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RESEARCH ARTICLE

# The incidence of potential drug–drug interactions in elderly patients with arterial hypertension

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**Abstract** *Objective* To assess the incidence and type of potential, clinically significant drug–drug interactions in elderly outpatients with arterial hypertension. *Setting* Three community pharmacies in Croatia. *Method* Eligible patients were aged 65 or older, treated for arterial hypertension and received 2 or more drugs. Potential interactions were identified by Lexi-Interact software. The software categorized each potential interaction according to clinical significance in five groups: (A) No known interaction; (B) Specified agents may interact, but there is little to no evidence of clinical concern; (C) Specified agents may interact in a clinically significant manner. Monitoring therapy is suggested; (D) The two medications may interact in a clinically significant manner. Modification of therapy is suggested; (X) Contraindicated combination. Interactions of level C, D and X were considered clinically significant. *Main outcome measure* The incidence and type of potential drug–drug interactions. *Results* There were 265 patients included in the study. Potential, clinically significant drug interactions were identified in 240 (90.6%) patients, out of which 97.9% had interactions with clinical significance C, 20.4% D, and 0.8% X. The median number of drug interactions per patient was 4. We identified 215 drug combinations with the potential to cause clinically significant interaction, out of which 83.3% had clinical significance C, 16.3% clinical significance D, and 0.4% clinical significance X. *Conclusion* Drug–drug interactions are common in elderly hypertensive patients. Computer-based screening could help pharmacists and physicians to recognize potential, clinically significant interactions.

**Keywords** Arterial hypertension · Croatia · Drug–drug interactions · Elderly · Software

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## Impact of findings on practice

- Almost half of drug–drug interactions in elderly hypertensive patients do not involve antihypertensive drugs.
- The risk of potential, clinically significant drug–drug interactions is not significantly associated with the number of prescribed antihypertensives.
- Better control of arterial hypertension in many patients can be achieved by switching from NSAID to paracetamol.

## Introduction

Drug interactions are important because they can diminish or enhance a drug effect and cause adverse drug reactions

in patients receiving multi-drug therapy. About 6% of hospital admissions in elderly are associated with adverse events caused by drug interactions [1]. A number of studies have demonstrated that the elderly are at a greater risk of experiencing interactions compared to the remained of the population. The prevalence of interactions in this population has increased sharply in last decade with aging changing in pharmacodynamics and pharmacokinetics, frailty, decreased homeostasis, and complexity of cases [2, 3].

Aging is characterised by a progressive loss of functional capacities of most organs and reduction in homeostatic mechanisms. Reduction in renal function, particularly glomerular filtration rate, affects the drug clearance. Several studies have shown age-related reduction in liver metabolism of many drugs [4]. These changes significantly influence pharmacokinetics. On the other hand, pharmacodynamic changes in the elderly are commonly ascribed to alternation in the sensitivity to drugs, irrespective of changes in drug disposition [5]. Polypharmacy is common in the elderly. It is estimated that more than 40% of persons aged 65 or older use 5 or more, and 12% use 10 or more different medications [6]. It makes this population very susceptible to side effects of drug interactions since the risk of interactions increases exponentially with the number of drugs [7]. The incidence of potential drug interactions increases from 13% for two drugs to 82% for seven or more drugs [8].

Croatian population is aging. In 2007, Croatia had 4,435,982 inhabitants. Persons aged 65 and older made up 17.2% (762,989) of the population; this ratio is projected almost to double by 2051 [9]. Cardiovascular diseases are the leading cause of death in this group of patients; in Croatia they caused 52.8% of deaths in 2002 [10]. Arterial hypertension is the most important independent risk factor of cardiovascular diseases in Croatia, with prevalence of 45.6% in men and 43.0% in women, which is comparable to prevalence in other industrialised countries of continental Europe. Age group of 65 years and older has the highest prevalence of arterial hypertension of 78.9% [11]. Elderly patients usually need 2 or more antihypertensive drugs to control blood pressure [12]. Many studies have shown that antihypertensive drugs were most frequently associated with drug–drug interactions [7, 13, 14].

## Aim

The aim of this study was to evaluate the incidence and type of potential, clinically significant drug–drug interactions in elderly outpatients with arterial hypertension.

## Method

This prospective study was carried out at three community pharmacies in Croatia. The study included outpatients who visited pharmacies over a 1-month period (March 1–31, 2009). Identification of patients was made through the pharmaceutical record, prescription paper or by direct questioning.

