ADVERSE DRUG REACTIONS INDUCED BY ANTIBACTERIALS FOR SYSTEMIC USE

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Abstract. The aim of the study was to assess the characteristics of adverse drug reactions (ADRs) induced by antibacterials for systemic use (AB) in patients hospitalized in the Clinic of Dermatology and Venereology in Stara Zagora (July 1999 - July 2007). ADRs were classified by type, severity and causality. AB (most frequently penicillins and quinolones) were the culprit drugs in 42 cases. Cutaneous reactions (73.8%) represented the most common clinical pattern. AB induced “type B” ADRs more commonly in comparison with other drugs (RR=1.74; 95% Cl: 1.38-2.19). Due to their frequent association with these non-predictable ADRs AB are considered high-risk drugs.
Key words: adverse drug reactions, antibacterials.

INTRODUCTION

An adverse drug reaction (ADR) is defined as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prophylaxis, diagnosis, or therapy or for modification of physiological function [12]. ADRs may be associated with transitory or permanent organ damage, including death. Data from large epidemiological studies on ADRs indicate that the incidence rate of ADRs in hospitalized patients may range from 1.5 to 35% [1,4].

A systematic review of prospective and retrospective studies on ADRs published from 1966 to 1999 worldwide shows that antibiotics are among the six classes of drugs that are more likely to cause ADRs [11]. Antibacterials and NSAIDs are the two classes of drugs that account for an important proportion of ADR reports received by the WHO Uppsala Monitoring Centre, thus indicating an intrinsic hazard linked to their use [8]. ADRs induced by antibacterials for systemic use (AB) may present with a wide clinical spectrum and variable severity.

The aim of the present study is to assess the clinical pattern, type and severity of ADRs induced by AB in patients hospitalized in a specialized dermatology department and to compare their characteristics with those of ADRs induced by other drug groups.

PATIENTS AND METHODS

The present investigation is a part of a prospective pharmacovigilance study carried out among patients admitted to the Clinic of Dermatology and Venereology in Stara Zagora from July 1999 to July 2007. Patients with readmissions to hospital within two consecutive months were excluded. For patients with suspected ADRs data were entered in a structured form, containing information on patient sociodemographic characteristics, primary diagnosis, concomitant diseases, history of previous ADRs and drug history covering the last three months preceding hospitalization (dosage regimen, route of administration and duration of therapy), clinical description of the adverse event (onset, course, outcome, systemic and topical treatment), laboratory tests, reviews of consultants depending on the character of concomitant diseases, a complete list of medications administered during hospitalization (dosage regimen, time of start of therapy and time of withdrawal) and the probable ADR-inducing drugs. Data were reviewed by a team consisting of dermatologists and a pharmacologist.

ADRs were defined according to WHO [12]. Drug-induced exacerbations of preexisting dermatoses were also included. Therapeutic failures were excluded. Patients with non-skin ADRs recognized during hospitalization in the department were consulted by respective specialists (cardiologists, endocrinologists, etc.). ADRs were classified by clinical manifestation using WHO-ART Adverse Reaction Terminology [3] and by type as "type A" if related to the pharmacological properties of the suspected drug and "type B" if otherwise [9]. 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 minor/no organ dysfunction). In cases with skin and mucosal involvement morphological criteria based on the definitions of severe skin reactions of Braun-Falco et al.

[2] were also applied. The relationship between the drug and the reaction was scored as "definite", "probable", "possible" and "doubtful" following the method of Naranjo et al. [7].

Drugs involved in ADRs were categorized according to the anatomical therapeutic chemical (ATC) classification.

The statistical analysis compared the characteristics of ADRs to AB with those of ADRs to other therapeutic groups. Variables considered for the study were ADR type, ADR organ involvement ("skin" or "non-skin") and the presence of hospitalization due to an ADR. Chi-square analysis was used with the results expressed as relative risk (RR) and 95% confidence intervals (Cl). A value of $p<0.05$ was considered statistically significant. All analyses were performed using SPSS for Windows version 9.0.

