Interakcije zdravil z zaviralci angiotenzinske konvertaze

Drug interactions with angiotensin-converting enzyme inhibitors

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Izvleček

V članku predstavljamo pregled potencialno klinično pomembnih interakcij zdravil (DDIs) z zaviralci angiotenzinske konvertaze (ACE). Na osnovi pregleda dveh knjig Stockley's Drug Interactions in dveh preko spleta dostopnih podatkovnih zbirk o DDIs smo opisali več kot deset takih DDIs, razložili njihove mehanizme, opredelili njihov klinični pomen ter navedli možnosti za njihovo preprečevanje oz. ustrezno obravnavo. Večina DDIs z zaviralci ACE je farmakodinamičnih, le nekaj jih je na nivoju farmakokinetike. Največ DDIs z zaviralci ACE se odraža kot prekomerno znižanje krvnega tlaka, hiperkaliemija ali nefrotoksičnost. Dokazali so tudi, da zaviralci ACE zvečajo toksičnost litija in da lahko vplivajo na pojav hudih preobčutljivostnih reakcij pri bolnikih, ki so prejeli parenteralne pripravke železa, ali pri bolnikih, ki sočasno jemljejo alopurinol. Prav tako je zaviralce ACE zaradi

Abstract

We reviewed potentially clinically significant drug–drug interactions (DDIs) with angiotensin-converting enzyme inhibitors (ACEIs) using Stockley's Drug Interactions books and two online DDI databases. We identified >10 such DDIs and described their mechanisms, clinical evidence and importance, as well as their management. Most DDIs with ACEIs were pharmacodynamic; only a few were pharmacokinetic. Most DDIs with ACEIs involved drugs that can lead to excessive reduction of blood pressure, hyperkalemia and impaired renal function. There is some evidence linking ACEIs with the induction of lithium toxicity. Severe hypersensitivity reactions may occur in patients treated with ACEIs with concomitant use of allopurinol or parenteral applications of iron. ACEIs should be combined carefully with hepatotoxic drugs due to their

njihove lastne hepatotoksičnosti potrebno previdno kombinirati z drugimi hepatoksičnimi zdravili. Zaradi velike porabe zaviralcev ACE je pogostost neželenih učinkov zdravil zaradi DDIs z zaviralci ACE visoka. Ugodno pa je, da lahko v večini primerov teh DDIs ustrezno ukrepamo že s primernim kliničnim in laboratorijskim spremljanjem bolnikov oz. s prilagoditvijo odmerkov sočasno predpisanih zdravil.

own potential hepatotoxic effects. The prevalence of adverse drug reactions due to DDIs might be high because they are prescribed frequently. Fortunately, most of such DDIs can be managed by clinical and laboratory monitoring of patients or by dosage adjustments of concomitantly used drugs.

INTRODUCTION

Drug–drug interactions (DDIs) occur if the effect of one drug is altered (enhanced/diminished) by the presence of other drugs (1, 2). DDIs can have adverse or beneficial effects, and are classified into three types: pharmacodynamic, pharmacokinetic, and pharmaceutical.

Pharmacodynamic DDIs usually result from combining drugs with a similar mechanism of action, and can be synergistic, additive, or antagonistic. In the case of pharmacokinetic DDIs, a drug alters the absorption, distribution, metabolism or excretion and consequently concentrations of another drug at its site of action (ADME interactions) (1, 2). Pharmaceutical DDIs occur if chemically incompatible active ingredients or excipients, mixed outside the body before drug administration, result in the inactivation of one or more active ingredients (2).

Although some DDIs may be life-threatening, many are clinically trivial. The estimated prevalence of clinically relevant DDIs is 3–20% (1, 3). However, some authors have estimated it to be <3% (4, 5) or >20% (6, 7). DDIs can be modified by variability in certain parameters (age, co-morbidities, genetics, lifestyle), by drug dosing regimens, and by the route of drug administration (1, 2). The risk of DDIs increases exponentially with the number of drugs taken (8).

Several studies have shown that antihypertensive drugs are frequently associated with DDIs because they are widely prescribed (9, 10). In 2009, 1,211,192 prescriptions of angiotensin-converting enzyme inhibitors (ACEIs) were prescribed in Slovenia, which represented ≈38% of all prescribed antihypertensive agents in Slovenia in 2009 (9). ACEIs are often prescribed in combinations with other antihypertensives, cardiovascular drugs and various other drugs (10, 11).

We studied the relevant literature for potentially clinically significant DDIs with ACEIs (contraindicated DDIs or DDIs for which modification of therapy was suggested). The proposed mechanisms and clinical outcomes of the DDIs as well as other therapeutic possibilities are described and discussed in this contribution.