Patients were eligible if they were 65 or older, treated for arterial hypertension and received 2 or more drugs. All consecutive patients who met inclusion criteria were included in the study. Patients were excluded from the study if it was impossible to obtain reliable information about the drug therapy.

After the patient had given written consent, the following characteristics were noted: gender, age, and diagnoses. Information regarding prescription drugs use was obtained via structured patient interviews using a series of questions. The interviews were conducted by pharmacist. Medications derived from the research interview were also compared with the pharmacist and physician record to determine accuracy of medication lists.

The potential drug–drug interactions were identified by Lexi-Interact software. The software automatically categorised each identified potential drug interaction according to clinical significance as follows [15]:

(A) *No known interaction*. Data has not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.

(B) *No action needed*. Data has demonstrated that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.

(C) *Monitor therapy*. Data has demonstrated that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.

(D) *Consider therapy modification*. Data has demonstrated that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realise the benefits and/or minimise the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empirical dosage changes, choosing alternative agents.

(X) *Avoid combination*. Data has demonstrated that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Interactions of level C, D and X were considered clinically significant.

### Statistical analysis

Standard descriptive statistics were used to describe the study population, their drug utilisation and number of identified potential drug–drug interactions. Mean, 95% confidence interval (CI), median and range were calculated for age, number of diagnoses, number of drugs prescribed and number of recorded potential drug–drug interactions. For categorical data (sex, proportions of potential drug-interactions) proportions were calculated. Associations with overall number of potential drug–drug interactions for age, overall number of prescribed drugs and number of antihypertensive drugs were evaluated using multiple regression for continuous predictors. Statistical significance was set at $P < 0.05$. All tabulations and statistical analyses were done using Statistics for Windows, Version 8.0, StatSoft, Inc. (2008).

## Results

There were 265 patients included in this study, 70.6% were female, the median age was 73 (range, 65–95), and the median number of diagnoses was 3 (range, 2–8) (Table 1). The most common comorbidities were hyperlipidemia (33.2%), osteoarthritis (32.8%), diabetes mellitus (30.6%), neurotic, stress-related and somatoform disorders (25.7%), and dilated cardiomyopathy (15.5%). The median number of prescribed drugs per patient was 5 (range, 2–12).

The most common pharmacological classes of drugs taken by patients were angiotensin-converting enzyme inhibitors—ACEI (72.0%), benzodiazepines (52.0%), thiazides (49.0%), dihydropyridine calcium antagonists (35.5%), statins (32.5%), oral antidiabetics (30.2%), and nonsteroidal antiinflammatory drugs—NSAID (29.0%).

Potential clinically significant drug–drug interactions were identified in 240 (90.6%) patients (Table 2). In this group of patients interactions with clinical significance C were identified in 97.9%, D in 20.4%, and X in 0.8% patients. The median number of clinically significant potential drug interactions per patient was 4 (range, 1–19), of interactions with clinical significance C 4 (range, 1–15), D 1 (range, 1–6), and X 1 (range, 1–1).

**Table 1** Demographic and clinical data of study patients

| | |
|---|---|
| Total number of patients | 265 |
| Gender (number of patients, %) | |
| Female | 187 (70.6%) |
| Male | 78 (29.4%) |
| Age, years (median, minimum–maximum) | 73 (65–95) |
| Number of diagnoses (median, minimum–maximum) | 3 (2–8) |
| The most frequent diagnoses (number of patients, %) | |
| Hyperlipidemia | 88 (33.2%) |
| Osteoarthritis | 87 (32.8%) |
| Diabetes mellitus | 81 (30.6%) |
| Neurotic, stress-related and somatoform disorders | 68 (25.7%) |
| Dilated cardiomyopathy | 41 (15.5%) |
| Gastritis | 37 (14.0%) |
| Angina pectoris | 32 (12.1%) |
| Chronic obstructive pulmonary disease | 31 (11.7%) |
| Depression | 24 (9.0%) |
| Dementia | 20 (7.5%) |
| Atrial fibrillation | 13 (4.9%) |
| Cerebrovascular disease | 12 (4.5%) |
| Osteoporosis | 12 (4.5%) |
| Number of drugs prescribed to patients (median, minimum–maximum) | 5 (2–12) |
| Number of antihypertensive drugs prescribed to patients (median, minimum–maximum) | 2 (1–5) |
| The most frequent classes of drugs prescribed to patients (number of patients, %) | |
| ACEI | 191 (72.0%) |
| Benzodiazepines | 138 (52.0%) |
| Thiazides | 130 (49.0%) |
| Dihydropyridine calcium antagonists | 94 (35.5%) |
| Statins | 86 (32.5%) |
| Oral antidiabetics | 80 (30.2%) |
| NSAID | 77 (29.0%) |
| Beta blockers | 74 (27.9%) |
| Nitrates | 51 (19.2%) |
| Loop diuretics | 49 (18.5%) |
| Opioids | 44 (16.6%) |
| ARB | 36 (13.6%) |
| Antipsychotics | 31 (11.7%) |
| Antidepressives | 29 (11.0%) |
| Proton pump inhibitors | 27 (10.2%) |
| Digoxin | 26 (9.8%) |
| Ranitidin | 24 (9.0%) |
| Paracetamol | 24 (9.0%) |
| Theophylline derivates | 20 (7.5%) |
| Insulin | 19 (7.2%) |
| Warfarin | 16 (6.0%) |
| Acetilsalicil acid | 14 (5.3%) |
| Verapamil | 13 (4.9%) |

