# Extent of potential drug interactions among patients receiving anti-hypertensive medications

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## ABSTRACT

**Objective:** To investigate the frequency of potential antihypertensive drug interactions among patients with cardiovascular diseases receiving antihypertensive medications.

**Methods:** The study took place in Nablus, Palestine starting April through October 2003. Patients with cardiovascular diseases (n= 876) or who were receiving one or more antihypertensive medications were evaluated. All drugs prescribed for the patients were obtained from their medical files. A drug interaction database was developed based on updated Drug Interaction Facts to examine potential and level of drug interactions in each patient's regimen. Data were entered and analyzed using SPSS software.

**Results:** The number of "unique" pairs of potential drug interactions among the antihypertensive agents present in the data was 433. These included 16 cases (3.7%) level one; 34 cases (7.8%) level 2; 116 cases (26.8%) level 3; 136 cases (31.4%) level 4, and 131 (30.3%) level 5 interactions. Both increasing age and number of drugs were significantly associated with the potential for significant interactions at all levels with a *p* value less than 0.025.

**Conclusions:** This study found a high frequency of potential drug interactions with agents typically used for hypertension. Similar investigations need to be carried out among patients with other types of chronic diseases. Drug interaction software might be necessary in governmental pharmacy departments.

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A large number of anti-hypertensive drugs are introduced every year, and thus, new possible interactions between medications are increasing, leading to increased risk of hospitalization.[1-4] Multiple drug regimens used for the treatment of complicated hypertension also, carry the risk of adverse interactions. A drug interaction occurs when the effects of one drug are altered by the effects of another drug. This can result in either an increased or decreased effect of the object drug. In Palestine, the health system is dependent on individual skills to identify and correct possible interactions. No software is utilized in Palestinian governmental health centers that can detect or monitor prescriptions for possible drug interactions. Most pharmacists and physicians depend on their own experience to detect or avoid drug interactions. Studies thus far have not provided conclusive data with respect to the frequency of drug interaction and the occurrence of adverse events caused by drug interactions among outpatients. Reported incidences in outpatients ranged from 9.2-70.3% for drug interactions of any severity and from 1.2-23.3% for those considered of major relevance.[5-10] The aim of this report is to investigate the frequency and extent of potential interactions with antihypertensive medications among patients attending outpatient Palestinian governmental clinics.

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Methods. The study was carried out in Nablus district, the largest district in north Palestine, with a population of 325,269 inhabitants.[11] The access to patients' medical files was made after permission of the Palestinian health authorities. The permission was given to researchers through an-Najah university officials. The health authorities assigned a pharmacist in each governmental center for technical help to the researchers. Patients with cardiovascular diseases (n=876) or who were receiving one or more antihypertensive medications were evaluated. These files were selected randomly from the 4 governmental outpatient primary health care centers in Nablus district in north Palestine. The 4 centers are: Al-Makhfiah Center, Al-Wosta Center, Al-Garbehe and Balata Centers. These centers were run by both specialists and general practitioners. These health care centers provide primary medical health services to patients registered at the Ministry of Health (MOH) as chronic patients and who dispense their medications on a regular basis. In each primary health care center, every other file was obtained and if it belonged to a patient with a cardiovascular disease, it was considered part of the study. Files that belong to patients suffering from non-cardiovascular diseases were not taken for the study. The total number of files present at the 4 centers where the study took place was more than 8000 files. Eight hundred and seventy-six randomly selected medical files fit the criteria and were considered for the study. The criteria were as follows: 1. The patient has been using the prescribed medication for at least 6 months; 2. The medication profile contains at least one of the drugs that belong to the anti-hypertensive agents; 3. The patient is treated on an outpatient basis and, finally, 4. The patient is diagnosed with one or more cardiovascular diseases, such as congestive heart disease, hypertension, ischemic heart diseases, or arrhythmia. In each medical file, the data regarding age, gender, drug history (all drugs prescribed for the patient) and the prescribing physician was obtained and analyzed using SPSS version 10. The reference source for drug interactions was the updated Drug Interaction Facts.[12] A list of all antihypertensive medications was generated and categorized into 8 drug classes. A database was created that included each interacting drug pair (antihypertensive plus interacting drug) and the significance of the interaction. The significance of the interaction was rated from one through 5 as present in the Drug Interaction – Facts and Comparison which, has been used as a classification reference for this work: 1 = major, 2 = moderate, 3 = minor (where levels 1, 2, or 3 could be of suspected documentation of the interaction), 4 = major/moderate (with only possible documentation of the interaction), and 5 = either minor and possible documentation of interaction or unlikely documentation of an interaction. Highly significant interactions were considered those rated as level one or 2 by Drug Interaction Facts. The significance of the potential interactions listed in the Facts and Comparison book is based on the probability and clinical relevance as determined from the literature. Drug interaction pairs were given unique codes created and then analyzed using SPSS. Data collection was made over a period of 6 months starting April 2003 until October 2003. The chi-square test was used to determine the differences between proportions. A $p$ value $<0.05$ was considered to represent statistical significance.