RESULTS

AB (ATC code J01) were found to be the offending drugs in 42 cases of ADRs occurring in 41 patients (age range: 6-79 years, mean age: 50.33 yrs ± 20.09). Elderly patients (65 years or older) were 11 (26.2%) and the female/male ratio was 2:1. History of a previous drug reaction was found in 9 (21.4 %) patients. In 22 cases (52.4%) an ADR to AB had been the cause of hospital admission. The organ/system classification of ADRs to AB revealed four main ADR groups: 31 cases (73.8%) of cutaneous reactions, 9 cases (21.4%) of gastrointestinal reactions, 1 case (2.4%) of resistance mechanism disorders and 1 case (2.4%) of vascular disorders. Cutaneous ADRs presented with a variety of clinical manifestations (tabiel), the prevalent clinical pattern being exanthematous. Rare nosological entities like acute generalized exanthematous pustulosis (AGEP) were diagnosed. Gastrointestinal ADRs manifested most commonly as acute drug-induced colitis with benign course (table 1). In all cases with drug-induced diarrhoea stool cultures were negative for Candida species and bacteria. The distribution of ADRs according to ADR type yielded 32 (76.2%) "type B" reactions and 10 (23.8%) "type A" reactions. ADR distribution according to severity showed that 21 cases (50%) were evaluated as "mild" and 20 cases (47.6%) - as "moderate". Only 1 severe ADR (urticaria and Quincke's edema due to azithromycin) was detected. Regarding imputability 35 ADRs were scored as "possible" and the remaining 7 as "probable". The distribution of ADRs according to AB therapeutic subgroups (figurel) shows a high incidence of ADRs due to penicillins (J01C) and quinolones (J01M). Single cases of ADRs induced by tetracyclines, aminoglycosides, lincosamides, etc., were verified (figurel). Overall 15 active principles causing ADRs were identified (table 1).

A total of 236 ADRs to drugs belonging to various therapeutic groups were detected during the study period, thus AB were responsible for a proportion equivalent to 17.8% of all ADRs, being the second ranking group of ADR-inducing drugs following glucocorticosteroids. The number of all cutaneous ADRs amounted to 136 (57.6%). The distribution of those ADRs according to their type revealed that type "A" reactions were 119 (50.4%) and type "B" reactions were 117 (49.6%). A total of 110 ADRs (46.6%) had been the cause of admission to hospital.

AB induced "type B" ADRs more commonly in comparison with other therapeutic groups (RR=1.74; 95% Cl: 1.38-2.19) and the organ more frequently affected was the skin (RR=1.37; 95% Cl: 1.09-1.70). The risk of hospital admission due to AB-induced ADRs was not significantly higher than the risk of admission because of ADRs caused by other groups of drugs (RR=1.15; 95% Cl: 0.83-1.60).

DISCUSSION

The study established four clinical presentation patterns of AB-induced ADRs among which cutaneous and gastroenterological were most common. Cutaneous reactions comprised a substantial part of all ADRs to AB not only because of the specificity of the investigated cohort of patients. Skin has been found to be the most frequently involved organ in reports of ADRs, concerning antibacterials in hospitalized and in out-patients [8, 10]. Various morphological manifestations of cutaneous ADRs to AB found in the study may explain the difficulties in diagnosing such ADRs as early as possible, and the need for hospitalization in many cases. The exanthematous reaction, also designated as "maculopapular rash" is known to be the commonest clinical presentation of cutaneous ADRs and this has been demonstrated by our study where these reactions were 67.7% of all skin disorders. The gastrointestinal tract is a commom site of ADRs. The majority of gastrointestinal AB-associated ADRs in this study presented as acute colitis, the principal etiologic agent being ciprofloxacin. Diarrhoea occurs in up to 30% of individuals treated by antimicrobial agents (Beaugerie, 1996). The overall incidence of gastrointestinal ADRs for quinolones ranges from 2 to 20% and these ADRs are thought to be due to either local irritation, a CNS effect, or both, in case pseudomembranous colitis is ruled out in patients with diarrhoea [5]. The prevalence of type "B" reactions can be explained with the high proportion of allergic cutaneous reactions.

As indicated by others [8, 10] beta-lactams are most frequently implicated in ADRs to AB. However, results from this study clearly show another subgroup of AB, quinolones, to be emerging along with beta-lactams as a leading cause of ADRs among antibacterial agents.