**Table 1** Demographic and clinical data of study patients

| | |
|---|---|
| Amiodarone | 9 (3.4%) |
| Spironolactone | 6 (2.3%) |
| Fibrates | 4 (1.5%) |

*ACEI* angiotensin-converting enzyme inhibitors, *NSAID* nonsteroidal antiinflammatory drugs, *ARB* angiotensin II receptor blockers

**Table 2** Patients with potential clinically significant drug–drug interaction

| | |
|---|---|
| Overall number of patients | 240 |
| Number of patients with different interaction (%) | |
| C | 235 (97.9%) |
| D | 49 (20.4%) |
| X | 2 (0.8%) |
| Number of interactions per patient (median, minimum–maximum) | 4 (1–19) |
| Number of different interactions per patient (median, minimum–maximum) | |
| C | 4 (1–15) |
| D | 1 (1–6) |
| X | 1 (1–1) |

**Table 3** Potential clinically significant drug–drug interaction

| | |
|---|---|
| Number of interactions | 215 |
| Interactions which involved antihypertensive drugs (number of interactions, %) | 110 (51%) |
| Interactions which did not involve antihypertensive drugs (number of interactions, %) | 105 (49%) |
| Clinical significance of drug interactions (number of interactions, %) | |
| C | 179 (83.3%) |
| D | 35 (16.3%) |
| X | 1 (0.4%) |
| Mechanism of interactions (number of interactions, %) | |
| Pharmacokinetic | 84 (39.1%) |
| Pharmacodynamic | 131 (60.9%) |

We identified 215 drug combinations with potential to cause clinically significant drug interaction (Table 3). Antihypertensive drugs were involved in 51% of interactions. 83.3% of interactions had clinical significance C, 16.3% clinical significance D, and 0.4% clinical significance X. The majority of interactions were pharmacodynamic (60.9%). The most common drug combinations with potential to interact are summarised in Table 4.

In multivariable analysis, the overall number of prescribed drugs was identified as a significant predictor of potential drug interactions (Table 5). Gender, age and number of antihypertensives were not identified as predictors of potential drug interactions.

## Discussion

The present study demonstrates that 90.6% of elderly patients with arterial hypertension have at least one potential, clinically significant drug–drug interaction. To our knowledge, none of published studies recorded such a high incidence of potential drug interactions. The study which included younger hypertensive patients identified up to 48% of patients with potential interactions of high significance [16]. This difference in incidence of interaction is a consequence of comorbidity and polypharmacy which occur in elderly patients. An emergency department study of patients aged 65 or older identified 31.1% incidence of potential interactions, by using a computer programme [17]. In general medical wards, the rate of potential drug interactions has been approximately 60% [18].

The only clinical parameter which was significantly associated with potential drug interactions in this study was the overall number of the drugs patient received. The number of prescribed antihypertensive drugs was not significantly associated with risk of interactions. This could be expected since almost half of interaction pairs did not include antihypertensive drugs.

The majority of interactions in our study had clinical significance C (83.3%). The most common potential interaction in this group which appeared in 149 patients was the interaction between NSAID and antihypertensive drugs. Almost 33% of patients included in the study suffered from osteoarthritis which justified therapy with NSAID. It is well known that NSAID can increase blood pressure and interfere with lowering effect of many classes of antihypertensive drugs. Even small rises in blood pressure due to therapy with NSAID may significantly increase cardiovascular risk, if sustained over a long time [19, 20]. According to the published data, interaction between NSAID and cardiovascular drugs are the most common interactions in the elderly associated with adverse patient outcomes [21, 22]. Our results support this finding.