DATABASES DEVOTED TO DDIS

The control and monitoring of DDIs is complicated because drugs are often prescribed to patients by different physicians or are dispensed in different pharmacies. In Slovenia, this was improved in 2010 by the implementation of a new online system in the health insurance card system. This system provides access to personal medical data (e.g., drug history) to health professionals (12). Furthermore, automatically applied DDI screening programs or databases for DDI recognition are used by physicians and pharmacists in Slovenia.

Many screening programs or databases for DDIs are available worldwide. These include the British National Formulary, Drug Interaction Facts, Drug-Reax, ePocrates MultiCheck, Lexi-Interact, Pharmavista, Stockley's Drug Interactions, The Medical Letter, and

Vidal (13). They differ in the contents of DDIs and severity levels of particular DDIs, as well as in their layout, frequency of updating, search functions, and price. DDI databases often grade DDIs according to their severity, usually to three or four levels (13).

Our review is based primarily on four sources of DDIs: two books (Stockley's Drug Interactions (1) and Stockley's Drug Interactions Pocket Companion (14)) and two online databases (Lexi-Interact (15) and Drug Interaction Checker (16)).

The hard copy Stockley's Drug Interactions was chosen as a "gold standard" source because it is one of the most comprehensive and authoritative reference books on DDIs in the world (13). Monographs in this book do not carry hazard/severity ratings for the DDIs. However, in Stockley's Drug Interactions Pocket Companion, a four-level rating symbol is assigned for each monograph. These ratings are the same as those used in the electronic Stockley's Interaction Alerts (1, 14). In these two books, there are references at the end of each monograph (1, 14).

According to a recent study, Lexi-Interact showed high sensitivity (97%) and specificity (90%) (13, 17). The DDI online version of Lexi-Interact is updated daily, has a four-level severity rating and references at the end of each monograph. It is widely used among healthcare professionals in Slovenia and includes information on drugs on the market in the USA and Europe (15).

The Drug Interaction Checker contains information on DDIs for drugs approved by the Food and Drug Administration (FDA) marketing the USA. However, we chose to examine it because it is one of the rare freely accessible DDI databases and thus rather widely used. It is updated monthly, but does not contain references. It has three levels of severity rating (16). The severity ratings for DDIs used for the content that we reviewed are shown in Table 1.

DRUG INTERACTIONS WITH ACEIS

ACEIs are poorly characterized in terms of the quantitative aspects of pharmacokinetics and pharmacodynamics. Numerous factors complicate the analyses: their prodrug form; two binding sites at the ACE with different binding constants for the inhibitor; and slow rate of dissociation of inhibitors from the ACE (18). Most DDIs with ACEIs are pharmacodynamic and are described in more detail below, whereas only a few DDIs with ACEIs are pharmacokinetic (19).

Table 1: *Levels of severity rating for drug–drug interactions presented in this review*

Data source	Contraindicated	Caution
Stockley's Drug Interactions Pocket Companion 2010	DDIs have a life-threatening outcome, or concurrent use with other drugs is contraindicated by the manufacturers.	Concurrent use may result in a significant hazard to the patient and therefore dosage adjustment or close monitoring is needed.
Lexi-Interact	X These agents are generally considered to be contraindicated.	D Specific actions must be taken to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, or choice of alternative drugs.
Drug Interaction Checker	**Major** Highly clinically significant. Avoid combinations; the risk of the DDIs outweighs the benefit.	

DDI = drug–drug interaction; X = contraindicated combination; D = drugs may interact in a clinically significant manner and modification of therapy is suggested

One possible pharmacokinetic DDI results from concomitant use of ACEIs and antacids; antacids can adsorb ACEIs, and this can lead to a reduced bioavailability of ACEIs. Therefore, antacids should be taken ≥2 h before or after an ACEI (1, 15, 20). ACEIs do not appear to undergo DDIs via cytochrome P450, so there are only a few metabolic pharmacokinetic DDIs associated with ACEIs (19). Potentially clinically significant DDIs collected from different data sources are described in Table 2.

Effects on blood pressure (BP)

Many of the DDIs with ACEIs are involved with drugs that also affect BP. Consequently, the result is increased or decreased hypotensive effect of ACEIs (1, 15, 16).

ACEIs are frequently used intentionally with other antihypertensive drugs in everyday practice due to the additive or synergistic antihypertensive effects of the drug; these DDIs are not extensively evaluated in our review. However, the hypotensive effect is not always deliberately sought or anticipated, especially with concomitant use of drugs for which hypotension is an adverse side effect (e.g., alcohol (in some situations), alprostadil, antipsychotics, dopamine agonists, levodopa, monoamine oxidase inhibitors, nicorandil, tizanidine, and rituximab) (1, 14–16).

