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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Actual drug–drug interactions in elderly patients discharged from internal medicine clinic: a prospective observational study

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Abstract
Purpose The aim of the study was to evaluate the incidence and type of actual drug–drug interactions (DDIs) that result in adverse drug reactions (ADRs) or diminished therapeutic effect in elderly patients within 30 days of discharge from an internal medicine clinic.
Methods A prospective observational study was conducted at the Internal Medicine Clinic of University Hospital Dubrava, Zagreb, Croatia, between October and December 2011. Patients aged ≥65 years discharged from the Internal Medicine Clinic during the study period with a prescription for two or more medications were eligible for inclusion in the study. A total of 222 patients were ultimately enrolled in the study. For each patient, potential DDIs were identified using Lexi-Interact software. The follow-up visit was scheduled approximately 30 days after discharge. Causality between DDIs and ADRs or diminished therapeutic effect of drugs was assessed by two independent clinicians.
Results Potential DDIs were identified in 190 (85.6 %) patients. Actual DDIs were detected in 21 (9.5 %) patients. In 19 patients, DDIs resulted in an ADR. Diminished therapeutic effect resulting from DDIs was detected in two patients. Angiotensin-converting enzyme inhibitors were the drug class most frequently associated with DDI-related ADRs.
Conclusions A significant incidence of actual DDIs suggests that DDIs play an important role in patient safety. Drug therapy should be initiated if absolutely necessary, and the number of drugs used to treat elderly patients should be minimized to reduce the incidence of DDI-related adverse patient outcomes.

Keywords Adverse drug reactions · Croatia · Diminished therapeutic effect · Drug–drug interactions · Elderly patients

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Introduction

A drug–drug interaction (DDI) occurs when the effects of one drug are modified by the prior or concurrent administration of another drug [1]. They may arise from alteration of the absorption, distribution, biotransformation or elimination of one drug by another, or from a combination of their pharmacodynamic effects. Although some DDIs may be used for therapeutic benefit, interactions may also increase the effects of drugs, leading to an increased frequency and severity of adverse drug reactions (ADRs) or, conversely, they may inhibit the effect of a drug, leading to a diminished therapeutic benefit [2].

Age-related physiological changes and altered pharmacokinetic and pharmacodynamic consequences place elderly patients (aged ≥65 years) at high risk for DDI-related adverse events [3, 4]. This risk can be influenced by many factors, such as chronic diseases, polypharmacy, genetics and

lifestyle. Many studies have measured the prevalence of potential DDIs in elderly patients. Bjorkman et al. found that 46 % of elderly outpatients from six European countries had at least one potential DDI [5]. In another study, the authors estimated that 4.8 % of hospital admissions in the elderly were caused by DDIs [6]. In recent decades, there has been a sharp increase in the prevalence of potential DDIs in elderly patients [7].

Studies investigating potential DDIs should be distinguished from those assessing actual interactions resulting in adverse patient outcomes (e.g. ADRs, diminished therapeutic effect). Since a DDI may not result in adverse outcome, previous studies evaluating the prevalence of potential DDIs may have overestimated the clinical significance of the interactions [8]. Thus, studies focusing on DDIs that led to adverse patient outcomes may have estimated the real risk of DDIs more accurately [2]. However, limited data are available on DDIs leading to adverse outcomes. Previous studies evaluating actual DDIs mainly focused on ADRs and did not analyze the diminished therapeutic effect caused by DDIs. According to data obtained from the Spontaneous Reporting Database of Pharmacovigilance Department of Croatian Agency for Medical Products and Medical Devices, 7.8 % of reported ADRs were caused by DDIs [9], with more than half of these being serious. Although DDIs cause only a small proportion of ADRs, these ADRs are often predictable and therefore avoidable [10].

The aim of our study was to evaluate the incidence and type of actual DDIs resulting in ADRs or diminished therapeutic effect in elderly patients within 30 days of discharge from an internal medicine clinic.

Methods

Study design and setting

This was a prospective, observational study conducted at the Internal Medicine Clinic of University Hospital Dubrava, Zagreb, Croatia, between October and December 2011. The hospital is a 600-bed teaching institution providing care to the population of approximately 250,000 inhabitants. The study protocol was approved by the Hospital's Ethics Committee. All patients included in the study provided written informed consent.

Study population

Patients aged ≥65 years who were discharged from the Internal Medicine Clinic during the study period with a prescription for two or more medications were eligible for enrolment in the study. Exclusion criteria were cognitive disorders that would interfere with the patient's participation, terminal illness with a life expectancy of <1 month or an inability to be followed-up.

