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Determination of frequencies by the number of active substances used in a hypertensive population.

Dilek Oztas[1], Huseyin Balcıoglu[2*], Yasemin Saglan[3], Yunus Emre Sari[2]

[1]Department of Public Health, Faculty of Medicine, Yildirim Beyazıt University, Turkey

[2]Department of Family Medicine, Eskisehir Osmangazi University, Turkey

[3]Eskişehir Public Health Directorate, Turkey

Abstract

Aim: The present study aimed to evaluate the distribution of antihypertensive drugs prescribed to patients with hypertension who were granted drug exemption report in the period of June 2016-2017 with respect to their classes and active substances and to investigate which class of drugs and active substances are used more frequently.
Material and methods: Drug exemption reports from the hospital's digital database granted between 2015 and 2016 were evaluated. Patients with a diagnosis code of hypertension were included, and approximately 65,000 records were obtained.
Results: Study records showed that there were 36 active substances, with 28 active substances used in combination with these active substances. Therefore, a total of 64 different active substances are present. It was demonstrated that participants in the study concomitantly used up to seven active substances.
Discussion: The main objective in the treatment of hypertension is to prevent the occurrence of cardiovascular events, reduce the risk, and prevent organ damage. Lifestyle changes (salt-free diet, achieving ideal weight and exercise) are the first steps of treatment and should be offered in all treatment steps.

Keywords: Antihypertensive drugs, Substances, Hypertension.

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Introduction

Hypertension is a public health problem that is considered among the risk factors for several serious diseases, particularly cardiovascular diseases, but can be controlled and prevented. Population-based epidemiological studies on adults in Turkey reported the prevalence of hypertension to be 31.8% (36.1% in females, 27.5% in males).

The patent study is another study conducted on hypertension in Turkey. The study by The Turkish Society of Hypertension and Renal Diseases conducted in 2003 included approximately 5,000 individuals aged 18-80 y, and it found that the prevalence of hypertension was 31.8%. In the same study, sex-adjusted prevalence of hypertension was higher in females (36.1%) than in males (27.5%). The rate of awareness of hypertension in females (47.9%) was higher than that in males (27.9%). The rate of awareness increased with age and was higher in females than in males in all age groups. In addition, the overall rate of awareness of blood pressure was 40.7%, whereas the rate of patients receiving medication was 31.1% (20.7% in males and 37.0% in females) and blood pressure control rate was 8.1% (8.0% in males and 8.2% in eight females). The control rate in patients who were aware of their high blood pressure condition and who were receiving medication was 20.7%, and this control rate was higher in males than in females (31.1% *versus* 17.4%) [1-3].

The Tekharf study is an extensive study on the prevalence of hypertension in Turkey, which was 63% of males and 74% of females diagnosed with hypertension received drug therapy. It was demonstrated that full control was achieved in patients receiving medication, is still low (blood pressure 140-159 and/or 90-94 mm/Hg).

To start antihypertensive therapy, risk factors and comorbidities should be considered along with blood pressure values [1]. There are classes of antihypertensive drugs in medical treatment. These include diuretics, beta blockers, alpha blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists. Currently, large-scale studies have demonstrated similar efficacy for all drug classes. Drug selection is determined based on patient's medical history and comorbidity [4].

The present study aimed to evaluate the distribution of antihypertensive drugs prescribed to patients with hypertension who were granted drug exemption report in the period of June 2016-2017 with respect to their classes and active substances

and to investigate which class of drugs and active substances are used more frequently.

Materials and Methods

In Turkey, when target blood pressure is achieved in a patient with hypertension, a report called "drug exemption report" is issued so that the patient is exempt from specific payments required by the insurance institution, and the doctor has the permission to prescribe the medication for a longer period with reference to the report. The reports are issued for 1 or 2 y and re-issued depending on patient condition. Atatürk Education and Research Hospital, Ankara, is a health center located in the capital city of Ankara, where patients from nearby provinces can apply. Therefore, data collected by the center are considered generalizable for Turkey as a whole.

For the purposes of the study, drug exemption reports from the hospital's digital database granted between 2015 and 2016 were evaluated. Patients with a diagnosis code of hypertension were included, and approximately 65,000 records were obtained. Data were randomly selected using IBM SPSS Statistics v 21.0 package program based on simple random sampling. Following the selection process, 16,392 people were granted a drug exemption report.

