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Original Research

Adverse drug reactions induced by cardiovascular drugs in outpatients

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ABSTRACT*

Considering increased use of cardiovascular drugs and limitations in pre-marketing trials for drug safety evaluation, post marketing evaluation of adverse drug reactions (ADRs) induced by this class of medicinal products seems necessary.

Objectives: To determine the rate and seriousness of adverse reactions induced by cardiovascular drugs in outpatients. To compare sex and different age groups in developing ADRs with cardiovascular agents. To assess the relationship between frequencies of ADRs and the number of drugs used.

Methods: This cross-sectional study was done in cardiovascular clinic at a teaching hospital. All patients during an eight months period were evaluated for cardiovascular drugs induced ADRs. Patient and reaction factors were analyzed in detected ADRs. Patients with or without ADRs were compared in sex and age by using chi-square test. Assessing the relationship between frequencies of ADRs and the number of drugs used was done by using Pearson analysis.

Results: The total number of 518 patients was visited at the clinic. ADRs were detected in 105 (20.3%) patients. The most frequent ADRs were occurred in the age group of 51-60. The highest rate of ADRs was recorded to be induced by Diltiazem (23.5%) and the lowest rate with Atenolol (3%). Headache was the most frequent detected ADR (23%). Assessing the severity and preventability of ADRs revealed that 1.1% of ADRs were detected as severe and 1.9% as preventable reactions. Women significantly developed more ADRs in this study (chi square = 3.978, P<0.05). ADRs more frequently occurred with increasing age in this study (chi square = 15.871, P<0.05). With increasing the number of drugs used, the frequency of ADRs increased (Pearson=0.259, P<0.05).

Conclusion: Monitoring ADRs in patients using cardiovascular drugs is a matter of importance since this class of medicines is usually used by elderly patients with critical conditions and underlying diseases.

Keywords: Product Surveillance, Postmarketing. Cardiovascular Agents. Iran.

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REACCIONES ADVERSAS INDUCIDAS POR MEDICAMENTOS CARDIOVASCULARES EN PACIENTES AMBULATORIOS

RESUMEN

Teniendo en cuenta el aumento del uso de medicamentos cardiovasculares y las limitaciones en los estudios pre-comercialización, parece necesaria la evaluación de reacciones adversas (RAM) producidas por este grupo de medicamentos.

Objetivos: Determinar la tasa y la gravedad de las RAM producidas por medicamentos cardiovasculares en pacientes ambulatorios. Comparar las diferencias de sexo y edad en la aparición de reacciones adversas con medicamentos cardiovasculares. Evaluar la relación entre las frecuencias de RAM y la cantidad de medicamento usado.

Métodos: Este estudio transversal se realizó en la clínica cardiovascular del hospital universitario. Se evaluó a todos los pacientes durante un periodo de 8 meses en busca de RAM inducidas por medicamentos cardiovasculares. Se analizaron las variables de pacientes y las reacciones. Se comparó el sexo y la edad de los pacientes con y sin RAM utilizando el test chi cuadrado. Mediante un análisis de Pearson se evaluó la relación entre la frecuencia de RAM y los medicamentos usados.

Resultados: El número de pacientes visitados en la clínica fue de 518. Se detectaron RAM en 105 pacientes (20,3%). Las RAM más frecuentes aparecieron en el grupo de 51-60 años. La tasa más alta de RAM registrada estaba inducida por dialtiazem (23,5%) y la más baja con atenolol (3%). La RAM más frecuente fue el dolor de cabeza. Al evaluar la gravedad y preventabilidad de las RAM se reveló que el 1,1% de las RAM detectadas eran graves, y el 1,9% eran prevenibles. Las mujeres desarrollaron significativamente más RAM en este estudio (chi cuadrado=3,978, p<0,05). Las RAM aparecieron más frecuentemente con la edad (chi cuadrado=18,871, p<0,05). Al aumentar el número de medicamentos, la frecuencia de RAM aumentaba (Pearson=0.259, P<0.05).

Conclusión: Es de gran importancia seguir las RAM en pacientes que usan medicamentos cardiovasculares ya que este grupo de medicamentos es utilizado generalmente por ancianos en condiciones críticas y con enfermedades subyacentes.

Palabras clave: Vigilancia de productos post-comercialización. Agentes cardiovasculares. Irán.

