

Pharmacotherapeutic Analysis and Prescription Pattern of Antihypertensive Drugs Dispensed at Community Pharmacies in Palestine

التحليل الدوائي العلاجي لوصفات ارتفاع ضغط الدم في فلسطين

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Abstract

The objective of this study is to explore the influence of current therapeutic recommendations on the prescribing trends of anti-hypertensive drugs in general medical practice in Palestine. Five hundred and seventy four anti-hypertensive prescriptions were analyzed. The percentage of mono-therapy prescriptions was 48.25% and that for combinational therapy prescriptions was 51.75%. Among the mono-therapy prescriptions, β -blockers were the most commonly prescribed, while diuretics were under-utilized. Inappropriate dose strength of atenolol was seen in mono-therapy prescriptions. Expensive and newer angiotensin converting enzyme inhibitor drugs (ACE-I) and calcium channel blocking drugs (CCB) were frequently seen in mono therapy prescriptions. Among the combinational therapy, the β -blockers / diuretics was most common. Irrational combinational therapy of β -blockers / ACE-I was noticed. Use of modern and new CCB, ACE-I and angiotensin II type 1 receptor antagonists (AT1-RA) was seen in both mono therapy and combinational therapy. The overuse of nonpreferred drugs and the under-use of preferred medications is indicative that education of JNC VI guidelines for physicians and health professionals in Palestine is needed.

ملخص

الهدف من هذه الدراسة هو بحث تأثير التوصيات الحديثة على عملية وصف أدوية الضغط بين ممارسي مهنة الطب في فلسطين. ٥٧٤ وصفة ضغط قد تم تحليلها ودراستها. نسبة الوصفات الفردية كانت ٤٨,٢٥% أما نسبة الوصفات المتعددة فكانت ٥١,٧٥%. مثبطات بيتا كانت الأكثر استعمالاً بين الوصفات الفردية بينما كانت مدرات البول الأقل استعمالاً. الجرعات الدوائية لمثبطات بيتا كانت غير مناسبة. وكذلك فإن أدوية مثبطات إنزيم (أ سي ي) ومثبطات قنوات الكالسيوم غالبية الثمن كانت منتشرة في الوصفات الفردية. في الوصفات المتعددة كانت مثبطات بيتا ومدرات البول أكثر شيوعاً. لوحظ وصفات تحتوي على مثبطات بيتا ومثبطات إنزيم (أ سي ي) لوحظ أيضاً استعمال الأدوية الحديثة التابعة لمثبطات قنوات الكالسيوم ومثبطات (أ سي ي) في الوصفات الفردية والمتعددة. إن هذا الإستعمال غير العلمي أحياناً لأدوية ارتفاع ضغط الدم يتطلب تنقيفاً أكثر للعاملين في الحقل الطبي للتوصيات العالمية.

Introduction

The creation of a drug database from prescriptions obtained from community pharmacies allows for various types of studies and analysis on drug therapy. This project aims at studying the patterns and rationality of prescribing antihypertensive drugs by analyzing the prescription database. Our ultimate goal is to explore the influence of current therapeutic recommendations on the prescribing pattern of anti-hypertensive drugs in general medical practice in Palestine. This is relevant, as hypertension is the most important treatable risk factor for cerebro-vascular complications⁽¹⁻⁶⁾. The choice of antihypertensive drug(s) should be guided by several considerations. The *Sixth Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI) contains the main guidelines for the pharmacotherapy of hypertension⁽⁷⁻⁸⁾. The JNC VI document is the result of the efforts of more than 120 consultants, containing 254 references important to hypertension management. Similar therapeutic guidelines were made by the *British Hypertension Society* and the *World Health Organization / International Society of Hypertension* (WHO/ISH)⁽⁹⁻¹⁰⁾. The JNC VI recommends that anti-hypertensive drugs documented to reduce cardiovascular morbidity and mortality be the agents of choice and should be prescribed in their minimum effective dose. The JNC VI further recommends that polypharmacy should be avoided in hypertension therapy as much as possible⁽⁷⁾. The JNC VI recommends that diuretics and β -blockers be used as first-choice agents in the treatment of hypertension 'unless they are contraindicated or unacceptable'⁽⁷⁾. These drugs are recommended as first line therapy because they are the only classes of anti-hypertensive drugs that have been shown in long-term controlled clinical trials to reduce cardiovascular morbidity and mortality⁽¹¹⁻¹³⁾. In clinical trials, β -Blockers have not been found to be superior to diuretics in uncomplicated hypertension not associated with concomitant conditions, and most of their prescription has been as step two therapy especially among elderly patients⁽¹⁴⁾. JNC-VI also acknowledges that angiotensin-converting-enzyme (ACE) inhibitors, calcium-channel blockers, α -1-receptor blockers, and angiotensin-receptor antagonists are as efficacious as β -blockers and diuretics in reducing blood pressure. However, these drugs are expensive compared to β -blockers and diuretics. Furthermore, there is no current strong evidence that these drug classes reduce the risk of morbidity and mortality among hypertensive patients and that is why the JNC VI recommendations prefer that ACE inhibitors or calcium channel