Results. The 876 patients received a total of 1962 antihypertensive agents. The patients have a mean age of 61.2 ± 15.4 years. The percentage of female patients (52.4%) was close to males (47.6%). There were 194 patients (22.1%) receiving only one antihypertensive agent, 383 patients (43.7%) receiving 2 antihypertensive agents, 226 patients (25.8%) receiving 3 antihypertensive agents, and 81 patients (9.2%) receiving 4 or more antihypertensive agents. The average number of antihypertensive medications per patients was 2.2 drugs. The net frequency of use of major antihypertensive classes out of the 1962 drug total was: beta-blockers (BB) 22.6%, angiotensin converting enzyme inhibitors (ACE-I) 22.1%, calcium channel blockers (CCB) 18.3%, loop diuretics 16.1%, thiazide diuretics 15.2%, antiadrenergic agents 3% potassium-sparing diuretics 2.7%, and angiotensin II receptor blocker 0.0%. The number of unique (duplicate antihypertensive interactions were counted once, for example, propranolol and verapamil or verapamil and propranolol are considered one unique pair. Pairs of potential drug interactions with antihypertensive agents present in the data was 433. These included 16 cases of level one (3.7%); 34 cases of level 2 (7.8%); 116 cases of level 3 (26.8%); 136 cases of level 4 (31.4%), and 131 cases of level 5 (30.3%) interactions. Correlation between potential drug interactions and patient factors such as age and total number of drugs prescribed was investigated (**Tables 1 and 2**). Both increasing age and number of drugs were significantly associated with the potential for significant interactions at all levels with a $p$ value of less than 0.025. That is, elderly patients with multiple drug therapy, have the highest possibility of drug interactions of any level. The percentage with which various categories of antihypertensive agents were found to have a potential interaction with another drug was also analyzed (**Table 3**). Among the patients who were receiving BB, the extent of potential drug interaction was 31.1%. This means that the chances that a BB would cause a potential interaction when added to a typical

Table 1 - Percentage of patients with potential drug interactions by age and gender.

| Patient characteristics | | Frequency of interaction (%) | | | | | |
|---|---|---|---|---|---|---|---|
| **Age** | **Gender** | **L1** | **L2** | **L3** | **L4** | **L5** | **Total** |
| 30 – 50 | M | 0.1 | 0.1 | 1.9 | 1.5 | 1.1 | **4.7** |
| 51 – 60 | M | 0.4 | 0.4 | 2.1 | 3.3 | 5.3 | **11.5** |
| 61 – 70 | M | 0.9 | 1.8 | 4.3 | 3.9 | 4.9 | **15.8** |
| 71 - 97 | M | 0.4 | 1.5 | 4.9 | 6.2 | 5.1 | **18.1** |
| 30 – 50 | F | 0.1 | 0.4 | 1 | 2 | 1.7 | **5.2** |
| 51 – 60 | F | 0.8 | 1 | 3.9 | 4 | 2.8 | **12.5** |
| 61 – 70 | F | 0.7 | 1.4 | 4.3 | 5.2 | 4.5 | **16.1** |
| 71 – 95 | F | 0.3 | 1.2 | 4.4 | 5.3 | 4.9 | **16.1** |
| **Total** | | **3.7** | **7.8** | **26.8** | **31.4** | **30.3** | **100** |