Data collection and analysis of potential DDIs

One of the investigators (clinical pharmacist) collected data from medical records on patient age, gender, prescribed medications and discharge diagnoses within 24 h before hospital discharge. The data were entered into an electronic database developed by the investigators to use in the study.

Patients who met none of the exclusion criteria and who were prescribed with two or more drugs during a minimum 5-day overlap in therapy [11] had their current medical record entered into the Lexi-Interact software [12] to search for potential DDIs. The software categorized each identified potential DDI according to clinical significance level as follows: (A) no known interaction; (B) specified agents may interact, but there is little or no evidence for clinical concern; (C) the specified agents may interact in a clinically significant manner and monitoring of therapy is suggested; (D) the two medications may interact in a clinically significant manner and modification of therapy is suggested; (X) contraindicated combination.

We considered potential interactions of level C D, and X to be clinically significant. Patients with potential X-level interaction were excluded from the study and the attending physician was alerted.

Follow-up visit

The follow-up visit was scheduled approximately 30 days after discharge (±5 days). For patients who were not able to come to the hospital, the visit was arranged at their home. During the visit, a physician specialist in clinical pharmacology assessed the patients for the occurrence of actual DDIs, including manifestation of any new or worsening symptoms. Patients were asked if there had been any unscheduled physician visits, visits to the emergency department (ED) or readmission to hospital after the discharge from the hospital. If any of these clinical events was reported, supporting medical documentation was requested to determine the cause of the event. The computerized hospital database was accessed and patients' medical records were reviewed. Medical records in the hospital database are filled out by hospital physicians and contain data on hospitalizations, ED visits, and physician visits. Laboratory test results and radiological and other findings are also stored in the database.

The Naranjo ADR probability scale was used to assess the probability of an ADR being the cause of new symptoms, unscheduled physician visits, ED visits, hospital readmissions or death [13]. The 'Possible' rating on the Naranjo scale was considered the lower limit of acceptance for an ADR [14].

The physician wrote a case summary for each patient with suspected ADR, reporting on the worsening of symptoms, unscheduled visit(s) to the physician and/or ED readmission to hospital or death. To create the case summary, the information from the interview was combined with that obtained from patient's medical record. All case summaries were independently reviewed by two physicians, one a specialist in internal medicine and the other a specialist in clinical pharmacology. These reviewers were also given a list of potential DDIs for each patient. They ultimately determined whether the patient's adverse outcome was caused by DDIs. If both reviewers determined that the adverse outcome was caused by a DDI, that interaction was classified as an actual DDI. If both reviewers found no evidence that outcome was caused by a DDI, it was rejected as a cause of adverse outcome. If there was a disagreement, the case was discussed until consensus was achieved. If consensus could not be reached, a third reviewer (specialist in clinical pharmacology) rated the event independently to determine the final rating [15].

Statistical analysis

Standard descriptive statistics were used to describe the study population, drug utilization and number of identified DDIs. The median with range was calculated for continuous variables. Proportions were calculated for categorical variables. All tabulations and statistical analyses were performed using Statistics for Windows, vers. 8.0 (StatSoft, Inc., Tulsa, OK).

Results

In total, 222 patients were enrolled in the study, of whom 56.3 % were female. The median age was 72 (range 65–91) years, and the median number of diagnoses was four (range 1–8). The most frequent diagnoses were arterial hypertension (72.1 %) and diabetes mellitus (42.3 %). The median number of prescribed drugs was six (range 2–14) (Table 1).

Potential DDIs were identified in 190 (85.6 %) patients. The median number of potential DDIs per patient was 5 (range 0–28). We detected 144 different drug pairs that could result in a DDI. A total of 120 and 24 potential interactions had level-C and level-D clinical significance. No level-X interactions were detected. The most frequent potential DDIs are summarized in Table 2.

Actual DDIs were detected in 21 (9.5 %) patients. In 19 patients, DDIs resulted in a possible ADR. Diminished therapeutic effect resulting from DDIs was detected in two patients (Table 3). We detected 12 different drug pairs that led to actual DDIs. A total of nine actual DDIs were assessed to have level-C clinical significance, and three actual DDIs had level-D clinical significance. Angiotensin-converting enzyme inhibitors (ACEIs) represented the drug class most frequently associated with actual DDIs. Two patients died during the follow-up period, but their deaths were not linked with possible ADRs or DDIs.