blockers not to be used as initial therapy for patients with uncomplicated hypertension or those with hypertension without special needs⁽⁷⁾. The JNC VI recommends ACE inhibitors as second-line agents in most patients with hypertension and as first-line choices only in selected patients, including those with left ventricular systolic dysfunction and those with diabetes and microalbuminuria or proteinuria⁽⁷⁾. A new class of antihypertensive drugs are the Angiotensin II receptor antagonist (AT-R1-antagonists). These drugs (e.g. Losartan, Candesartan cilexetil and Valsartan) do not inhibit the synthesis of angiotensin, rather they block the effects of angiotensin at the receptor level⁽¹⁵⁾. Calcium channel blockers (CCB, e.g. Nifedipine, Verapamil, Diltiazem and Amlodipine) prevent calcium from entering the muscle cells of the heart and blood vessels, thus relaxing blood vessels and decreasing blood pressure and are preferred in elderly patients^(16, 17). Dihydropyridine class of CCB (e.g. Nifedipine and Amlodipine) is the most commonly prescribed for hypertension. Diltiazem (a benzothiazepine) and Verapamil (an aryl alky amine) are CCB belonging to a totally different class and much less frequently as antihypertensive agents, rather they are used as adjunct therapy in angina pectoris and arrhythmias. Clinical trials now support the safety and efficacy of the long-acting dihydropyridines for patients with both uncomplicated and diabetic hypertension, although conventional therapies and, in the latter case, angiotensin-converting enzyme inhibitors have superior proof of benefit⁽⁷⁾.

Methodology

This work is part of a large continuous project run by our group and was initiated in the early 2000. The goal of this project is to collect approximately 75,000 out-patient prescriptions at the end of 2003 (20,000 prescriptions/ year). These prescriptions were dispensed at community pharmacies and were issued from private clinics, private hospitals, governmental clinics or charitable clinics. The community pharmacies refer to private pharmacies that are open to the public and sell and dispense medications. Complete data on the total prescriptions collected will be described and presented at the end of the project in separate publications by the same author's group. The purposes of creation of such a prescription collection (database) are: 1) to study prescribing pattern and prescribing rational in Palestine and 2) to do a pharmacoepidemiological surveys for major and specific drugs in Palestine. Such studies, to the best of author's knowledge, have not been carried out in Palestine before.

The current work is based on a small sample of prescriptions (574) out of 8,987 prescriptions that were available at the time this manuscript was written.

These out-patient prescriptions were collected by An-Najah third, fourth and fifth grade pharmacy students who spend their summer courses in the third and fourth year training in community pharmacies. The collection period was roughly between January 2000 and May 2001.

In this current work, the data in the prescriptions were handled manually and using Microsoft Excel. However, the current prescription database is handled using SPSS for Windows version 10. The data entered and analysed include the source of the prescriptions, the age and gender of the patient, number of drugs, class and type of drugs prescribed and finally whether the drugs are locally manufactured or imported.

