventricle dysfunction, coronary disease or tachyarrhythmia (22-24).

Regarding the use of ACEI and ARA II, there is evidence of micro- and macro-vascular complications having been reduced in diabetics (25).

CaA are divided into two pharmacological subgroups having different receptor selectivity (26). Amlodipin is a reasonable option in diabetic patients who do not have renal disease (confirmed by microalbuminury) (3). Non-DHP CaA which is available under the BP (verapamyl) should not be one of the first-line options due to certain pharmacokinetic aspects, specifically its short action duration, in addition to not having been approved by the US Food and Drug Administration for diabetic nephropathy (3, 26-28).

Effective pharmacological groups must be prescribed which have shown their ability to reduce cardiovascular morbidity and mortality as well as reducing AP in controlled studies (29,18,30). The following would thus be considered to be effective: ACEI, ARA II, TD CaA, and BB. On the contrary, the role of central action alpha agonists, direct vasodilators and non-thiazide diuretic drugs have not been fully established; specifically, alpha adrenergic blockers are not recommended as first-line agents in hypertense diabetics (3).

43.86 % of contributory regime patients (cf 31.65 % subsidised regime) responded to ideal therapy with figures showing controlled AT. Patients' lack of response to what was considered ideal therapy was worrying; such results could probably have been due to comorbidity, bearing in mind the chronic and degenerative course of AHT when a patient is receiving medicaments for other pathologies and a lack of suitable prescription for each stage of the disease considering their complications and previous treatment (whether or not considered to be part of ideal therapy).

Having used a previous study's database should be mentioned as being one of this study's limitations. Even though the data was debugged by prior quality controls, it could have suffered from the problems inherent in all databases. The differences in age between both affiliation regimes could be explained by the sampling strategy used for sampling subjects from the entity attending contributory regime patients, which was not randomly.

The 13.38 % clinical and non-statistical difference found in ideal prescription for contributory and subsidised regime subjects could be explained

by sample size (effects of such difference in percentages and meant a power of only 0.3144). Control for age as a potentially confusing variable in multivariate analysis showed the explanatory ability of age on the subjects in this study on ideal prescription when included in a model also related to affiliation regime.

The differences found in type of treatment according to affiliation regime should draw attention to the current state of treatment of one of the pathologies having the greatest prevalence in Colombia. Bearing a pathology's greater complexity in mind and the greater difficulty in treating it, then this leads to inequality produced by patient identification and management system failures, previously stated determinants of inequity representing an unjust relationship between unsuitable therapy and affiliation to GHSS subsidised regime. A study having a greater sample size and which is more inclusive regarding patients from several health insurance companies should be carried out in the future to re-examine differences caused by age amongst hypertense subjects from the contributory and subsidised regimes found in this study and apparent differences in ideal prescription of antihypertensive drugs amongst contributory and subsidised regime subjects. Strategies must be implemented for unifying management schemes for these patients so that they do not become subjected to the influence of market strategies and their availability in HPIs.

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