



Original Contribution

URTICARIAL ADVERSE DRUG REACTIONS TO ACE INHIBITORS AND BETA-BLOCKERS

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ABSTRACT

PURPOSE. To evaluate the incidence of urticarial adverse drug reactions (ADRs) to ACE inhibitors and beta-blockers, patient demographics, drug causality, and treatment outcome. **METHODS.** An epidemiological study including 154 patients with urticarial ADRs, out of a total of 3554 hospitalized patients in the Clinic of Dermatology and Venereology, for a 7-year period. ADRs were defined according to the WHO and the Naranjo algorithm was used for case drug causality assessment.

RESULTS. Urticarial ADRs were found in 4,1% of the study population (≥ 18 years), the average age was 50,2 years, and female prevalence was established. Concomitant cardiovascular diseases were found in 45,2% of the patients and 30,1% declared using ACE inhibitors and/or beta-blockers. The suspected drug was withdrawn, and alternative therapy was recommended by a cardiologist. The Naranjo algorithm showed 4.5% “definitive”, 45,5% “possible”, and 50% “probable” urticarial ADRs. Systemic antihistamines were administered to all patients and single short corticosteroid courses were added in 81,8%. Clinical recovery was achieved in 59% of the patients and improvement in 41%. **CONCLUSIONS.** The need for drug therapy and hospitalization in severe cases of urticarial ADRs to ACE inhibitors and beta-blockers are factors contributing to the overall socio-economic burden of ADRs.

Key words: urticaria, cardiovascular drugs

INTRODUCTION

Urticaria is a common heterogeneous, polyetiologic and polypathogenetic systemic disease (1, 2). It is characterized by the spontaneous or induced (by physical factors) appearance of hives, angioedema, or both and has an acute (≤ 6 weeks) or chronic (> 6 weeks) clinical course (3, 4). Urticarial adverse drug reactions (ADRs) are referred synonymously as “drug-induced urticaria (DIU)” or “urticaria

medicamentosa”. According to the International Classification of Diseases 11th Revision (ICD-11), this form of urticaria is classified into Section 14 - Diseases of the skin, EH61 for DIU (5). It is important to emphasize that urticaria may not only be induced but also aggravated by some drugs. The diagnosis is clinical (3,4), and requires a comprehensive drug history.

The aim of the study is to evaluate the incidence of urticarial ADRs to ACE inhibitors, beta-blockers, patient demographics, drug causality and treatment outcome.

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MATERIALS AND METHODS

The investigation is a prospective part of an epidemiological study (6) carried out among the patients with urticarial ADRs admitted to the Clinic of Dermatology and Venereology at UMHAT "Prof. Dr. Stoyan Kirkovich" AD, Stara Zagora for the 7-year period (2013–2019). The study is based on a review of data from medical records (history of illness and/or epicrisis) and included 154 patients with urticarial ADRs, out of a total of 3554 hospitalized patients. The following data were extracted and entered in a structured form for each patient: demographics, comorbidities, drug history in the last three months, clinical examination, consultations with a cardiologist, therapeutic management, and treatment outcome. Urticarial ADRs were defined according to WHO (7). For standardized case drug causality assessment, the WHO-UMC system (8) and the Naranjo score system (9) were applied. The non-interventional and non-invasive study followed the Declaration of Helsinki guidelines (1964), it was institutionally approved by the ethics committee, and all participants have signed informed consent. For purposes of statistical analysis descriptive statistics, non-parametric Kolmogorov–Smirnov and Shapiro–Wilk test, and Chi-square/Fisher's exact test, were used. A p -value < 0.05 was considered statistically significant. Analyses and presentation of the data were performed with SPSS software for Windows (SPSS version 21.0) and MS Office Excel.