The prescriptions used and included for this current study were not collected from a particular area in the West-Bank of Palestine. In fact, the prescriptions for this current work and for our ongoing project were being collected from community pharmacies located everywhere in West-Bank of Palestine. The areas of prescription collection are cities, villages and camps in Qalqilia, Tulkaram, Jenin, Nablus, Ramallah, Hebron, Jericho, Bethlehem and Jerusalem. No area bias was made in the collection process. An-Najah pharmacy students are distributed everywhere and consequently the prescriptions were collected from all West-Bank areas. Nevertheless, the geographic distribution for the total prescriptions used in the current work and for the total prescriptions collected for the ongoing project show high percentage for Nablus, Ramallah and Hebron areas and this is expected based on the fact that these cities are the major and mostly populated cities in northern and southern parts of West-Bank / Palestine.

In the current work, the prescriptions included in the study were assumed to be dispensed for the first time at the community pharmacies. This assumption was based on the practice that most refills in community pharmacies in Palestine are made without prescriptions. This assumption might not be accurate. However, even if the prescription is being dispensed for the first time at the community pharmacy we can not guarantee that this prescription is the first prescription the patient has received to manage his/her hypertension. Furthermore, only prescriptions that have a clear name of the patient, to identify gender, and age of the patient were included in the study. This is important since age and gender are important parameters in pharmacotherapeutic analysis of drug utilization in general.

In this current work, the data was collected and analysed based on proprietary names and was aggregated by individual medication as well as by antihypertensive drug class. Only prescriptions containing anti-hypertensive medications were included. Prescriptions containing anti-hypertensives and other medications that might indicate the presence of other co-morbid conditions were excluded. Prescriptions containing antihypertensive drugs in combination with: antiplatelet / antithrombotic drugs; or hypoglycemic drugs; or cardiac glycosides possibly for congestive heart failure; or dysrhythmias; or adjuvant anti-migraine like prophylactic low-dose propranolol; or an adjuvant low dose propranolol for a thyroid condition were excluded from the study. The exclusions of these prescriptions were made to ensure that the prescriptions primarily represented uncomplicated cases of hypertension. The exclusion process is made by the researcher after the collection of the prescription and not by the community pharmacists at the time of dispensing the prescriptions. This is clearly imperfect and scientifically not ideal. It would be more perfect and better if the author was directly involved and the patient history was recorded and analyzed along with the prescriptions. Unfortunately, neither the authors nor the data available in our hands can provide us with the patient's disease or drug history. Based on this, we believe that our method is limited and that the presence of other co-morbid conditions or the intake of other medications can not be excluded. The presence of such co-morbid conditions might justify the presence of some drugs otherwise we believe and argue to be unjustifiable in our discussion. Nevertheless, the current work and the selection methodology we used for the prescriptions can still shed some light on the medical practices of treating patterns of hypertension in Palestine. Further clinically oriented studies on the same project are strongly recommended and this work will be the first step for such projects. Such studies must be based on either patient review or retrospective complete drug profile review. Such studies are currently being carried out in a private hospital and in a governmental clinic in Nablus city in Palestine by the author's group. The outcome of such studies will be stronger since they will be based on patient's history.

Given the exclusion criteria mentioned above, the total number of prescriptions that were included was 574. Those antihypertensive prescriptions were dispensed for the first time at community or private pharmacies. The anti-hypertensive prescriptions were categorized according to the guidelines of the subcommittee of the World Health Organization / International Society of Hypertension⁽⁸⁾ as follows: diuretics, β -blockers, ACE inhibitors, calcium

channel blockers (CCBs), angiotensin II receptor antagonists (AT1-RA), α -adrenoceptor blocking drugs, and other drugs, including centrally acting sympatholytic and directly acting vasodilators.

Finally, whenever the phrase “rational” is used in this manuscript it means that the drug use is in accordance with the JNC VI guidelines while “irrational” means that the use is not in accordance with the JNC VI guidelines.

Results

The 574 anti-hypertensive prescriptions belong to 309 males (53.8%) and 265 females (46.2%). Analysis of the 574 prescriptions showed that a total of 277 (48.25%) prescriptions were based on mono-therapy while 297 (51.75%) prescriptions were based on combinational therapy (table 1). The mono-therapy prescriptions belong to 129 females (46.5%) and 148 males (53.4%). Of the mono-therapy prescriptions, 38.6% contained β -blockers, 25.6% contained ACE-I, 15.1% contained CCB, 11.6% contained diuretics, 6.8% contained AT1-RA, 2% contained central sympatholytic and direct vasodilators.

