SCREENING FOR ADVERSE DRUG INTERACTIONS IN DERMATOLOGY PATIENTS

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ABSTRACT
PURPOSE. To perform a screening for potential adverse drug interactions (DIs) in patients hospitalized in the Clinic of Dermatology and Venereology at the University Hospital in Stara Zagora using available electronic resources, and identify the factors associated with their occurrence.
PATIENTS AND METHODS. All consecutive inpatients admitted to the Clinic for the period March-September 2009 were screened for potential adverse DIs using an electronic drug interactions checker. Adverse DIs were classified into the following categories: "caution advised", "monitor/modify therapy", "avoid/use altenative" according to clinical management.
RESULTS. A total of 157 patients were included in the study. Adverse DIs (77 in number) were detected in 40 patients. DIs from the category "Monitor/modify" were the prevalent type. The development of adverse DIs was significantly associated with a higher number of drugs (p=0.0001) and old age (p=0.0001). In two cases the adverse DI led to a manifest adverse drug reaction.
DISCUSSION. Adverse DIs were found in a significant part of dermatology patients. The study confirmed the role of polypharmacy for DIs. Although adverse DIs rarely result in manifest ADRs, these ADRs can be of high clinical importance due to their severity thus justifying close monitoring for potential DIs.

Key words: drug interaction, adverse drug reaction

INTRODUCTION

Potential drug interactions (DIs) represent an important risk factor for the development of adverse drug reactions (1). A prospective study of adverse drug reactions (ADRs) from the UK showed that 16.6% of ADRs leading to hospital admission are associated with DIs (2). Pharmacological drug groups of particular significance for dermatologists considering their potential for DIs are "general antiinfectives" including antibacterials, antimycotics, antivirals and "antihistamines" (3). The high incidence of concomitant diseases in dermatology patients (4) presumes a high probability of potential DIs of drugs pertaining to various pharmacological groups

like cardiovascular drugs, drugs affecting the central nervous system etc.

The detection and clinico-pharmacological assessment of adverse DIs require the use of specialized informational resources and time. The difficulties in identifying adverse DIs has led to the development and introduction of various screening programmes which differ as to the quantity of information they give (5).

The aim of the present study is to perform a screening for potential adverse DIs of the medication prescribed to patients hospitalized in the Clinic of Dermatology and Venereology at the University Hospital in Stara Zagora using available electronic resources, and identify the factors associated with their occurrence in this cohort of patients.

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PATIENTS AND METHODS
Patient population
The investigation is a part of a prospective pharmacovigilance study carried out among patients admitted to the Clinic of Dermatology and Venereology at the University Hospital in Stara Zagora. All consecutive inpatients admitted to the Clinic for the period March-September 2009 were screened for potential adverse DIs. Information on systemic medication was collected on the day of admission and the medical charts were followed for further changes during the period of hospitalization. Data were recorded and checked for adverse DIs using a drug interactions checker (https://online.epocrates.com). For each patient additionally the following data were recorded: demographic characteristics, primary diagnosis, concomitant diseases, history of previous ADRs, alcohol abuse, smoking, failure of excretory organs.

ADRs resulting from adverse DIs were recorded in a structured form containing further information on drug history covering the last three months preceding hospitalization, clinical description of the adverse event, laboratory tests and reviews of consultants.

Definition of DIs
DIs were defined according to Ritter et al., (6) as the modification of the action of one drug by another as a result of one or more of three different kinds of mechanisms: pharmaceutical, pharmacodynamic and pharmacokinetic. DIs may be beneficial or harmful (adverse DIs). Adverse DIs were classified into the following categories: "caution advised", "monitor/modify therapy",

"avoid/use alternative" (https://online.epocrates.com) according to clinical management. The DI checker lists for each interaction the expected or possible effects of the drug combination, and the proposed mechanism of interaction.

Definition of ADRs
ADRs were defined according to WHO (7).
Statistical analysis. Descriptive statistics and Chi-square test were applied. Continuous variables were tested for normality using Kolmogorov-Smirnov test. Because the study values were not normally distributed, the results were presented as median and interquartile range (25th–75th percentile). The non-parametric Mann-Whitney U test was used to determine between-group differences. 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)
A total of 157 patients, 89 female and 68 male with an age range 1-86 years (median: 52; interquartile range: 36- 63) were included in the study. The main causes for hospitalization by primary diagnosis coded by the International Classification of Diseases - version 10 were infectious dermatoses "L00-L08" (36.3%) and eczema/dermatitis "L20-L30" (30.6%). Concomitant disease states were detected in 98 cases (62.4%). Cardiovascular diseases were diagnosed in 59 patients (37.6%) and were the most frequent type of concomitant diseases. Endocrine disorders in 19 patients (12.1%) were second ranking concomitant diseases following cardiovascular.