L - level of interaction, M - male, F - female

Table 2 - Percentage of patients with potential drug interactions by total number of prescribed drugs.

| Total number of medications | Frequency of interaction (%) | | | | | |
|---|---|---|---|---|---|---|
| | **L1** | **L2** | **L3** | **L4** | **L5** | **Total** |
| 2 | 0 | 0 | 0.1 | 0.1 | 0.1 | **0.3** |
| 3 | 0.2 | 0.3 | 1.2 | 3.2 | 1.5 | **6.4** |
| 4 | 0.2 | 1 | 1.9 | 5 | 6.1 | **14.2** |
| 5 | 1 | 2.1 | 5.9 | 8.4 | 5.8 | **23.2** |
| 6 | 1.1 | 2 | 7.8 | 6.3 | 7.1 | **24.3** |
| ≥7 | 1.2 | 2.4 | 9.9 | 8.4 | 9.7 | **31.6** |
| **Total** | **3.7** | **7.8** | **26.8** | **31.4** | **30.3** | **100** |

L - level of interaction

Table 3 - Percentage of patients with potential drug interactions by drug class.

| Drug class | N | Frequency of interaction (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | **L1** | **L2** | **L3** | **L4** | **L5** | **Total** |
| BB | 443 | 0.9 | 1.7 | 8.9 | 10.1 | 9.5 | **31.1** |
| ACE-1 | 434 | 0.7 | 1.2 | 7.2 | 6.9 | 7.4 | **23.4** |
| CCB | 359 | 1 | 2.1 | 6.3 | 4.3 | 4.2 | **17.9** |
| L-D | 316 | 0.6 | 1.6 | 2.8 | 4.3 | 4.1 | **13.4** |
| T | 298 | 0.3 | 0.8 | 1.1 | 5.2 | 4.8 | **12.2** |
| α-blockers | 59 | 0.1 | 0.1 | 0.2 | 0.4 | 0.1 | **0.9** |
| K-D | 53 | 0.1 | 0.3 | 0.3 | 0.2 | 0.2 | **1.1** |
| AT-RA | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| **Total** | **1962** | **3.7** | **7.8** | **26.8** | **31.4** | **30.3** | **100** |

L - level of interaction, BB - beta blockers, ACE-I - angiotensin converting enzyme inhibitors, CCB - calcium channel blockers, L-D - loop diuretics, T – thiazide, α-B - alpha blockers, K-D - potassium sparing diuretics, AT-RA - angiotensin II receptor antagonist

regimen for a patient are higher than that with ACE-I or other antihypertensive drug classes.

Discussion. A literature survey using "Drug Interaction" key words in PubMed yielded approximately 10,000 publications in this field indicating the importance of this topic in the health practice. However, very few of them discussed the extent of potential drug interaction among patients suffering from cardiovascular diseases and taking antihypertensive agents.[13] Consequences of drug interaction are serious to the extent that a recent study carried out in the Netherlands claimed that approximately 15% of hospital admissions of elderly patients are caused by adverse effects of drugs.[14] Such adverse effects are mainly due to drug interactions occurring among patients with polypharmacy. Drug interactions can sometimes abolish a drug from the market as has been seen with terfenadine, mibefradil and cisapride.