The combinational antihypertensive prescriptions belong to 140 females (47.1%) and 157 males (52.9%) (table 2). Combinational anti-hypertensive prescriptions contained either two or three -drug combinations. The two-drug combinations found were: β -blockers + diuretics (35.5%), ACE-I + diuretics (17.5%), β -blockers + ACE-I (16.8%), ACE-I + CCB (9.6%), CCB + diuretics (8.9%), AT1-RA + diuretics (4.1%), β -blockers + CCB (3.8%), AT1-RA + β -blockers (2.7%) and other less common ones that include direct vasodilators (1%). Triple-drug prescriptions were not common and constitute approximately 1% of the total prescriptions. In all the prescriptions (mono-therapy and combinational therapy), β -blockers ranked first (49.3%), diuretics ranked second (40.1%), ACE-I ranked third (35.2%), CCB ranked fourth (19.2%) and AT1-RA ranked fifth (6.7%). Central sympatholytics and direct vasodilators ranked last (table 2).

Within mono-therapy prescriptions, traditional and newer generation drugs were used (table 3). In the β -blockers class, the drugs used were: atenolol (64/107) with both 50 and 100 mg strengths, Propranolol (29/107) and Metoprolol (4/107). In ACE-I class, the drugs used were: Enalapril (33/71) with both 10 and 20 mg strengths, Captopril (27/71), Benzapril (9/71) and Ramipril (2/71). In the CCB class, the drugs commonly used were: Nefidipine (21/42) and Amlodipine (13/42). In the diuretics class, the drugs used were HCT/Triameten

(26/31) and Furosemide (5/31). In AT1-RA class, the drugs used were Valsartan (6/19), Candesartan cilexetil (5/19) and Losartan (8/19). Multiple therapy prescriptions contained similar drugs to those found in mono therapy prescriptions but with different strengths and with less use of conventional or classical drug prototypes.

Table (1): Analysis of the 574 prescriptions containing the anti-hypertensive drugs by gender and type of therapy with reference to classes of drugs used.

Parameter	Frequency	Percentage
Gender		
Male	309	53.8%
< 60	131	43.4 %
> 60	178	57.6 %
Female	265	46.2%
< 60	127	47.75%
> 60	138	53.25%
Mono-therapy	277	48.25%
BB	107	38.6%
ACE-I	71	25.6%
CCB	42	15.1%
Diuretics	31	11.2%
AT1- RA	19	6.8%
Direct vasodilators	4	1.4%
Central Sympatholytics	3	1.0%
Two-drug	291	50.6%
Combinational therapy		
BB + Diuretic	103	35.4%
ACE-I + Diuretics	51	17.5%
BB + ACE-I	49	16.8%
ACE-I + CCB	28	9.6%
CCB + Diuretics	26	8.9%
AT1-RA + Diuretics	12	4.1%
BB + CCB	11	3.8%

... continue table (1)

Parameter	Frequency	Percentage
AT1-RA + BB	8	2.7%
BB + D. Vasodilator	2	<1%
Diuretics + D. Vasodilator	1	<1%
Three-drug	6	1%
Combinational therapy		
BB + Diuretic + ACE-I	3	50%
BB + Diuretic + CCB	2	33.4%
ACE-I + CCB + Diuretic	1	16.6%

Table (2): Total drug class utilization in the 574 prescriptions.

Drug Class	Percentage of Utilization
	(# of prescriptions containing that particular drug regardless as in mono or multiple therapy divided by the total # of prescription. The sum need not to be 100%)
<i>BB</i>	49.3% (283/574)
<i>Diuretics</i>	40.1% (230/574)
<i>ACE-I</i>	35.2% (202/574)
<i>CCB</i>	19.2% (110/574)
<i>AT1- RA</i>	6.7% (39/574)
<i>Direct vasodilators</i>	1.2% (7/574)
<i>Central Sympatholytics</i>	0.5% (3/574)

Table (3): drugs prescribed in mono therapy.