The study population consisted of all patients with a drug exemption report within the specified period and recorded in the electronic system.

Statistical analysis

Descriptive data were given in percentages (%). Pearson's chi square, Yates' correction, and Fisher's exact tests were used for analyzing the generated cross tables. Analyses were performed using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). A p value of <0.05 was considered statistically significant.

Results

Approximately 65,000 individuals who were diagnosed with hypertension at Ankara Atatürk Education Research Hospital between 2015 and 2016 were enrolled. Using simple random sampling, 16,392 individuals were randomly selected, and active substances of the prescribed drugs were examined using drug exemption reports. In the treatment of hypertension, single drugs as well as combination treatments were used.

Sex distribution of patients was 8,894 (54.3%) females and 7,498 (45.7%) males. The mean age of the study group was 63.08 ± 12.31 (range, 16-107) y. The mean age was 64.11 ± 12.27 y for females and 61.86 ± 12.26 y for males. The age of females participating in the study was significantly higher than that of males ($p<0.001$). The distribution of active substances was examined by age by categorizing individuals as over or under 55 y as well as over or under 65 y.

When comorbid diseases were evaluated in 16,392 patients diagnosed with hypertension, it was found that 3,381 (20.6%) individuals had diabetes mellitus, 47 (0.3%) had chronic obstructive pulmonary disease, and 69 (0.4%) had asthma.

Study records showed that there were 36 active substances, with 28 active substances used in combination with these active substances; therefore, a total of 64 different active substances is present. Table 1 presents the frequency distributions of active substances and shows two different percentages: one expressed as percentage of the number of persons and the other as percentage of active substances. Percentage by number of persons indicates the percentage of medication use in all units participating in the study, whereas percentage by active substances refers to the percentage of active substances used. Acetylsalicylic acid is the most commonly used active substance in the study for cardiovascular prevention, with 4,345 patients using it. It was also used by 26.51% of patients who participated in the study, with a 14.82% overall rate of use among all active substances. The second and third most frequently used active substances in the study were metoprolol and amlodipine, which are used by 4,218 and 2,423 individuals, respectively. The least commonly used active substance combination was the combination of amlodipine, indapamide, and perindopril.

Differences in active substance use according to sex distribution were examined as well (Table 1). It was demonstrated that amlodipine and valsartan combination was used by 354 (4.0%) males and 251 (3.3%) females and was significantly higher in males than in females ($p=0.032$). Acetylsalicylic acid as an active substance was used by 1,803 (20.3%) males and 2,543 (33.9%) females, and the use was significantly higher in females than that in males ($p<0.001$). Atenolol as an active substance was used by 75 (0.8%) males and 38 (0.5%) females, and the use significantly higher in males than in females ($p=0.012$). Atenolol and chlorthalidone combination as an active substance was used by 71 (0.8%) males and 26 (0.3%) females and the combined use was significantly higher in males than in females ($p<0.001$). Bisoprolol fumarate as an active substance was used by 104 (1.2%) males and 63 (0.8%) females and the use was significantly higher in males than in females ($p=0.037$). Doxazosin mesylate as an active substance was used by 282 (3.2%) males and 348 (4.6%) females. The use of doxazosin mesylate as an active substance was found to be significantly higher in females than in males ($p<0.001$). Fosinopril and hydrochlorothiazide combination as an active substance was used by 68 (0.8%) males and 37 (0.5%) females, and the use of fosinopril and hydrochlorothiazide was significantly higher in males than in females ($p=0.030$). Indapamide as an active substance was used by 28 (2.6%) males and 114 (1.5%) females, and the use of indapamide was significantly higher in males than in females ($p<0.001$). Irbesartan and hydrochlorothiazide combination as an active substance was found to be 412 (4.6%) in males and 198 (2.6%) in females and the combination as an active substance was significantly higher in males than in females ($p<0.001$). Isosorbide mononitrate as an active substance was used by 109 (1.2%) males and 187 (2.5%) females and its use as an active substance significantly higher in females than in males ($p<0.001$). Candesartan