Discussion

Prospective, population-based studies are very useful in evaluating the consequences of DDIs in clinical practice. Our literature search found no similar prospective, observational study that evaluated actual DDIs in elderly patients discharged from an internal medicine clinic. This information may help clinicians to assess the risk in specific patients and guide therapeutic decision-making. We found a significant incidence of actual DDIs, suggesting that DDIs play an important role in patient safety. Most of the actual DDIs resulted in ADRs and involved ACEIs. The incidence of potential DDIs in our study was higher compared to published data. Studies that assessed potential DDIs in medical patients reported the incidence of interactions to be between 25 and 63 % [16–20]. These differences could be attributed to different inclusion criteria and methodology. The same studies identified cardiovascular drugs as the main drugs involved in potential DDIs, which corresponds to our results.

As could have been expected, the incidence of actual DDIs was lower than the incidence of potential DDIs. The incidence of actual DDIs detected in our study was similar to that published in prospective studies evaluating actual DDIs in elderly outpatients. In a recent study by Obreli-Neto et al., the incidence of DDI-related ADRs in elderly outpatients with at least one potential DDI was 6.5 % [21]. Glassman et al. analyzed ADRs in a population of 913 patients in the ambulatory care setting and found that DDIs caused ADRs in 10.3 % of patients [22]. Other studies in elderly patients have reported that 5–15 % patients suffered clinically significant ADRs due to DDIs [23, 24]. In these studies, the incidence of actual DDIs might have been underestimated because DDIs resulting in diminished therapeutic effect were not assessed.

In our study, the four most common drug combinations with a potential for interaction included ACEIs. Many other studies have also detected ACEIs as a drug class that most frequently caused potential DDIs [25, 26]. In addition to potential DDIs, ACEIs were the most frequent drugs involved in actual DDIs in our study. Age-related changes in renal function make elderly patients susceptible to the nephrotoxic effect of ACEIs, especially if administered concomitantly with other drugs that can influence renal function (e.g. furosemide) [27]. Also, altered renal function puts elderly patients at great risk of medication-induced alterations in potassium homeostasis [28]. The interaction between ACEIs and other potassium concentration-increasing drugs

Table 1 Demographic and clinical characteristics of study patients

Characteristic	Number of patients
Total number of patients	222
Gender, *n* (%)	
Male	97 (43.7)
Female	125 (56.3)
Median age, years (minimum–maximum)	72 (65–91)
Median number of diagnoses (minimum-maximum)	4 (1–8)
Median number of prescribed drugs (minimum–maximum)	6 (2–14)
The most frequent diagnoses, *n* (%)	
Arterial hypertension	160 (72.1)
Diabetes mellitus	94 (42.3)
Ischemic hearth disease	79 (35.6)
Hearth failure	64 (28.8)
Atrial fibrillation	51 (23.0)
Hyperlipidemia	46 (20.7)
The most frequently prescribed drug classes and individual drugs, *n* (%)	
ACEIs	140 (63.1)
Acetylsalicylic acid	106 (47.7)
Beta blockers	102 (45.9)
Furosemide	99 (44.6)
Statins	94 (42.3)
CCBs	84 (37.8)
Potassium chloride	78 (35.1)
PPIs	76 (34.2)
Thiazides	70 (31.5)
Insulin	54 (24.3)
Warfarin	46 (20.7)

ACEI Angiotensin-converting enzyme inhibitor; CCB calcium channel blocker; PPI proton pump inhibitor

is one of the most frequent DDIs in hospitalized and non-hospitalized patients [21, 29, 30].

Age-related changes in the gastrointestinal system increase the sensitivity of this system to the standard concentrations of drugs and account for the increased frequency of ADRs in the elderly [31]. The second most frequent actual DDI in our study involved a proton pump inhibitor (PPI) and iron salts. This interaction can result in gastrointestinal ADRs or a diminished therapeutic effect of iron salts. Previous studies that evaluated actual DDIs did not identify this interaction as being clinically significant [2, 21, 32]. On the other hand, there are case reports that describe anemic patients who failed to respond to oral iron treatment while taking a PPI, but whose iron status improved after the PPI had been withdrawn from the therapeutic regimen [33]. Furthermore, none of the patients in our study who received iron salts without PPI developed ADRs, indicating the clinical importance of interaction between iron salts and PPI in elderly patients.

Warfarin is known for its numerous drug and dietary interactions, which can lead to life-threatening ADRs [34]. However, we found only two patients with bleeding complications due to concomitant therapy with warfarin and acetylsalicylic acid. In the previous studies, this drug combination was the most frequent cause of ADRs [4, 21, 35]. The difference could be attributed to different practices in prescribing and pharmacotherapy monitoring in our setting.