Our data reveal that the potential drug interactions occurring with antihypertensive medications are common among patients with cardiovascular diseases. There are several possible reasons for this high percentage of potential drug interactions. One reason is that patients may receive new drugs from the physician on duty without consideration to previous or existing medications. A second possible reason is the fact that many patients who attend the governmental centers may attend private clinics for other problems and medications prescribed may not be checked for possible drug interaction with those prescribed at the governmental centers. A third possible explanation is the lack of a clinical pharmacist and shortage of a dispensing pharmacist in governmental centers who should check for possible drug interaction among patient's medications. A fourth explanation is the lack of updated and quick resources on drug interactions in the hands of health providers. The findings that the extent of potential drug interaction is high among the sample tested is similar to the findings of a study carried out in Iowa, USA.[13] In the USA study, carried out on 1574 patients, there was a very high frequency of potential drug interaction. In our tested sample, the frequency of potential interactions significantly increases with increase in age, or with increase in the total number of drugs prescribed, or both. As is known, the prevalence of hypertension increases with advancing age, as does the prevalence of co-morbid conditions and the total number of medications taken. Multi-drug therapy, advancing age and co-morbid conditions are the key risk factors for adverse drug reactions and drug interactions. Gender has no significant effect on frequency of potential drug interaction (data not shown). To detect and solve the problem of drug interactions, both the private and governmental pharmacy units need to appoint skilled pharmacists and to be supplied with drug-interaction software, which has been available for many years. Another suggestion would be to train the pharmacists on how to detect drug interactions using available literature. Unfortunately, published articles indicated that pharmacists identify many interactions and alert physicians, however, many interactions go unchanged and the computer alert is simply overridden by the pharmacist.[15,16] Some other published work has indicated that drug interaction software when used properly made no difference on therapy and patient's health outcome.[17,18]

Our data also indicated that BB and ACE-I are more likely to cause drug interactions. This might be due to the fact that these drug classes are most commonly prescribed for the treatment of hypertension and have been present for more than 20 years. In contrast, agents that are new, as the new generation CCB, or not commonly prescribed as angiotensin II receptor antagonist, may be less likely to have documented potentially high level drug interaction.

There are many mechanisms by which anti-hypertensive drugs interact with other medications. Many antihypertensive drugs are metabolized in the liver (CCB, lipid soluble BB, and some ACE-inhibitors) via the cytochrome-oxidase system. Many medications taken by the patient can accelerate the breakdown of antihypertensive agents leading to decrease in their plasma concentration. Conversely, other medications like cimetidine, which inhibits oxidase system, can increase antihypertensive drug levels, resulting in greater therapeutic effect. Hepatic blood flow can be modified by propranolol and nifedipine secondary to a change in cardiac output or blood vessel diameter leading to a decrease or an increase in the clearance of another concomitantly administered drug. In the kidney, some anti-hypertensive agents interact with other cardiovascular drugs by competing for renal clearance; CCB alter the renal clearance of digoxin, but the mechanism remains unclear. In vascular muscle cells, excess vasodilatation or vasoconstriction can be observed. The combination of an alpha 1-blocking agent with a dihydropyridine can induce hypotension, which maybe severe. Non-steroidal anti-inflammatory drugs (NSAIDs) are able to lessen the antihypertensive effects of BB, diuretics and ACE-inhibitors, via vascular prostaglandin inhibition. The cardiac pharmacodynamic interactions of BB and CCB, verapamil and diltiazem, at the sino-atrial node, atrio-ventricular node, conduction system and myocardium are well established and must be avoided. The main interactions with BB are related to CCB, class I antiarrhythmic drugs and NSAIDs.

It is important to consider here that although drugs investigated pharmacologically belong to antihypertensive drug class, yet these agents might be used for cardiovascular diseases other than hypertension. This report is a valid description of the potential interactions of antihypertensive drug class. Another important argument that must be taken into consideration here is that the significance rating for any specific interaction is determined by the documentation and interpretation of evidence in the literature. This literature is dynamically changing, and hence the significance will also follow.

In conclusion, this study found a high frequency of potential drug interactions (approximately 40%) with medications typically used to treat hypertension. More than 60% of the interactions were not clinically of high significant rating. It is likely that similar frequencies of interactions might be expected in other populations receiving multiple medications. Investigation of drug interactions among other chronic disease groups is important, also providing dispensing pharmacists with drug interaction software alerts is important.

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