Drug Class	Drugs Used
<i>BB</i>	Atenolol (59.8%): 54% (50 mg); 46% (100 mg) Propranolol (27%) Metoprolol (13.2%)
<i>Diuretics</i>	Hydrochlorothiazide/Triametrene (83.8%) Furosemide (16.7%)
<i>ACE-I</i>	Enalapril (46.4%) Captopril (38%) Bezaprill (12.6%) Ramipril (3%)
<i>CCB</i>	Nifedipine (50%) Amlodipine (31%)

...Continue table (3)

Drug Class	Drugs Used
<i>Central Sympatholytics</i>	Methyl-Dopa (100%)
<i>ATI- RA</i>	Losartan (42%) Candesratan cilexetil (26%) Valsartan (31.5%)
<i>Direct vasodilators</i>	Hydralazine (100%)

Discussion

Recent publications by the *Palestinian Bureau of Central Statistics* (PCBS) has shown that hypertension is the most prevalent chronic health condition in Palestine, when compared to other chronic diseases like diabetes mellitus, cardiovascular diseases, cancer, ulcers, asthma and epilepsy⁽¹⁸⁾. This indicates the importance of the proper management and rational selection of antihypertensive drug therapy in order to improve the overall health of the Palestinian population. Few published studies were carried out in the Arab world to assess this issue. Of relevant importance is a study carried out in Bahrain in the Arab Gulf⁽¹⁹⁾. In that study the authors evaluated the antihypertensive prescribing pattern in elderly individuals aged 65 years or above in seven out of total eighteen health centers in Bahrain. The data for the study were collected using cards known as chronic dispensing cards especially designed for chronically ill patients. Each card contains the drug history of the patient. The authors of the Bahrain study concluded that the general principles of geriatric pharmacotherapy and the guidelines for antihypertensive combinational therapy were poorly followed. A second study carried out in Bahrain by the same group mentioned above compared family physicians' and general practitioners' approaches to drug management of diabetic hypertension⁽²⁰⁾. In this study, the authors carried out a retrospective prescription-based study on 1266 diabetic hypertensive patients. A study conducted in USA and published in year 2003 found that twice the number of patients (7.3 million) were taking ACE-I and CCB compared to diuretics and β -blockers (3.1 million) as the first line therapy which is in sharp contrast to the JNC VI guidelines⁽²¹⁾. Another study done in Ontario / Canada using administrative database containing information on more than 1.2 million elderly patients have found that simplified practice guidelines for hypertension did not have notable effects on prescribing pattern on Ontario⁽²²⁾.

The JNC VI guidelines emphasize the use of low dose thiazide diuretics or β -blockers mono-therapy as the initial treatment of hypertension in the absence of compelling factors or co-morbid diseases. In contrast, our data (table 1 and 2) shows that there is (1) an underutilization of diuretic mono-therapy when compared with β -blockers, ACE-I and CCB and (2) a tendency to use combinational therapy (51.5% : 2 and 3 drug therapy versus 48.5% for mono-therapy). Our study shows that diuretics constitute only 11.2% of the mono-therapy prescriptions and that the overall utilization of diuretics in the prescription database was 40.1%, ranking second after beta-blockers (table 2 and 3). This might suggest that diuretics are mostly used as an “add on” in combinational therapy. Possible reasons for the low utilization of diuretics mono-therapy include (1) lack of knowledge and education about the JNC VI guidelines, (2) the excessive promotion and marketing of other new medications by pharmaceutical companies and (3) the perception that diuretics produce serious metabolic and electrolyte adverse effects. However, data indicates that changes in glucose and cholesterol metabolism, as well as the electrolyte imbalance, caused by thiazides are minor, especially when the recommended smaller doses are used⁽²³⁻²⁶⁾.

β -blockers were extensively prescribed as seen from the prescription database. β blockers ranked first among mono-therapy prescriptions (38%) and in the overall utilization (57%) considering all prescriptions (table 1 and 2). The use of β blockers as first line therapy in mild or uncomplicated hypertension is in accordance with the JNC IV report recommendations although it is not preferred over thiazide diuretics. Atenolol 50 and 100 mg strengths were found in mono-therapy prescriptions (table 3). The 100 mg strength atenolol beta blocker accounts for approximately 46% of atenolol mono-therapy prescriptions suggesting that dose - increment recommendations may not be followed appropriately.