cilexetil and hydrochlorothiazide combination as an active substance was used by 797 (9.0%) males and 427 (5.7%) females, and this combination use was significantly higher in males than in females (p<0.001). Lacidipine as an active substance was used by 94 (1.1%) males and 53 (0.7%) females, and the use of lacidipine as an active substance was found to be significantly higher in males than in females (p=0.018). Lercanidipine Hcl as an active substance was used by 327 (3.7%) males and 182 (2.4%) females, and the use of lercanidipine Hcl as an active substance was significantly higher in males than in females (p=0.018). Losartan potassium and hydrochlorothiazide potassium as an active substance was 469 (5.3%) in males and 281 (3.7%) in females, and the combined use was significantly higher in males than in females (p<0.001). Metoprolol as an active substance was used by 1,855 (20.9%) males and 2,363 (31.5%) females. Metoprolol use was significantly higher in females than in males (p<0.001). Nebivolol Hcl as an active substance was used by 630 (7.1%) males and 438 (5.8%) females and the use of Nebivolol Hcl was significantly higher in males than in females (p=0.001). Olmesartan medoxomil as an active substance was used by 149 (1.7%) males and 91 (1.2%) females, and its use was significantly higher in males than in females (p=0.014). Olmesartan medoxomil and hydrochlorothiazide combination was used by 299 (3.4%) males and 184 (2.5%) females. The combined use was found to be significantly higher in males than in females (p<0.001). Perindopril as an active substance was used by 232 (2.6%) males and 332 (4.4%) females. The use of perindopril as an active substance was significantly higher in females than in males (p<0.001) and the combined use of perindopril and amlodipine was 218 (2.5%) in males and 260 (3.5%) in females. The combined use was significantly higher in females than in males (p<0.001). The combined use of perindopril and indapamide as an active substance was found to be 403 (4.5%) males and 426 (5.7%) females. The combined use of perindopril and indapamide as an active substance was significantly higher in females than in males (p=0.001). Ramipril as an active substance was used by 454 (5.1%) males and 748 (10.0%) females, and the use of ramipril as an active substance was found to be significantly higher in females than in males (p<0.001). The combined use of ramipril and hydrochlorothiazide as an active substance was used by 265 (3.0%) in males and 391 (5.2%) in females. The combined use of ramipril and hydrochlorothiazide was significantly higher in females than in males (p<0.001). Cilazapril as an active substance was used by 34 (0.4%) males and 66 (0.4%) females. The use of Cilazapril was significantly higher in females than in males (p<0.001). Spironolactone as an active substance was used by 64 (0.7%) males and 80 (1.1%) females. The use of spironolactone as an active substance was significantly higher in females than in males (p=0.018). Telmisartan and hydrochlorothiazide combination was used as an active substance by 295 (3.3%) males and 156 (2.1%) females. The combined use of Telmisartan and Hydrochlorothiazide was significantly higher in males than in females (p<0.001). Trandolapril as an active substance was used by 39 (0.4%) males and 69 (0.9%) females and its use was significantly higher in females than in males (p<0.001). Valsartan as an active substance was used by 236 (2.7%) males and 163 (2.2%) females, and its use was significantly higher in males than in females (p=0.048). Valsartan and hydrochlorothiazide combination as an active substance was used by 1,044 (11.7%) in males and 655 (8.7%) in females. The combined use of Valsartan and Hydrochlorothiazide as an active substance was found to be significantly higher in males than in females (p<0.001).

Table 1. *Active antihypertensive substance and acetylsalicylic acid (for cardiovascular prevention) use according to sex distribution.*

	Sex		**P value**
	Male	**Female**	
Amlodipine	1308 (14.7%)	1115 (14.9%)	0.768*
Amlodipine+Atorvastatin Fixed Dose Combination	6 (0.1%)	4 (0.1%)	0.763**
Amlodipine+Indapamide+Perindopril	1 (0.0%)	1 (0.0%)	1.000**
Amlodipine+Valsartan	354 (4.0%)	251 (3.3%)	0.032*
Amlodipin+Valsartan+Hydrochlorothiazide	37 (0.4%)	26 (0.3%)	0.475*
Acetylsalicylic Acid	1803 (20.3%)	2542 (33.9%)	<0.001*
Atenolol	74 (0.8%)	38 (0.5%)	0.012*
Atenolol+Chlortalidone	71 (0.8%)	26 (0.3%)	<0.001*
Barnidipine Hcl	5 (0.1%)	1 (0.0%)	0.229**
Benazepril Hcl	7 (0.1%)	6 (0.1%)	0.976*
Benazepril Hcl+Hydrochlorothiazide	30 (0.3%)	16 (0.2%)	0.178***
Benidipine Hcl	167 (1.9%)	120 (1.6%)	0.178*