Many hypertensive elderly patients require chronic pain relief. In these patients paracetamol is the safest alternative to NSAID [23]. In our study only 9% of patients were treated with paracetamol, while 29% received NSAID therapy. The guidelines for the management of degenerative disorders of joints recommend paracetamol as the most appropriate first-line analgesic for mild to moderate pain [24]. By adherence to these guidelines, we could probably improve treatment of arterial hypertension and prevent many adverse reactions of NSAID.

Many patients in the study needed two or more antihypertensive drugs. The majority of interactions between antihypertensives had the clinical significance category C. The prescription of two or more antihypertensives is a planned exploitation of known and expected pharmacodynamic

**Table 4** The most common drug combinations with the potential to interact

| Drugs with the potential to interact | Number of cases | Description |
|---|---|---|
| *Interactions with clinical significance C* | | |
| NSAID + antihypertensive drugs | 149 | NSAID may diminish the therapeutic effect of antihypertensive drugs |
| ACEI + thiazides or loop diuretics | 146 | Diuretics may enhance the hypotensive and nephrotoxic effect of ACEI |
| Dihydropyridine calcium antagonists + thiazides or loop diuretics | 65 | Diuretics may enhance the hypotensive effect of calcium antagonists |
| Beta blockers + thiazides or loop diuretics | 47 | Diuretics may enhance the hypotensive effect of beta blockers |
| Thiazides + antidiabetics | 46 | Thiazides may diminish the therapeutic effect of antidiabetic agents |
| ACEI + beta blockers | 40 | Additive or synergistic hypotensive effects may result from concomitant use of these agents |
| Nitrates + thiazides or loop diuretics | 37 | Diuretics may enhance the hypotensive effect of nitrates |
| ACEI + nitrates | 35 | Additive or synergistic hypotensive effects may result from concomitant use of these agents |
| Opioids + benzodiazepines | 35 | The concomitant use of these agents has the potential to depress CNS function |
| Benzodiazepines + benzodiazepines | 29 | The concomitant use of two benzodiazepines has the potential to depress CNS function |
| ARB + thiazides or loop diuretics | 26 | Diuretics may enhance the hypotensive and nephrotoxic effect of ARB |
| Beta blockers + nitrates | 21 | Additive or synergistic hypotensive effects may result from concomitant use of these agents |
| SSRI + benzodiazepines (diazepam and alprazolam) | 20 | SSRI may decrease the metabolism of benzodiazepines |
| Dihydropyridine calcium antagonists + nitrates | 18 | Additive or synergistic hypotensive effects may result from concomitant use of these agents |
| Potassium + ACEI | 17 | Potassium salts may enhance the hyperkalemic effect of ACEI. |
| *Interactions with clinical significance D* | | |
| Verapamil + benzodiazepines | 8 | Verapamil may decrease the metabolism of benzodiazepines |
| ACEI + allopurinol | 8 | ACEI may enhance the potential for allergic or hypersensitivity reactions to allopurinol |
| Theophylline derivatives + benzodiazepines | 7 | Theophylline derivatives may diminish the therapeutic effect of benzodiazepines |
| Opioids + SSRI | 6 | Opioides may enhance the serotonergic effect of SSRI. This may cause serotonin syndrome |
| SSRI + NSAID | 4 | SSRI may enhance the antiplatelet effect of NSAID |
| Amiodarone + digoxin | 4 | Amiodarone may increase the serum concentration of digoxin |
| Amiodarone + statins | 4 | Amiodarone may decrease the metabolism of statins. |
| Mirtazapine + SSRI | 3 | The concomitant use of agents that enhance serotonin activity increases the risk of serotonin syndrome |
| Beta blockers + alpha blockers | 3 | Beta blockers may enhance the orthostatic effect of alpha blockers |
| Amiodarone + warfarin | 2 | Amiodarone may enhance the anticoagulant effect of warfarin |
| *Interactions with clinical significance X* | | |
| Gemfibrozil + repaglinide | 2 | Gemfibrozil may increase the serum concentration of repaglinide |

