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ADVERSE DRUG REACTIONS TO CARDIOVASCULAR DRUGS

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ABSTRACT

PURPOSE. To assess the clinical pattern and risk factors for adverse drug reactions (ADRs) induced by cardiovascular drugs (CD) in hospitalized patients.
PATIENTS AND METHODS. A prospective study was carried out among patients admitted to the Clinic of Dermatology and Venereology in Stara Zagora for a 5-year period (June 1999 - June 2004). ADRs were classified by type, severity and causality. Case-causality was scored according to Naranjo et al.
RESULTS. A total of 1207 admissions were analyzed. Concomitant cardiovascular diseases were detected in 392 cases. The number of ADRs to CD was 28 and they occurred in 27 patients. The incidence of ADRs to CD was 7.41% in patients exposed to cardiovascular medication. Cutaneous ADRs were most frequent the prevalent clinical patterns being exanthematous and urticarial. Severe ADRs were detected in 2 cases. The factors significantly associated with ADRs were the use of beta-blockers (RR 3.77; 95% CI 1.77-8.01) and organic nitrates (RR 2.46; 95% CI 1.10-5.51).
DISCUSSION. ADRs to CD have multiorgan clinical presentation. In rare cases they may be life-threatening. The study shows a moderate incidence of ADRs induced by CD. It emphasizes the importance of drug-related factors for the occurrence of ADRs to CD.

Key words: adverse drug reaction, cardiovascular drugs, risk factors

INTRODUCTION

Adverse drug reactions (ADRs) during hospitalization are a major cause of patient morbidity and hospitalization costs. The percentage of hospitalized patients experiencing an ADR has been reported to range from 1.5 to 35 % (1). Risk factors for ADRs are considered to be age, sex, excretory organ dysfunction, smoking, alcohol consumption, previous reactions to drugs, polypharmacy, specific drug classes etc. (2,3).
Because of high cardiovascular morbidity use of cardiovascular medication is frequent. ADRs to CD may affect tolerability and patient compliance. Discontinuations of antihypertensive drugs due to adverse events occurred most frequently with calcium channel blockers (6.7%) and alpha-adrenergic blockers (6.0%) according to a meta-analysis of 190 studies conducted from 1990 to 1999 (4).
The aim of the study is to assess the clinical pattern and risk factors for ADRs induced by CD in hospitalized patients.

PATIENTS AND METHODS

A prospective pharmacovigilance study was carried out among patients consecutively admitted to the Clinic of Dermatology and Venereology in Stara Zagora for a 5-year period from June 1999 to June 2004. Data on patient sociodemographic characteristics, primary diagnosis, concomitant diseases and drug therapy were collected from the electronic patient records. For patients with suspected ADRs data were entered in a structured form, containing information on past medical and drug history, clinical description of the adverse event and eventual outcome. Data were reviewed by a team consisting of a dermatologist and a pharmacologist.
ADR was defined as any noxious, unintended and undesired effect of a drug that can occur at

doses used for prophylaxis, diagnosis or therapy (5). ADRs were classified by clinical manifestation (Adverse Reaction Terminology, WHO) and by type as "type A" if related to the pharmacological properties of the suspected drug and "type B " if otherwise (6). According to their severity ADRs were assessed as "severe" (life-threatening or serious condition with progressive organ dysfunction), "moderate" (fair condition, transitory organ dysfunction) and "mild" (good condition with no organ dysfunction).The relationship between the drug and the reaction was scored as "definite", "probable", "possible" and "doubtful" following the method of Naranjo et al. (7). The statistical analysis compared the characteristics of patients with an ADR to CD with those of patients who were exposed to CD but exhibited no such reaction. A total of 15 cases with no drug therapy or no data on therapy were excluded from the analysis. Variables considered for the study were age, sex, drinking and smoking habits, history of a previous ADR, failure of excretory organs and use of specific groups of CD. Chi-square analysis was used with the results expressed as relative risk (RR) and 95% confidence intervals. A value of $p<0.05$ was considered statistically significant. Analyses were performed using SPSS for Windows version 9.0.

RESULTS

1. Patient characteristics (Table 1)

Table 1. *Characteristics of the patients*

	Value (Valid %)		
Characteristic	Total population (%)	Pts with cv diseases (%*)	Pts with ADR to CD (%*)
Age above 65 years	262 (21.7%)	174 (44.4%)	15 (55.5%)
Female	690 (57.2%)	219 (55.9%)	14 (51.8%)
Drinker	116 (11.6%)	45 (11.5%)	1 (3.7%)
Smoker	214 (21.5%)	49 (12.5%)	4 (14.8%)
Previous ADR	102 (10.2 %)	47 (12.0%)	4 (14.8%)
Excretory organ failure	6 (0.6%)	6 (1.5%)	0 (0%)

pts - patients, cv-cardiovascular, % - percent of total ; %- percent of pts in the respective group*

A total of 1207 patients with an age range 2-91 years (mean age: 48.95±18.8) were included in the study. The main causes for hospitalization by primary diagnosis were eczema/dermatitis (21.37%), erythemato-papulo-squamous diseases (16.9%) and infectious dermatoses (16.8%). Concomitant disease states were detected in 802 cases (66.4%). Cardiovascular diseases (International Classification of Diseases - version 10) were diagnosed in 392 patients. Most frequent were hypertensive diseases (I10-I15) - 307 cases, ischaemic heart diseases (I20-I25) - 240 cases and heart failure (I50) - 175 cases.