Bisoprolol Fumarate	104 (1.2%)	63 (0.8%)	0.037*
Bisoprolol+Hydrochlorothiazide	5 (0.1%)	3 (0.0%)	0.734**
Diltiazem Hcl	143 (1.6%)	115 (1.5%)	0.704*
Doxazosin Mesylate	282 (3.2%)	348 (4.6%)	<0.001*
Enalapril+Hydrochlorothiazide	3 (0.0%)	4 (0.1%)	0.710**
Enalapril Maleate	12 (0.1%)	9 (0.1%)	0.963***
Enalapril+Lercanidipine	26 (0.3%)	20 (0.3%)	0.873**
Enalapril+Nitrendipine	27 (0.3%)	18 (0.2%)	0.532***
Felodipine	15 (0.2%)	16 (0.2%)	0.634***
Fosinopril	7 (0.1%)	11 (0.1%)	0.283***
Fosinopril+Hydrochlorothiazide	68 (0.8%)	37 (0.5%)	0.030*
Furosemide	343 (3.9%)	329 (4.4%)	0.087*
Hydrochlorothiazide+Triamterene	1 (0.0%)	1 (0.0%)	1.000**
Indapamide	228 (2.6%)	114 (1.5%)	<0.001*
Irbesartan	52 (0.6%)	60 (0.8%)	0.095*
Irbesartan+Hydrochlorothiazide	412 (4.6%)	198 (2.6%)	<0.001*
Isosorbide Dinitrate	3 (0.0%)	5 (0.1%)	0.482**
Isosorbide Mononitrate	109 (1.2%)	187 (2.5%)	<0.001*
Candesartan Cilexetil	180 (2.0%)	122 (1.6%)	0.060*
Candesartan Cilexetil+Hydrochlorothiazide	797 (9.0%)	427 (5.7%)	<0.001*
Captopril	4 (0.0%)	3 (0.0%)	1.000***
Carvedilol	298 (3.4%)	284 (3.8%)	0.132*
Quinapril Hcl	5 (0.1%)	6 (0.1%)	0.777***
Quinapril Hcl+Hydrochlorothiazide	25 (0.3%)	19 (0.3%)	0.849***
Lacidipine	94 (1.1%)	53 (0.7%)	0.018*
Lercanidipine Hcl	327 (3.7%)	182 (2.4%)	<0.001*
Lisinopril	27 (0.3%)	25 (0.3%)	0.842***
Lisinopril+Hydrochlorothiazide	99 (1.1%)	73 (1.0%)	0.382*
Losartan Potassium	172 (1.9%)	142 (1.9%)	0.852*
Losartan Potassium+Hydrochlorothiazide	469 (5.3%)	281 (3.7%)	<0.001*
Metoprolol	1855 (20.9%)	2363 (31.5%)	<0.001*
Nebivolol Hcl +Hydrochlorothiazide	19 (0.2%)	13 (0.2%)	0.686***
Nebivolol Hcl	630 (7.1%)	438 (5.8%)	0.001*
Nifedipine	381 (4.3%)	286 (3.8%)	0.130*
Olmesartan Medoxomil	149 (1.7%)	91 (1.2%)	0.014*
Olmesartan Medoxomil+Hydrochlorothiazide	299 (3.4%)	184 (2.5%)	<0.001*
Perindopril	232 (2.6%)	332 (4.4%)	<0.001*
Perindopril+Amlodipin	218 (2.5%)	260 (3.5%)	<0.001*

Perindopril+Indapamide	403 (4.5%)	426 (5.7%)	0.001*
Ramipril	454 (5.1%)	748 (10.0%)	<0.001*
Ramipril+Hydrochlorothiazide	265 (3.0%)	391 (5.2%)	<0.001*
Cilazapril	34 (0.4%)	66 (0.9%)	<0.001*
Cilazapril+Hydrochlorothiazide	79 (0.9%)	65 (0.9%)	0.884*
Spironolactone	64 (0.7%)	80 (1.1%)	0.018*
Spironolactone +Hydrochlorothiazide	21 (0.2%)	20 (0.3%)	0.815***
Telmisartan	63 (0.7%)	48 (0.6%)	0.596*
Telmisartan+Hydrochlorothiazide	295 (3.3%)	156 (2.1%)	<0.001*
Trandolapril	39 (0.4%)	69 (0.9%)	<0.001*
Valsartan	236 (2.7%)	163 (2.2%)	0.048*
Valsartan+Hydrochlorothiazide	1044 (11.7%)	655 (8.7%)	<0.001*
Verapamil Hcl	36 (0.4%)	17 (0.2%)	0.063***
Verapamil Hcl+Trandolapril	76 (0.9%)	57 (0.8%)	0.503*

Note: *Pearson's chi square test; ** Fisher's exact test; ***Yate's correction.