***Table 1.** Characteristics of the patient population*

Characteristic	Number of pts (%)	Pts with adverse DIs (%*)
Age above 65 years	36 (22.9%)	17 (42.5%)
Female	89 (56.7%)	25 (62.5%)
Drinker	11 (7.0%)	1 (2.5%)
Smoker	11 (7.0%)	2 (4.8%)
Previous ADR	20 (12.7 %)	9 (22.5%)
Excretory organ failure	1 (0.6%)	0 (0%)

pts – patients; % - percent of total; %*- percent of pts in the respective group

2. Adverse DIs (Table 2, Table 3)
Adverse DIs occurred in 40 patients - 15 male and 25 female with an age range 15-83 years (median: 61; interquartile range: 55.25 – 68.0).

The total number of detected adverse DIs was 77. In 19 cases the patient had more than one DI, either from one or from different DI types,

the maximum number of adverse DIs per patient being 6.

Adverse DIs marked as "Avoid/use alternative" included drugs from various groups - antiaggregants, anticoagulants, diuretics, antidiabetic agents, antiinfectives, etc. **(Table 3)**. They were result mainly of additive effects: increased risk of bleeding (aspirin-anticoagulants), increased risk of ototoxicity and nephrotoxicity (amikacin-furosemide), CNS depression (clonazepam-valproate). Antagonistic effects on glucose metabolism and lipids were found in DIs like bisoprolol-insulin and fenofibrate-hydrochlorothiazide.

DIs from the category "Monitor/modify" were the prevalent type of DIs **(Tables 2, 3)**.With only single exceptions all of them included some cardiovascular preparation (diuretic, beta-blocker, ACE-inhibitor, etc.). The expected ADR resulting from the most common DI in the group "ACE-inhibitor plus diuretic" (13 cases, 16.9% of all DIs) was hypotension. Hypokalemia was expected to develop from DIs like digoxin plus thiazides (3 cases), furosemide plus thiazides (4 cases), thiazides plus glucocorticosteroids (2 cases).

DIs necessitating caution **(Table 3)** included preferentially H_1-blockers, glucocorticosteroids, calcium-channel blockers. Combinations of various H_1-blockers (5 cases) due to additive effects increase the risk of CNS depression. What is more the same effect is expected from H_1-blockers interacting with other drugs suppressing CNS like clonidine (3 cases), benzodiazepine (1 case), etc. Generally CNS depression was due from 12.9% of all DIs.

Table 2. *Adverse DIs - distribution by type*

Adverse DI type	Number of pts (%)	Number of adverse DIs (%)
Caution advised	15 (37.5%)	18 (23.4%)
Monitor/modify therapy	26 (65.0%)	52 (67.5%)
Avoid/use alternative	7 (17.5%)	7 (9.1%)
Total	40	77

Eight patients had more than one type of adverse DI.