INTRODUCTION

The incidence of cardiovascular diseases (CVDs) has been increased in recent decades, it has been estimated that CVDs are the most common cause of death in Iran.[1,2] As a result cardiovascular drugs has moved to the third place among all drug classes prescribed in the country. With introducing new cardiovascular drugs to the market, Pharmacotherapy of CVDs has improved rapidly during last few years. The problem of adverse drug events accompanied with different drug therapies has been reported since 1961. It has been reported that adverse drug events are considered as 4th to 6th cause of death in the US.[3] Studies show that cardiovascular drugs are among the most commonly cause of adverse events in hospitalized patients.[4] Some studies report that cardiovascular drugs may cause half of all hospital admissions due to adverse drug reactions.[5] Another study describes that 4% of adverse events induced by cardiovascular drugs are serious ADEs.[6] Almost 10% of all medication-related office visits result from cardiovascular drug reactions, and most of those visits are related to dermatological reactions.[7] In a literature review of ten studies published between 1994 and 2001, cardiovascular drugs were implicated for 17.9% of preventable adverse drug events.[8] There are several studies on hospitalized patients to detect the rate of adverse events induced by cardiovascular drugs but there are no studies on outpatients to the best of our knowledge. This is the first study evaluating adverse events following cardiovascular drugs use in outpatients.

METHODS

This cross-sectional study was conducted in the cardiovascular clinic of a 1000 bed tertiary teaching hospital in Tehran. All patients visited in the cardiovascular clinic during an eighth months period were evaluated for cardiovascular drugs induced adverse reactions. Patients previously used or newly started on cardiovascular drugs were monitored and followed for detecting and recording of ADRs. Adverse drug reactions were detected by daily interviewing patients, consulting with physicians and reviewing patient charts. The WHO definition for "adverse drug reaction" was used in this study: "Any noxious or unintended response to a drug, which occurs at doses normally used in human for prophylaxis, diagnosis or treatment of disease or for the modification of physiological function".[9]

If a sign or symptom suspected to be induced by cardiovascular drug was found, the national form for ADRs (yellow card) was filled. Patient demographics, pre-existing diseases and drug history were recorded. The time of onset and duration of the reaction, suspected drug, outcome and actions taken for managing the adverse reaction were precisely recorded. The ADRs were recorded based on WHO terminology.[10] Causality assessments were performed using WHO criteria.[11] Seriousness of recorded ADRs were assessed based on WHO definition, which involves any ADRs resulted in death, life threatening situation, hospitalization, prolonged hospital stay, disability and birth defect.[12] Preventable adverse events were determined applying Schumock questionnaire.[13]

All patients entered the study were classified to two different groups: Patients who developed at least one ADR (ADR patients) and patients who never experienced an ADR (Non-ADR patients). These two groups of patients were compared in sex and age by using chi-square test. Also the duration of drug usage were compared in ADR and Non-ADR patients using t-test. For assessing the relationship between frequencies of ADRs occurred and the number of drugs used, Pearson analysis was performed.

Table 1. Number of ADRs in different age groups.

Age	Patients with ADRs (%)	Patients without ADRs (%)	Total (%)
≤10	0	2 (100%)	2 (100%)
11-20	0	18 (100%)	18 (100%)
21-30	5 (11.4%)	39 (88.6%)	44 (100%)
31-40	9 (13.8%)	56 (86.2%)	65 (100%)
41-50	26 (26.0%)	74 (74.0%)	100 (100%)
51-60	37 (27.6%)	97 (72.4%)	134 (100%)
≥61	28 (18.1%)	127 (81.9%)	155 (100%)
Total	105 (20.3%)	413 (79.7%)	518 (100%)