Althouh the study identified a low percentage of severe ADRs to AB, close monitoring of patients on antimicrobials is recommended since the administration of these agents is significantly associated with "type B" ADRs which are generally considered difficult to be predicted and prevented.

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Table 1. ADRs - clinical manifestation and etiologic agents

Organ/ system	Nosological entity/symptom	Cases n (%)	Etiologic agent (cases n)
Skin and appendages	Exanthematous reaction	21 (50.0%)	amoxicillin (7); midecamycin (6); ciprofloxacin (2); chloramphenicol (1); oxacillin (1); cefazolin (1); gentamycin (1); lincomycin (1); nitroxoline (1)
	Acute urticaria	3 (7.1%)	phenoxymethylpenicillin (1); co-trimoxazole (1); tinidazole (1)
	Ac. urticaria and Quincke's edema	1 (2.4%)	azithromycin
	Erythema multiforme	2 (4.8%)	amoxicillin (1); co-trimoxazole (1)
	Fixed drug eruption	1 (2.4%)	co-trimoxazole
	AGEP	1 (2.4 %)	amoxicillin
	Erythema nodosum	1 (2.4%)	co-trimoxazole
	Psoriasiform dermatitis	1 (2.4%)	doxycyclin
Gastro-intestinal	Nausea and vomiting	1 (2.4%)	ciprofloxacin
	Colitis	8 (19.0%)	ciprofloxacin (7); midecamycin (1)
Vascular	Allergic vasculitis	1 (2.4%)	co-trimoxazole
Resistance mechanism	Candidiasis	1 (2.4%)	cefadroxil

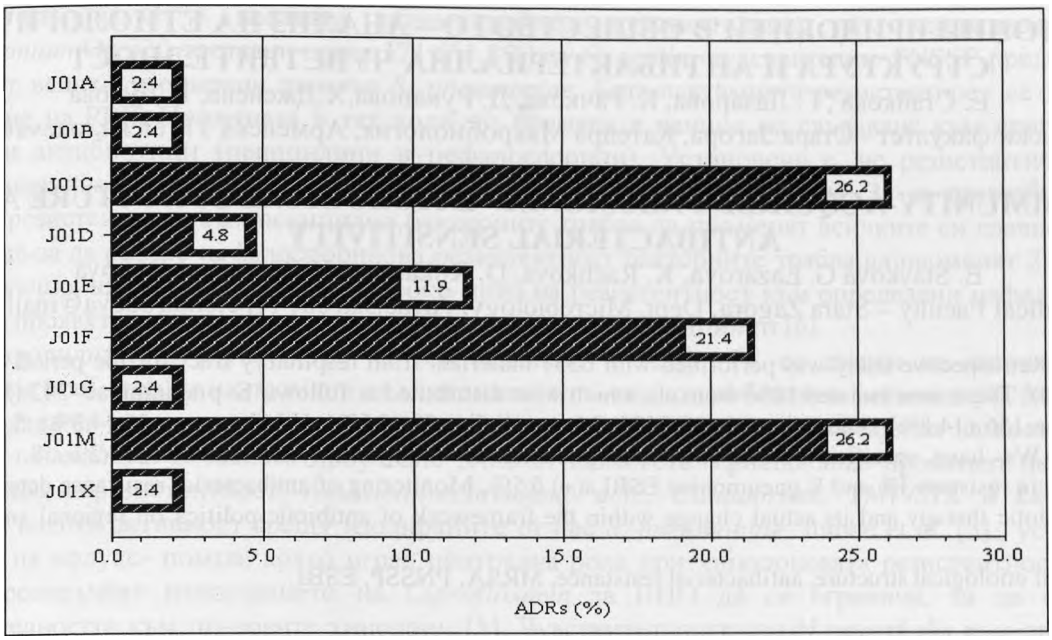

figure 1. Antibacterials for systemic use involved in ADRs (ATC classification)

Legend: J01A - Tetracyclines; J01B - Amphenicols; J01C - Penicillins; J01D - Other beta-lactams; J01E - Sulfonamides and trimethoprim; J01F - Macrolides and lincosamides; J01G - Aminoglycosides; J01M - Quinolones; J01X - Other antibacterials