Table 3. *Adverse DIs - pairs of drugs and number of cases*

Avoid/ use altenative	fenofibrate-hydrochlorothiazide; aspirin-nadroparin; aspirin-clopidogrel; amikacin-furosemide (2); bisoprolol-insulin; clonazepam-valproate
Monitor/ modify	fenofibrate-glimepiride; glimepiride-hydrochlorothiazide; glimepiride-indapamide; glimepiride-metformin (2); hydrochlorothiazide-metformin; indapamide-metformin (3); hydrochlorothiazide-valsartan; indapamide-telmisartan (2); indapamide-lisinopril; indapamide-enalapril (3); indapamide-perindopril; furosemide-perindopril (2); atorvastatin-verapamil; lovastatin-verapamil; simvastatin-dilthiazem; clonidine-diltiazem; clonidine-verapamil (2); metoprolol- timolol; hydrochlorothiazide-fosinopril; hydrochlorothiazide-perindopril; hydrochlorothiazide-enalapril (2); bisoprolol-digoxin (3); digoxin-hydrochlorothiazide; digoxin-furosemide; digoxin-indapamide; furosemide-indapamide; furosemide-hydrochlorothiazide/triamteren (2); furosemide-hydrochlorothiazide; indapamide-salbutamol; ketoconazole-verapamil; amiodarone-hydrochlorothiazide; enalapril-triamterene; perindopril-triamteren-spironolacton; amikacin-cefuroxime; digoxin-tetracycline; metformin-methylprednisolone; metformin-ranitidine; hydrochlorothiazide-methylprednisolone (2)
Caution advised	clonidine-cyproheptadine (3); cyproheptadine-levocetirizine (4); aspirin-verapamil (2); ranitidine-verapamil; clemastine-cyproheptadine; aspirin-methylprednisolone; bisoprolol-salbutamol; prednisolone-verapamil; fluconazole-methylprednisolone; clonazepam-cyproheptadine; isosorbide dinitrate-verapamil; hydroxizine-maprotiline

Pharmacodynamic mechanisms were involved in most of the detected adverse DIs. Additive effects explain the increased risk of bradycardia and AV-block (bisoprolol-digoxin), of central nervous system depression (cyproheptadine-levocetirizine, clonazepam-cyproheptadine, clonidine-cyproheptadine, etc) of increased risk of bleeding (aspirin-clopidogrel). Synergistic effects are the reason for increased risk of hypotension with various combinations of antihypertensive drugs like ACE-inhibitors or angiotensin receptor blockers plus diuretics (indapamide-lisinopril, indapamide-telmisartan, etc). Antagonistic effects were found in some adverse DIs (bisoprolol-salbutamol, indapamide-metformin, fenofibrate-hydrochlorothiazide).

Pharmacokinetic mechanism of adverse DI included: 1) inhibition of hepatic metabolism and consequent increase of drug levels and risk of adverse effects of glucocorticosteroids (fluconazole-methylprednisolone, dehydrocortisone-verapamil), of antilipemic agents (atorvastatin-verapamil, lovastatin-verapamil, simvastatin-dilthiazem), of glimepiride (fenofibrate-glimepiride) and of verapamil (ketoconazole-verapamil); 2)

inhibition of digoxin inactivation by gastrointestinal flora (digoxin-tetracycline); 3) decreased renal excretion of drugs by competition for active tubular transport (metformin-ranitidine, ranitidine-verapamil).

In some cases the underlying mechanism of adverse DIs remains unknown - increased bleeding time due the combination aspirin-verapamil, increased risk of absence seizures when receiving clonazepam plus valproate.

The patients with adverse DIs received from 2 to 10 drugs per patient, median 6.5 (interquartile range 5.0 - 8.0) Patients without adverse DIs had median drug number per patient 2.0 (interquartile range 1.0 - 4.0) and received from 0 to 7 drugs per patient **(fig.1)**

The development of adverse DIs was significantly associated with a higher number of drugs (p=0.0001) and old age (p=0.0001). The clinico-pharmacological risk factors female sex, excretory organ failure, smoking and alcohol consumption were not linked to adverse DIs. The history of previous drug reaction was associated with adverse DIs (χ=4.237; p=0.04).
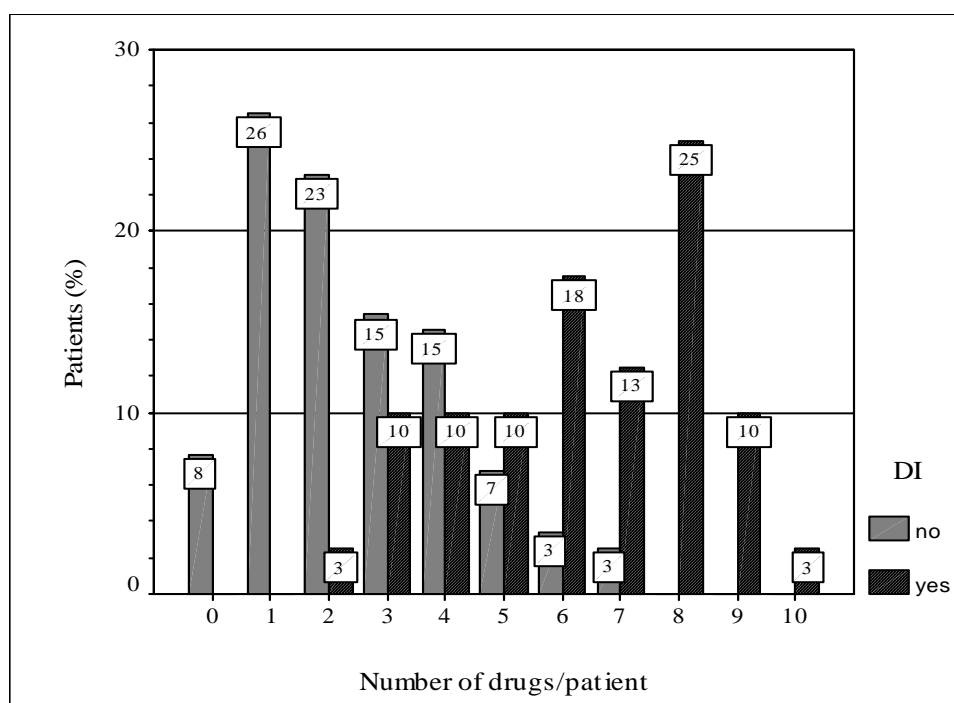