RESULTS

A total of 518 patients, 212 men and 306 women, using cardiovascular medications entered the study. One hundred and five patients (20.3%) including 34 men and 71 women experienced at least one ADR. There were 54 patients (51.4%) who developed more than one ADR. Two ADRs in 26 patients (24.8%), three ADRs in 21 (20%), four ADRs in 5 (4.8%), five ADRs in 1 (1%) and six ADRs in 1 (1%) patient was reported. Detected ADRs were mostly observed in the age group of 51-60 (Table 1). Calcium channel blockers and potassium sparing diuretics had the highest and lowest rate of ADRs respectively (Table 2). The highest rate of ADRs was recorded to be induced by Diltiazem (23.5%) and the lowest rate was related to Atenolol (3%). Central nervous system and Gastrointestinal system disorders were the most frequent system-organ classes affected with ADRs. (Table 3) Headache, vertigo, weakness, nausea and vomiting were the most frequent reactions. (Table 4) Among ADRs evaluated, 1.1% was recognized as serious and 1.9% as preventable ADRs. Causality assessment of ADRs revealed that the most frequent ADRs (75.9%) were recognized to be certain, followed by 19.2% as possible, 3% as probable and 1.9% as unlikely. Withdrawal of suspected drug was necessary in 22.2% of ADR patients, the treatment was continued in 65.6%, the dosage was decreased

in 6.3%, the treatment was continued by alternate drug in 3.7% and 2.2% of the patients went through symptomatic therapy. The most common outcome of ADRs was "not yet recovered", which refers to the ADRs not completely recovered by the end of the study (Table 5).

Table 2. Number of ADRs induced by different subclasses of cardiovascular agents.

Pharmacologic classification	Patients with ADRs (%)	Patients without ADRs (%)	Total (%)
Angiotensin converting enzymes Inhibitors	40 (21.1%)	150 (78.9%)	190 (100%)
Calcium channel blockers	24 (27.3%)	64 (72.7%)	88 (100%)
Beta – blockers	18 (5.2%)	330 (94.8%)	348 (100%)
Nitrates	37 (11.6%)	283 (88.4%)	320 (100%)
Loop diuretics	15 (19.5%)	62 (80.5%)	77 (100%)
Thiazide diuretics	1 (16.7%)	5 (83.3%)	6 (100%)
Potassium sparing diuretics	2 (2.3%)	86 (97.7%)	88 (100%)
Carbonic anhydrase inhibitors	0	2 (100%)	2 (100%)
Alpha – blockers	3 (37.5%)	5 (62.5%)	8 (100%)
Peripheral vasodilators	1 (100%)	0	1 (100%)
Centrally – acting antiadrenergics	1 (7.1%)	13 (92.2%)	14 (100%)
Pyrimidine analogues	2 (16.7%)	10 (83.3%)	12 (100%)
Benzofuran derivatives	1 (20.0%)	4 (80.0%)	5 (100%)
Cardiac glycosides	17 (14.9%)	97 (85.1%)	114 (100%)
Cinchona alkaloids	0	1 (100%)	1 (100%)
Sodium channel antagonists	0	1 (100%)	1 (100%)
Total	162 (12.7%)	1113 (87.3%)	1275 (100%)

Table 3. Different system-organ classes affected by ADRs.

System-Organ Class	Frequency	Percent
Central Nervous System Disorders	134	49.6%
Gastrointestinal System Disorders	61	22.6%
Respiratory System Disorders	32	11.9%
Cardiovascular System Disorders	28	10.4%
Others	7	2.6%
Skin and Appendages System Disorders	4	1.5%
Genito-Urinary System Disorders	3	1.1%
Hematologic Disorders	1	0.4%
Total	270	100%

The result of chi-squared test for comparing sex between ADR and Non-ADR patients showed that women significantly developed more ADRs in this study (chi square = 3.978, $P<0.05$). Also the result of the chi-squared test for comparing the age groups between two groups of patients was significant, it appears that ADRs more frequently occurred with increasing age in this study (chi square = 15.871, $P<0.05$). Conducting t-test for comparing duration of drug usage between ADR and Non-ADR patients implicated that there is a significant relationship between two groups. It appears that the average duration of drug usage is longer in Non-ADR group ($t=-2.812$, $P<0.05$). The result of Pearson test implicated that there is a significant relationship between frequencies of ADRs occurred and the number of drugs used. It appears that with increasing the number of drugs used, the frequency of ADRs will increase (Pearson=0.259, $P<0.05$).

DISCUSSION

In this study 105 patients (20.3%) developed at least one ADR. This rate is higher than the rate of 15.3% previously reported in a similar study conducted in Denmark.[14] This difference may be due to the difference between the population studied, types and number of drugs used by patients, definition used for ADR and the susceptibility of patients for developing adverse reactions induced by cardiovascular drugs. Most ADR patients in this study were in the age group of 51-60. This is partly in accordance with the result of a previous study conducted in Iranian hospitalized patients in two internal medicine wards in the same hospital.[15] There is a controversy in the literature on the relationship between age and developing ADRs.[16] Some studies have shown that ADRs may increase with increasing age; this could be due to polypharmacy used in old patients. Considering the result of chi-square test for analytical evaluation of the influence of age on occurring ADRs, it appears that older patients are more likely to experience an ADR. Gender difference in patients with or without ADRs has been described earlier[17], our findings support the theory of increased number of ADRs in women.