RESULTS

Urticarial ADRs were found in 154 (4,3%) of the study population including 146 (4,1%) adults (≥ 18). The average age of the studied contingent ≥ 18 was 50,2 years, median 51, (IQR 36-64). The prevalence of females (women to men = 3:1) was established. The most common drugs suspected of triggering/aggravating urticarial ADRs are those of class M (musculoskeletal system) plus class N (nervous system) – in 85 (58,2%) of the patients, followed by class C (cardiovascular system) – in 44 (30,2%) and class J (anti-infectives for systemic use) – in 20 (13,7%).

Simultaneous use of four or more drugs for systemic use is found in 46/146 (31,5%) of patients with suspected urticarial ADRs. As a first step in the management of urticarial ADRs the intake of the suspected etiologic agent/agents was stopped in all 146 hospitalized patients. Registered cardiovascular diseases were detected in 66/146 (45,2%) of the patients (**Table 1**) and 44/146 (30,1%) of patients declared using ACE inhibitors and/or beta-blockers (**Figure 1**) on a regular basis or occasionally. It was estimated that 36/44 patients or 24,6% of all patients in the study were on regular therapy with ACE inhibitors and/or beta-blockers. For this subset of patients, alternative therapy was recommended by the consulting cardiologist. Withdrawal of beta-blockers was done after gradually decreasing the dose and introducing a drug from another pharmacological group if the substitution was necessary. The Naranjo algorithm score evaluation of the causal link between urticaria and suspected cardiovascular drugs showed 2/44 (4,5%) “definitive”, 20/44 (45,5%) “possible”, 22/44 (50%) “probable” and no “doubtful” reactions (**Table 2**). Patients with acute urticarial ADRs were 30/44 (68,2%) and 14/44 (31,8%) were with chronic urticaria (**Figure 2**). There was no significant association ($p = 0,46$) between drug use and the type of urticaria. Systemic antihistamines were applied in all patients. They were used in combination with systemic corticosteroids in 79,5% (116/146) of the study population and in 81,8% (36/44) of urticarial ADRs to ACE inhibitors and/or beta-blockers. Systemic corticosteroids were administered parenterally or orally in single short courses of 1 to 7 days. Clinical recovery was achieved in 74/146 (51 %) of the patients with urticarial ADR and in 26/44 (59%) of patients with urticarial ADRs to cardiovascular drugs, while clinical improvement in 72/146 (49%) and 18/44 (41%) respectively. Long-term treatment with antihistamines is recommended, but for the time being the next treatment step of the international guidelines with biologicals is not possible.

Table 1. Concomitant cardiovascular diseases in patients with urticarial ADRs.

ICD-10 code	Patients	
	N	% of total 146
I11 - Hypertensive heart disease	56	38,4%
I25 - Chronic Ischemic Heart Disease	2	1,4%
I48 - Fibrillatio atriorum et fluctuatio atriorum	1	0,7%
I50 - Heart failure	2	1,4%
Other cardiovascular diseases	5	3,4%