As individuals were prescribed with different medications at the same time, Table 2 presents the distribution frequency by the number of active substances used. It was demonstrated that participants in the study concomitantly use up to seven active substances. The number of people using a single active substance was 4,000 (24.40%), whereas 6184 (37.70%) used two active substances, 3721 (22.70%) used three active substances, 1862 (11.40%) used four active substances, 559 (3.40%) used five active substances, 64 (0.39%) used six active substances, and 2 (0.01%) used seven active substances.

Table 2. *Distribution frequency among the number of active antihypertensive drugs used.*

	Total number of active substances taken by individuals	**Total percentage (%) of active substances taken by individuals**
1	4000	24.4
2	6184	37.7
3	3721	22.7
4	1862	11.4
5	559	3.4
6	64	0.39
7	2	0.01

Discussion

In the present study, we aimed to evaluate the distribution of antihypertensive drugs prescribed to patients with hypertension who were granted drug exemption report with respect to their classes and active substances and to investigate which class of drugs and active substances are used more frequently. According to the findings of the present study, 84.80% of patients used three or less combination medications, whereas 15.2% of the patients used four or more drug combinations. A small number of patients (0.04%) used six or more drug combinations to control their blood pressure; these were the patients who used more than one diuretic at the same time.

When the overall rates of medication use were examined, although there were some differences between sexes, drugs that inhibit/block angiotensin and calcium channel blockers were used more frequently. The most preferred combination for patients was the combination of angiotensin inhibitor/blockers, calcium channel blockers, and diuretic (hydrochlorothiazide). All results were consistent with the current guideline recommendations [4,5].

The main objective in the treatment of hypertension is to prevent the occurrence of cardiovascular events, reduce the risk, and prevent organ damage. Lifestyle changes (salt-free diet, achieving ideal weight, and exercise) are the first steps of

treatment and should be offered in all treatment steps. To achieve optimal hypertension control, reducing blood pressure is crucial regardless of the medication selected. Depending on the patient condition, a specific drug may be superior to another. The combined treatment option may provide the most successful results in initial treatment [6,7].

With regards to the determination of treatment, follow-up, and care, individual needs and preferences should be taken into consideration, and patients should be explicitly informed about care and treatments and should be included in the decision-making process.

Beta blockers should not be preferred in initial treatment, but may be considered in young cases. In the fourth-line treatment of resistant hypertension, advanced diuretic therapy may be considered with low-dose sprinolactone or high-dose thiazide-like diuretics. Patients receiving multiple medications were those receiving advanced diuretic therapy. In these patients, namely those receiving advanced diuretic therapy, Na^+/K^+ level should be monitored within a 1-month period and the monitoring should be continued if necessary. Alpha or beta blockers may be administered in cases where advanced diuretic therapy is not tolerated or if there is any contraindication or treatment is inadequate [5].

Consequently, the desired effect of any antihypertensive drug in the treatment of hypertension is apparent after a period of 3-4 weeks. Therefore, patients undergoing antihypertensive drug therapy or a change in the treatment regimen should be assessed 3-4 weeks later to check if the blood pressure control is achieved [4-6].

If the medication does not show adequate efficacy in the specified period, another antihypertensive group or a combination therapy should be considered. Regular monitoring of the side effects of drugs is necessary, and no changes should be made in antihypertensive medications in cases where blood pressure is under control, unless there is another medical reason. It should be noted that unnecessary changes in the medication regimen may disturb treatment compliance. When necessary, additional medication should be prescribed in cases where BP is not under control. Sufficient time should be spared for the patient in order for the patient to explain his/her condition, and an effective communication with the patient should be established [4-6].

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*Correspondence to

Hüseyin Balcıoğlu

Department of Family Medicine

Eskisehir Osmangazi University

Turkey