The ACE-I and CCB constitute approximately 36% of the mono-therapy prescriptions (table 1 and 2). The use of expensive and newer agents of these classes (Benzapril, Ramipril and Amlodipine,) was also noticed indicating limited impact of JNC VI recommendations on current prescribing patterns. A possible reason why JNC recommendations might have had little impact on antihypertensive prescribing patterns is the need to individualize drug treatment for some patients because of the presence of other co-morbid conditions that were not apparent at the prescription level or the presence of contraindicating factors to the use of beta-blockers or diuretics. A second reason for the high

utilization of CCB and ACE-I is that some physicians tend to start hypertension therapy with CCB or ACE-I because these drug classes have less deleterious effects on the patient's sex life style than beta-blockers or diuretics⁽²⁷⁾. A third reason is that the considerable expertise of the pharmaceutical industry in aggressive marketing has played a significant role in the marketing of new generation CCB, ACE-I and AT1-RA drug classes.

The most common anti-hypertensive drug combination was beta-blockers with diuretics which is consistent with the JNC VI recommendations as well as other clinical studies that indicated the effectiveness of this combination⁽²⁸⁻³⁰⁾. Among the diuretics drug class, Thiazide/Triametrene was the most commonly used (81%) followed by Furosemide (19%) (table 3). The use of Furosemide in hypertensive patients may indicate the presence of heart failure. According to current literature, the use of furosemide is not justifiable in initial therapy of uncomplicated hypertension.

Among the combinational therapy, it is noticed that rational and irrational combinations are utilized at approximately the same percentage. For example, the irrational β -blocker / ACE-I combination and the rational ACE-I/diuretic combination were seen in approximately 17% of the combinational prescriptions (table 1). β -blockers are known to block renin release while ACE-I work on the subsequent step of renin-angiotensin system⁽³¹⁻²⁵⁾. However, β -blocker / ACE-I combination might be justifiable in practice as the β -blockers suppress ACE-I induced palpitation. The use of a diuretic with an ACE inhibitor in low doses, has been shown to be effective in lowering blood pressure especially among the elderly and has similar efficacy to conventional antihypertensive therapy (diuretics, β -blockers or both) in prevention of cardiovascular mortality and major morbidity⁽³²⁻³⁴⁾. It should be emphasized that the risk of diuretic-induced hypokalaemia is significantly attenuated by concurrent use of an ACE inhibitor⁽³⁵⁾.

Limitation of the Study

1. A major limitation in this work is that the prescriptions used for analysis do not give a clear idea about the patient's history or the presence of other co-morbid conditions or the drug profile of the patient.
2. The number of prescriptions (sample size) might not be statistically representative of the all antihypertensive prescriptions dispensed at the community pharmacies.

3. The prescriptions used for analysis were obtained from community pharmacies. None were obtained from hospital pharmacies or governmental pharmacies that might add more information to the existing data.
4. The exclusion criteria might not be practical since in most cases hypertension co-exist with other co-morbid diseases.
5. The researcher can not guarantee that the prescriptions being analyzed represent the first prescription the patient received to manage his/her hypertension.

It would be best to examine prescriptions directly from the practitioners' clinics as we would be able to determine that this was the first prescription patient received for diagnosis of uncomplicated hypertension.

Based on these limitations, we strongly recommend further studies to be carried out in the same field that would clarify the clinical practices of hypertension management. Such studies need to be based on patient and doctor's interviews rather than just prescriptions.

Conclusions and Recommendations

Despite all the limitations given above, this current work signals some important points to health policy makers and practicing physicians in Palestine. The general pattern of antihypertensive prescribing as analysed from community pharmacies data in Palestine is not in accordance with the guidelines of the Joint National Committee and the WHO guidelines issued in the late 1990s. The trend of antihypertensive drug prescription favors combinational therapy, and the utilization of newer classes of antihypertensive drugs had a generally high impact on prescribing practices. β -blockers were most frequently prescribed both as single and in combinational therapy while single diuretic therapy was used sparingly. A continuing education program for physicians regarding JNC VI and other current guidelines is recommended.

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