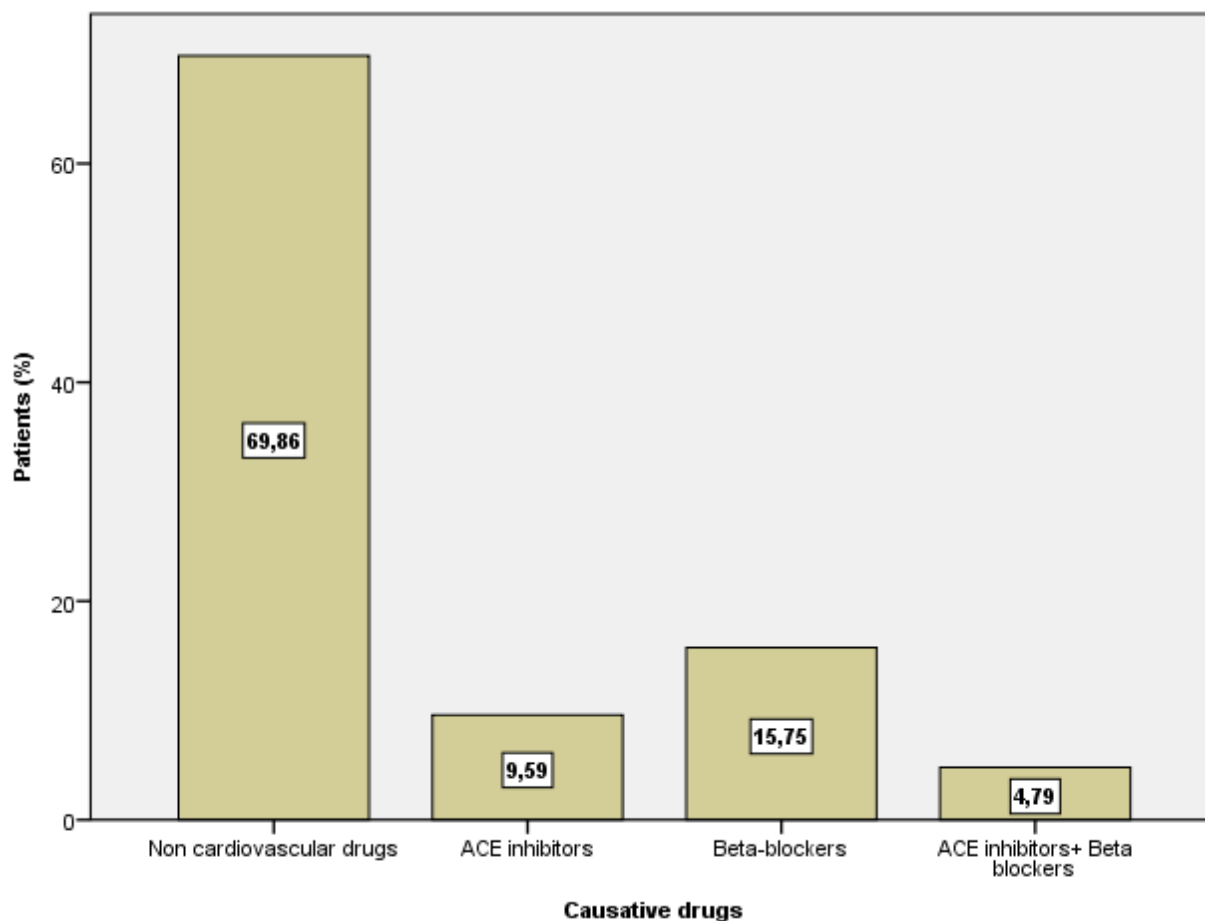


Figure 1. Distribution of patients with urticarial ADRs to ACE inhibitors and/or beta-blockers

Table 2. Drug causality assesment in patients with urticarial ADRs

Cardio-vascular drugs	Naranjo Algorithm			
	definitive	probable	possible	doubtful
ACE inhibitors	1	7	6	0
Beta-blockers	0	11	12	0
ACE inhibitors + Beta-blockers	1	2	4	0