Potassium chloride is inherently irritating to the gastric and esophageal mucosa because of its corrosive nature [36]. Anticholinergics (e.g. inhaled ipratropium) may impair gastric emptying and prolong the contact between potassium chloride and the gastrointestinal mucosa, leading to an increased frequency and severity of gastrointestinal lesions [37, 38]. Older persons are predisposed to drug-induced gastric damage as a result of age-related changes in the gastrointestinal system [39]. Thus, solid oral dosage forms of potassium chloride should be avoided in elderly patients and those on drugs with anticholinergic effects. In these patients, liquid or effervescent potassium preparations are possible alternatives [37]. In our study, two patients receiving concomitant therapy with inhaled ipratropium and potassium chloride developed gastrointestinal ADRs, despite the administration of potassium chloride in the form of oral solution.

One of our patients who received concomitant therapy with calcium channel blockers (CCBs) and clopidogrel

Table 2 The most frequent potential drug–drug interactions

Most frequent potential drug–drug interactions	Number of patients (%)	Description of interaction[a]
Drugs with potential for interactions of level-C clinical significance		
ACEIs + diuretics (furosemide or thiazides)	78 (35.1)	Diuretics may enhance the hypotensive and nephrotoxic effect of ACEIs
ACEIs + beta blockers	53 (23.9)	Additive or synergistic hypotensive effects may result from concomitant use of these agents
ACEIs + potassium chloride	46 (20.7)	Potassium salts may enhance the hyperkalemic effect of ACEIs
ACEIs + CCBs	36 (16.2)	Additive or synergistic hypotensive effects may result from concomitant use of these agents
Beta blockers + diuretics	34 (15.3)	Additive or synergistic hypotensive effects may result from concomitant use of these agents
Beta blockers + CCBs	31 (14.0)	Additive or synergistic hypotensive effects may result from concomitant use of these agents
ACEIs + nitrates	28 (12.6)	Additive or synergistic hypotensive effects may result from concomitant use of these agents
Beta blockers + nitrates	26 (11.7)	Additive or synergistic hypotensive effects may result from concomitant use of these agents
Drugs with potential for interactions with level-D clinical significance		
Warfarin + acetylsalicylic acid	11 (4.9)	Concomitant therapy with acetylsalicylic acid and oral anticoagulants has been shown to increase the risk of bleeding
ACEIs + allopurinol	10 (4.5)	ACEIs may enhance the potential for allergic or hypersensitivity reactions to allopurinol
Warfarin + levothyroxine	8 (3.6)	Thyroid products may enhance the anticoagulant effect of vitamin K antagonists
Warfarin + propylthiouracil	5 (2.3)	Antithyroid agents may diminish the anticoagulant effect of vitamin K antagonists
Spironolactone + potassium chloride	4 (1.8)	Potassium salts may enhance the hyperkalemic effect of potassium-sparing diuretics
Beta blockers + alpha blockers	4 (1.8)	Beta blockers may enhance the orthostatic effect of alpha blockers

Clinical signficance level: level C, the specified agents may interact in a clinically significant manner and monitoring of therapy is suggested; level D, the two medications may interact in a clinically significant manner and modification of therapy is suggested

[a] Description of interaction was obtained using Lexi-Interact software [12]

developed myocardial reinfarction during the follow-up period. Siller-Matula et al. assessed whether CCBs altered the effect of clopidogrel on platelets in patients undergoing percutaneous coronary intervention [40]. These authors found that 25 % of patients taking a CCB experienced the primary composite clinical endpoint of death from cardiovascular causes, nonfatal myocardial infarction, stent thrombosis or revascularization versus only 8 % of those not taking a CCB. The suggested mechanism of interaction was CCB-mediated inhibition of the metabolic activation of clopidogrel. Although this finding has not been confirmed [41], the clinical significance of this DDI can not be completely excluded.

Sometimes in clinical practice medical practitioners use DDIs to reach therapeutic goals (e.g. in the treatment of arterial hypertension). In this study we tried to analyze all DDIs that can result in ADRs. Since drug combinations that are normally prescribed together can cause ADRs if clinical and laboratory monitoring of patients is insufficient, we included these in the study.

The prospective design of our study and the combination of patient interview together with the assessment of medical record and laboratory tests enabled us to obtain reliable clinical evidence of actual DDIs. The most important advantage of our study is its focus on DDIs that result in a diminished therapeutic effect of drugs.