2. Drug utilization (Table 2)

Table 2*. Main drug classes used (Anatomical-Therapeutic-Chemical classification)*

Drug	Patients (n)	**% of all treated**
C08 Calcium channel blockers	183	47.5%
C03 Diuretics	159	41.3%
C02E Agents acting on RAS (ACE inhibitors)	142	37.6%
C02A Aantiadrenergic agents, centrally acting	46	12.2 %
C01DA Organic nitrates	44	11.9%
C01EB Trimetazidine	39	10.2%
C07 Beta-blockers	37	9.6%
C01A Cardiac glycosides	27	7.%

Drug treatment was applied in 378 patients suffering from one or more cardiovascular diseases. In 1 case beta-blockers were used for oesophageal varices. The most common CD used were calcium channel blockers (47.5%) and diuretics (41.3%). Combination therapy was applied in 219 cases (56.9%). Most frequent combinations were "calcium channel blockers + diuretics", "ACE inhibitors + diuretics" and "calcium channel blockers + ACE inhibitors + diuretics".

3. ADRs.

The number of ADRs to CD was 28 and they occurred in 27 patients (age range: 37-80 years, mean age: 64.41±10.37). The most commonly affected organs were the skin and appendages (17 ADRs) and the central nervous system (5 ADRs). Other clinical manifestations included cardiovascular, liver, respiratory and electrolytic dysfunctions. The prevalent clinical patterns of cutaneous ADRs were exanthematous and urticarial. Exacerbation of chronic dermatoses (psoriasis vulgaris) was found in 4 cases. The distribution of ADRs according to their type showed a slight prevalence of "type A" reactions - 54%. Regarding imputability 82% of ADRs were scored as "possible" and the remaining 18% as "probable". Severe ADRs (Quincke's edema) were detected in 2 cases (7.1%), moderate - in 18 cases (64,3 %) and mild - in 8 cases (28.6 %). The distribution of ADRs according to drug class shows a high incidence of ADRs due to combination therapy (Figure1). In those cases the offending drug could not be verified.

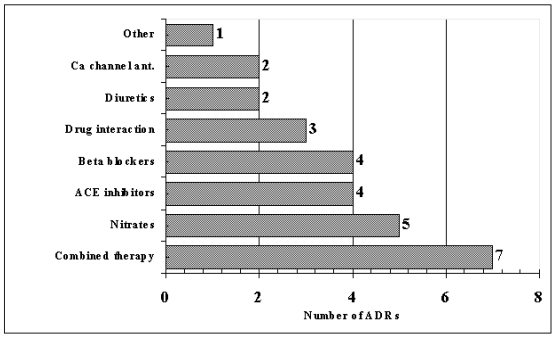

Figure 1*. Distribution of ADRs to according to drug class*

No statistically significant relationship was found between factors like gender, advancing age, excretory organ dysfunction, history of previous ADRs, regular alcohol consumption, smoking, combination therapy and the occurrence of ADRs to CDs. The relationship between ADRs and use of specific groups of CD (Table 3) was significant for beta-blockers (RR 3.77; 95% CI 1.77-8.01) and organic nitrates (RR 2.46; 95% CI 1.10-5.51).

Table 3*. Risk of ADRs related to specific groups of cardiovascular drugs*

Drugs	RR	95% CI
C01A Cardiac glycosides	0.50	0.07-3.54
C01DA Organic nitrates	2.46	1.10-5.51
C01EB Trimetazidine	0.33	0.05-2.39
C02A Aantiadrenergic agents, centrally acting	1.64	0.65-4.12
C02E Agents acting on RAS (ACE inhibitors)	1.79	0.87-3.69
C03 Diuretics	1.10	0.53-2.28
C07 Beta blockers	3.77	1.77-8.01
C08 Calcium channel blockers	0.45	0.20-1.00
Combination therapy	1.06	0.50-2.21

DISCUSSION

The study reveals a moderate incidence of ADRs to CD - 2.32% in the whole study population and 7.41% in patients exposed to cardiovascular medication. Because of the specialized setting of this study most frequent ADRs were cutaneous mainly exanthematous and urticarial reactions. The lack of "definite" ADRs can be explained with the fact that provocation tests were not performed because of ethical reasons. Use of beta-blockers and organic nitrates were the factors significantly associated with the occurrence of ADRs. Although beta-blockers have been found to have high incidence of ADRs in comparison with other antihypertensive drugs in some studies (8,

9), a recent investigation from Asia (10) shows that beta-blockers are widely prescribed and associated with fewer side effects. Our findings reveal a moderate utilization pattern of this drug class but a significant relationship between the use of beta-blockers and the development of ADRs. It is notable that a "severe" ADR manifesting as urticaria and Quincke's edema was associated with the concomitant use of metoprolol and enalapril and in this case the role of the beta-blocker could not be ruled out. In our study ADRs to organic nitrates presenting clinically as headache although of moderate severity are important because in most of the cases they led to discontinuation of the preparation.

Combination therapy with CD is widely used and is estimated to be safe probably because the drugs in the combinations are used in lower doses although this does not apply for type B reactions. ADRs in patients on combination therapy are often difficult to be assessed because the causative agent cannot be verified and all suspected drugs have to be stopped.

ADRs to CD may have multiorgan clinical presentation. They are not frequent but in some cases they may be life-threatening. This study shows that the risk of ADRs to CD is higher in users of beta-blockers and organic nitrates. It confirms the importance of drug-related factors for the development of ADRs to CD in a sample of patients from a specialized dermatology department.

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