*NSAID* nonsteroidal antiinflammatory drugs, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *SSRI* selective serotonin reuptake inhibitors

interactions between antihypertensive drugs, with the aim to decrease arterial blood pressure, and improve control of hypertension. To prevent adverse reactions resulting from this interaction, clinical and laboratory monitoring of patients is necessary, as well as dose adjustment when needed. The most common interaction in this group was the interaction between ACEI and thiazides or loop diuretics. This could be expected since majority of patients in our study were treated with these classes of antihypertensive drugs. ACEI have been the most commonly used class of antihypertensives in Croatia for many years, and they very often interact with other cardiovascular drugs [25]. For example, Radosevic et al. found that the most common potentially harmful drug combination in hospitalised patients was an ACEI with a potassium supplement [26]. Loop diuretics are more potent than thiazides, and more often cause hypovolemia and hyponatremia. That is why the risk of pharmacodynamic interactions is higher when loop diuretics are

**Table 5** Multivariable analysis for factors associated with drug interactions

| | Beta[a] | ±95% CI | *P*-value |
|---|---|---|---|
| Age | 0.001447 | −0.0027 to 0.0029 | 0.949 |
| Overall number of drugs | 0.007 | 0.000030–0.015 | 0.049 |
| Number of antihypertensive drugs | −0.002195 | −0.006081 to 0.001691 | 0.267 |

*CI* confidence intervals

[a] Standardised regression coefficient

combined with other antihypertensive drugs compared to thiazides.

Almost one-third of patients included in our study had diabetes mellitus. It is well known that diuretics may diminish the therapeutic effect of antidiabetic agents, and these interactions were recorded in many diabetic patients in our study. Fortunately, they do not appear to have important clinical consequences [27]. Concomitant therapy with ACEI or angiotensin II receptor blockers and diuretics is of key importance, and it has been proposed to start treatment of hypertension in diabetic patients with combination therapy in order to avoid postponement of effective treatment with the aim of normalising blood pressure [28].

Potential drug interactions of clinical significance D appeared in 20.4% of patients. The majority of these interactions involved drugs outside of the category of cardiovascular drugs. According to the published data, warfarin was the most common drug which caused such hazardous interactions in the elderly [29]. It is interesting that only 6% of patients in our study were treated with warfarin, and we recorded only a few interactions of clinical significance D that involved warfarin. None of patients had interaction that involved warfarin and NSAID. This may be a consequence of physicians' awareness of increased bleeding risk which can result from such combination.

The only interaction of clinical significance X which appeared in two study patients was the interaction between gemfibrozil and repaglinide. Repaglinide is predominantly metabolised by cytochrome P450 2C8 (CYP2C8). Gemfibrozil is an inhibitor of CYP2C8. It interferes with pharmacokinetic of repaglinide by prolonging its elimination half-life [30]. This may lead to a drastic increase in plasma concentration of repaglinide and an increased risk of adverse reactions [27]. Thus, concomitant use of gemfibrozil and repaglinide is contraindicated.

More than half of patients in our study ware treated with benzodiazepines. This percentage is much higher than reported in literature [31, 32]. Because of pharmacodynamic and pharmacokinetic changes, elderly are very sensitive to benzodiazepines. The concomitant use of other classes of drugs which influence the function of central nervous system (e.g. opioides, antidepresant, antipsyhotics, etc.) has the potential for additive depression of its function. Furthermore, some classes of drugs (e.g. calcium antagonists) may influence the metabolism of benzodiazepines. All these factors may alter the response to these drugs resulting in adverse drug reaction.

We used the Lexi-Interact software to detect potential drug–drug interactions. This program for the assessment of interactions has sensitivity of 97% and specificity of 90%. Sensitivity is defined as the ability of the software to correctly identify interaction pairs which are clinically important; specificity is the ability of the software to ignore interaction pairs which are clinically unimportant. Lexi-Interact has a high positive (90%) and negative (97%) predictive value [33]. Except drug interactions mechanism and management strategies, it also provides a comprehensive monograph which includes discussion of evidence surrounding the drug interactions. Software does not take into account drug dosage. This could be one of its deficiencies since possibility and severity of pharmacodynamic interactions depend on the drug dosage.

The major limitation of our study is the lack of information on the number of potential interactions that actually resulted to adverse events. It would not be ethical to evaluate possible clinical outcomes of recorded potential drug interactions in prospective manner without modifying or stopping the medications involved, if a harmful interaction is suspected.

## Conclusion

Results of our study emphasise the importance of monitoring of potential drug interactions in elderly patients with arterial hypertension. Fortunately, majority of these interactions can be managed by clinical and laboratory monitoring of patients or by dosage adjustments of one or both agents. This is especially important in the case of concomitant therapy with different classes of antihypertensive drugs. In other cases changes in drug therapy should be considered. Computer-based screening could help pharmacists and physicians to recognise potential clinically significant drug interactions and avoid undesirable adverse events.

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