Fig. 1 Distribution of patients according to the number of drugs per patient

3. ADRs

For the six-month study period 6 ADRs were recorded. In two of these cases an underlying adverse DI was identified: 1) hypotension in a 70-year old female with arterial hypertension and atrial flutter receiving a combination of ACE-inhibitor (enalapril, Enap® 40 mg daily), beta-blocker (metoprolol, Betaloc Zok® 50 mg daily) and diuretic (indapamide, Rawel SR® 1.5 mg daily); 2) melena in a 68-year old male with a history of chronic gastritis and myocardial infarction on medication with a beta-blocker, ACE-inhibitor, antilipemic agent, clopidogrel and aspirin who had received a 4-day NSAID treatment for radiculitis and a 2-day parenteral methylprednisolone application 120 mg daily for drug-induced urticaria prior to hospitalization.

DISCUSSION

Adverse DIs were found in a significant part of the patients hospitalized in the Clinic of Dermatology - 40 patients that constituted 25.5% of the study population. Other similar studies using various computerized screening methods have identified much higher proportions of patients with DIs - 49,7 % in the study of Cruciol-Souza and Thomson (8), 66 % in the study of Blix et al. (9). However in these investigations specialized clinico-pharmacological software for detecting potential DIs was used.

Most common were the DIs requiring careful monitoring of the prescribed medications or modification of the dosage regimen. The prevalent drugs in this category were cardiovascular drugs which were combined for therapeutic advantage (ACE-inhibitor plus diuretic, combination of 2 diuretics, etc.). One of these DIs resulted in a clinically overt ADR presented as hypotension which required withdrawal of the diuretic and a lower dosage of the ACE-inhibitor. The combination enalapril-indapamide increases the risk of hypotension due to synergistic effects.

Second ranking in incidence were mild DIs requiring caution in drug use. These DIs are typical for this cohort of patients since they included drug classes like H_1-blockers and glucocorticosteroids which are commonly prescribed in dermatology.

Adverse DIs marked as "Avoid/use alternative" were 9.1% of all DIs. In one case the DI including high risk drugs such as aspirin and clopidogrel due to additive effects led to a clinically manifest severe ADR - melena which was associated with additional treatment and prolongation of hospitalization. High doses of methylprednisolone and a NSAID have also contributed to the development of gastrointestinal bleeding in this case. Although adverse DIs rarely result in manifest ADRs (10), these ADRs can be of high clinical importance (2, 11) due to their severity thus justifying close monitoring of medications for potential DIs.

The study confirmed the role of polypharmacy for DIs. High morbidity and number of drugs in the elderly explain the association of DIs with old age. The chronicity of concomitant cardiovascular diseases, and the use of high-risk drugs like diuretics for their treatment may be the reason why DIs were significantly associated with the factor "history of previous ADR".

Identifying clinically relevant adverse DIs as a risk factor for the development of ADRs and appropriately intervening in patients` therapeutic management is a method of preventing ADRs in hospitalized patients. This can be achieved through the joined efforts of clinicians and clinical pharmacologists. Computerized screening is essential in quickly idendifying and controlling DIs as a risk factor for ADRs and thus assuring the safe use of drugs.

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