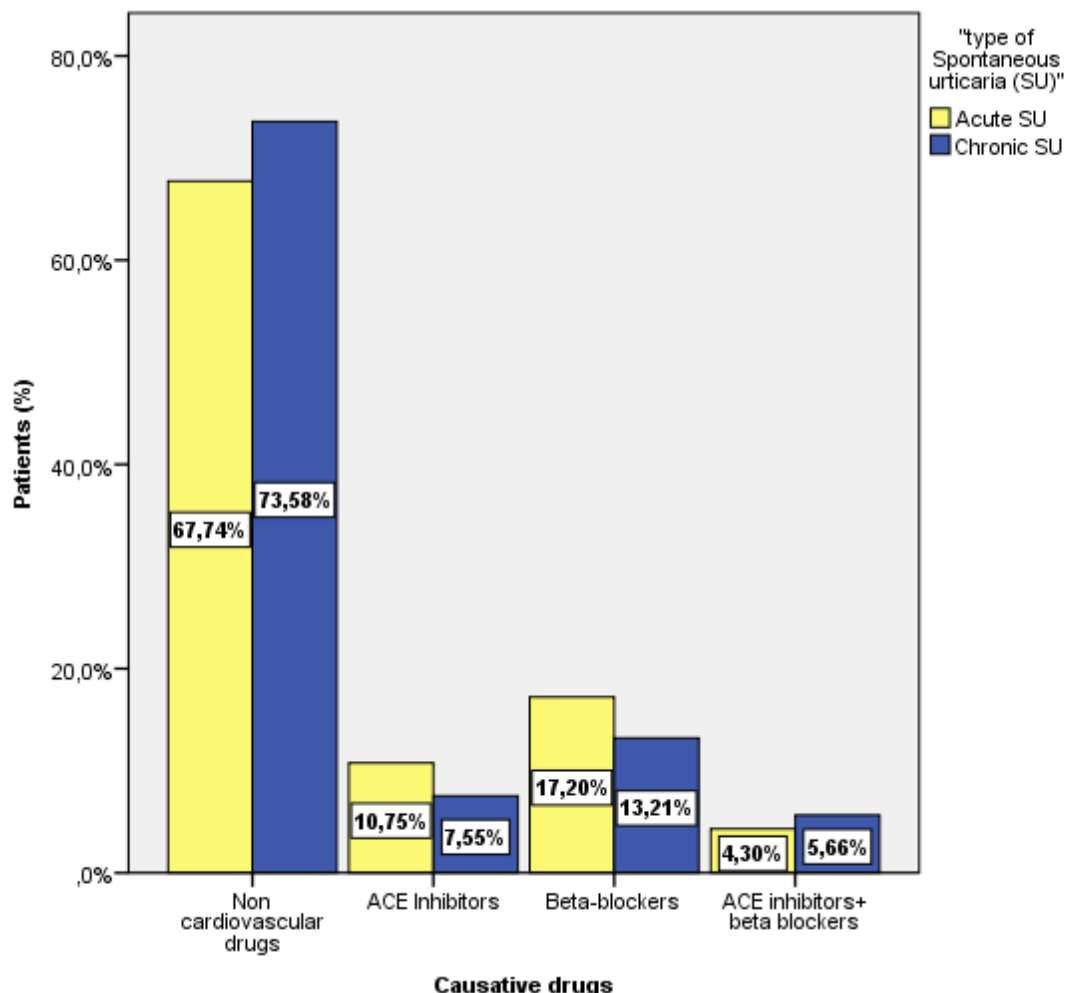


Figure 2. Distribution of patients with acute and chronic urticarial ADRs

DISCUSSION

Simultaneous use of four or more drugs for systemic use is found in a significant proportion (31,5%) of patients with suspected urticarial ADRs. Drugs for the treatment of diseases of the cardiovascular system (C) - ACE inhibitors and beta blockers are in second place in the study (30.2%). ACE inhibitors are a drug group with a higher incidence of inducing severe ADRs, pathogenetically they lead to an increase in plasma bradykinin due to ACE blockade and are therefore contraindicated in individuals with a history of angioedema with or without urticaria (10). Beta-blocker therapy can lead to cutaneous ADRs (11) and is a risk factor for allergic drug reactions (12, 13). Beta-blockers facilitate mediator release from mast cells and when anaphylactic reactions develop, although rare, they are severe, protracted and resistant to

treatment. The application of the Naranjo algorithm to evaluate the causal link between urticarial, and suspected cardiovascular drugs showed that most of the reactions were scored as “possible” or “probable”. Patients with urticarial ADRs to cardiovascular drugs and concomitant diseases require consultation with a cardiologist to prescribe proper alternative cardiac therapy and administration of systemic therapy regardless of culprit drug discontinuation.

CONCLUSION

Certain cardiovascular drugs such as ACE inhibitors and beta-blockers have the potential to trigger or aggravate, and/or prolong the course of urticaria. The need for drug therapy and hospitalization in severe cases of urticarial ADRs (acute or exacerbated chronic) to cardiovascular

drugs are some factors contributing to the overall socio-economic burden of ADRs.

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GANCHEVA T., et al.