Calcium channel blockers especially Diltiazem had the highest rate of ADRs in our study. The results of a study conducted in a university hospital showed that Nitrates, Digoxin, Propranolol, Heparin, Warfarin, Anti-hypertensive and Anti-arrhythmic drugs together produced 48.5% of ADEs. In the study performed by Mjorndal et al.[18] in a clinic of internal medicine at a Swedish university hospital, cardiovascular drugs were the most common class of drugs involved in the induction of ADRs constituting 36.3% of the drugs associated with ADRs. The most offending cardiovascular drugs in

that study were Metoprolol, Enalapril, Digoxin, Flodipine and Furosemide. Also in Danish trial[14], Diuretics, Beta-blockers and Calcium antagonists were responsible for 80% of all ADRs detected. Our study identified Central Nervous and Gastrointestinal System as the most frequent affected system-organ classes by ADRs, in which headache, vertigo, weakness, nausea and vomiting were the most reactions observed. This profile of adverse reactions is well adjusted with the pharmacological actions of most frequent suspected drugs for ADRs in this study, where as in other study conducted in Denmark hypokalemia was the most frequent ADR related to Thiazides.

Comparing our results with those in the literature, the percentage of preventable ADRs in this study (1.9%) is rather lower than those detected in other studies.[19] This may be partly due to different drug classes studied in different trials, e.g. in the similar study designed in two internal medicine wards 58.8% of detected ADRs were reported to be preventable based on the same questionnaire.[15] Also in a literature review conducted on ten studies published between 1994 and 2001, cardiovascular drugs were implicated for 17.9% of preventable adverse drug events.[8]

This study showed that the average duration of drug usage is longer in Non-ADR group. Also it appears that most detected ADRs have been occurred shortly after starting cardiovascular drugs and incidence of ADRs are not related to the duration of usage. Like many other studies, increasing the number of drugs led to increased frequency of ADRs.

CONCLUSIONS

Monitoring adverse drug reactions in patients using cardiovascular drugs is a matter of importance since this class of medicine is usually used by elderly patients with critical conditions and underlying diseases. The frequency of ADRs occurrence can be reduced by decreasing the number of drugs prescribed. ADRs of Cardiovascular drugs mostly occur in first days of treatment, therefore monitoring patients in first days of using cardiovascular drugs could help in preventing ADRs. To determine the rate and nature of adverse events induced by different subclasses of cardiovascular drugs, more studies are recommended in various populations.

Table 4. Different ADRs induced by cardiovascular agents.

Adverse Reaction	Frequency	% of the reaction in ADR Patients
Headache	62	59.0
Vertigo	37	35.2
Weakness	25	23.8
Nausea	23	21.9
Cough	20	19.0
Mouth dry	15	14.2
Hypotension	14	13.3
Constipation	11	10.4
Dyspnea	11	10.4
Vomiting	10	9.52
Dizziness	5	4.7
Edema	4	3.8
Chest pain	4	3.8
Pruritus	3	2.85
Nightmare	3	2.85
Paraesthesia	2	1.9
Erratic Blood sugar	2	1.9
Palpitation	2	1.9
Tingling	2	1.9
PVC	2	1.9
Throat itching	1	0.95
Hematuria	1	0.95
Insomnia	1	0.95
Polyuria	1	0.95
Epigastric pain	1	0.95
Micturation	1	0.95
Diarrhea	1	0.95
Hirsutism	1	0.95
Extremities coldness	1	0.95
Leg pain	1	0.95
Pancytopenia	1	0.95
ST inversion	1	0.95
AF rhythm	1	0.95
Total	270	100

CONFLICT OF INTEREST

None declared. No external funding sources declared.

Table 5. Outcome of detected ADRs induced by cardiovascular agents.

Outcome	Frequency	Percent
Unknown	77	28.5%
Recovered	79	29.3%
Not yet recovered	113	41.9%
Hospitalization	1	0.4%
Total	270	100%

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