This study has several limitations. Previous studies have shown that there is a considerable variability between various sources available to analyze potential DDIs in terms of their accuracy of detection and classification of DDIs [42, 43]. This is especially relevant for DDIs that are considered to be of the highest clinical significance [44]. In our study we used a single source to analyze potential DDIs. This could have resulted in a higher incidence of potential DDIs compared to those reported in studies which used several sources to detect DDIs. It is also possible that some potential DDIs, which could have evolved to actual DDIs, were not detected. We used Lexi-Interact software to detect potential DDIs. Several studies have reviewed drug interaction screening

Table 3 Actual drug–drug interactions resulting in possible adverse drug reactions or diminished therapeutic effect within 30 days of hospital discharge

Interacting drugs	Number of patients with actual/potential DDIs	Clinical significance level	Description of cases
ACEIs and furosemide	4/48	C	Furosemide may enhance the nephrotoxic effect of ACEIs. Asymptomatic increase in serum creatinine level was detected in 4 patients during a routine laboratory monitoring of therapy. Patients were treated with dosage adjustments of diuretic and ACEIs
ACEIs and potassium chloride	3/46	C	Potassium chloride may enhance the hyperkalemic effect of ACEIs. Asymptomatic hyperkalemia was detected in 2 patients during routine laboratory monitoring of therapy. Patients were treated with discontinuation of potassium chloride and ACEIs dose adjustment. The third patient was hospitalized for cardiac arrhythmia caused by hyperkalemia.
PPIs and iron salts	3/4	C	PPIs may decrease the absorption of iron salts leading to increased risk of gastrointestinal ADRs and reduced efficacy of oral iron preparations. Two patients experienced abdominal pain and constipation. One of them stopped therapy with iron salts without consulting a physician. The other patient took a laxative, which was prescribed by general practitioner. One patient with sideropenic anemia was hospitalized because of failure of therapy with oral iron preparations
Warfarin and acetylsalicylic acid	2/11	D	Concomitant therapy with acetylsalicylic acid and oral anticoagulants can increase the risk of bleeding. One patient was hospitalized because of bleeding stomach ulcer. The other patient developed epistaxis, which stopped spontaneously
Inhaled ipratropium and potassium chloride	2/3	D	Anticholinergic agents enhance the ulcerogenic effect of potassium chloride. Two patient experienced epigastric pain. One of them visited general practitioner and was proscribed an antacid. The other patient stopped therapy with potassium chloride without consulting a physician
CCBs and clopidogrel	1/2	C	CCBs may diminish the therapeutic effect of clopidogrel. One patient was hospitalized for myocardial reinfarction. Previous myocardial infarction had been treated with percutaneous transluminal coronary angioplasty with placement of drug-eluting stent
Beta blockers and alpha blockers	1/4	D	Beta blockers enhance the orthostatic effect of alpha blockers. One patient experienced hypotension and stopped antihypertensive therapy, without consulting a physician
Beta blockers and CCBs	1/31	C	Synergistic hypotensive effects may result from concomitant use of beta blockers and CCBs. One patient experienced hypotension. He consulted general practitioner who stopped therapy with CCB
Acetylsalicylic acid and clopidogrel	1/19	C	Combined therapy with two antiplatelet agents may increase risk of bleeding. One patient developed bruises on his hands after minimal trauma. The bruises resolved spontaneously
Furosemide and beta2-agonist	1/5	C	Beta2-agonists enhance the hypokalemic effect of loop diuretics. One patient visited ED because of asthma exacerbation. Laboratory testing reviled hypokalemia and potassium salt was introduced in therapy
Beta blockers and sulfonylurea	1/16	C	Beta-blockers enhanced the hypoglycemic effect of sulfonylureas. One patient visited ED because of hypoglicemia. The dose of sulfonylurea was reduced
Acetylsalicylic acid and alendronate	1/1	C	Acetylsalicylic acid increases the incidence of upper gastrointestinal ADRs in patients receiving concomitant therapy with alendronate. One patient visited general practitioner because of heartburn and therapy with a PPI was introduced.

DDI, Drug–drug interaction; ADR, adverse drug reaction; ED, emergency department

programs [45, 46], and Lexi-Interact, with its high sensitivity (97–100 %) and high specificity (80–90 %) received a quite favorable rating. A further limitation of our study is a relatively short follow-up period. A longer follow-up after discharge is needed to assess the outcome of DDIs with a delayed onset. Since the cardiovascular drugs were the most frequently used drug class in our study, we considered the follow-up period of 1 month to be long enough for the development of actual DDIs.

Conclusion

The very large difference between the incidence of potential DDIs and actual DDIs observed in our patient population suggests that adverse outcomes resulting from DDIs in the majority of patients can be prevented with an appropriate monitoring plan and dosage adjustments of one or both interacting agents. Many DDIs resulting in adverse patient outcome were enhanced by age-related physiologic changes. Therefore, drug therapy should be initiated only when absolutely necessary for the achievement of well-defined goals, and the number of drugs used to treat elderly patients should be minimized to reduce the incidence of DDI-related adverse outcomes.

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