Conversely, the antihypertensive efficacy of ACEIs might be reduced if there is concomitant use of ACEIs and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin (1, 15, 16). In some studies, aspirin doses >300 mg reduced the antihypertensive efficacy of ACEIs in ≈50% of patients. If higher doses of aspirin must be used concomitantly with ACEIs, BP should be monitored very closely and the ACEI dosage increased if necessary (1, 21). Some authors have not found the increase in BP to be clinically relevant (1, 15, 16), but even small increases in BP due to therapy with NSAIDs over a long time may significantly increase the risk of cardiovascular diseases (22). According to a recent study on the incidence of potential DDIs in 265 elderly patients in Croatia with arterial hypertension, the most common DDI of severity level C (according to Lexi-Interact) was the interaction between NSAIDs and ACEIs (17). The mechanism of this DDI is not well established, but it could be due to the inhibition of prostaglandin synthesis or sodium retention by NSAIDs (23). Prostaglandins may participate in controlling BP, and levels of angiotensin II can affect their synthesis. Recent studies indicate that sodium handling, mediated by macula densa, is predominately under the control of the cyclo-oxygenase 2 (COX-2) isoenzyme (23). Therefore, non-selective NSAIDs and selective COX-2 inhibitors yield increases in sodium retention and hence rises in BP. Among NSAIDs, indomethacin appears to have the most significant hypertensive effect (24).

Hyperkalemia

The most common adverse drug reaction of ACEIs is hyperkalemia. Hyperkalemia may occur more frequently in subjects with renal insufficiency or renal impairment, or those taking potassium supplements, potassium-sparing diuretics, angiotensin receptor-II antagonists or beta blockers (1, 15, 16). ACE inhibition prevents the conversion of angiotensin I to angiotensin II. This consequently leads to reduced aldosterone secretion from the adrenal cortex and thus to increased excretion of sodium and increased retention of potassium (25). In general, concomitant use of ACEIs and diuretics increases the risks of electrolytic imbalance and enhanced nephrotoxic effects, so monitoring is recommended (25). However, combining ACEIs and potassium-sparing diuretics is often necessary in patients with heart failure (25). The combination of ACEIs with loop diuretics or thiazide diuretics is usually safe. Thiazide diuretics and loop diuretics increase potassium secretion, so the risk of hypokalemia due to concomitant use of ACEIs is lowered (1, 15). Thiazide diuretics in low doses are recommended to be effective first-line therapy for uncomplicated arterial hypertension (25, 26). Loop diuretics are more potent than thiazide diuretics. Loop diuretics cause hypovolemia and hyponatremia, and therefore carry a higher risk of potential pharmacodynamic DDIs (1, 15, 16).

Hyperkalemia (concurrently with natriuresis) may also be a result of concomitant use of ACEIs and heparin or low-molecular-weight heparin (1, 14, 16). Therapeu-

tic doses of heparin decrease secretion of aldosterone from the adrenal cortex through several mechanisms. The most plausible mechanisms of heparin-induced hypoaldosteronism are (i) reduction in the number and affinity of angiotensin-II receptors in the zona glomerulosa of the adrenal gland and (ii) selective inhibition of steroid 11β,18-hydroxylase (the enzyme involved in the final step of aldosterone synthesis in the zona glomerulosa) (27). Prolonged administration of heparin has been shown to cause a marked reduction in the width of the zona glomerulosa (27). These side effects are more common in the elderly, in subjects with insufficiency or impairment of kidney function, and in diabetics (1, 15, 27).

Nephrotoxicity

ACEIs are particularly useful in the treatment of congestive heart failure, diabetic nephropathy, sclerodermal renal crisis, and proteinuric nephropathies, but they can also cause renal failure under peculiar circumstances (28). They inhibit angiotensin II-mediated efferent arteriolar vasoconstriction, causing a lowering of the pressure and rate of filtration in glomeruli. This is usually compensated by a reduction in systemic vascular resistance, increased cardiac output and hence increased renal blood flow (25, 28). Compensation is often insufficient in the elderly because of their limited myocardial reserve or volume depletion due to the use of diuretics, which leads to renal hypoperfusion (28). Other risk factors for ACEI-related acute renal failure include: widespread atherosclerotic disease (with bilateral disease or unilateral disease in a solitary kidney); congestive heart failure; hypovolemia; and renal insufficiency with serum creatinine concentrations >1.6 mg/dL (28). An important risk factor for nephrotoxicity induced by ACEIs is concomitant use of diuretics, NSAIDs or other nephrotoxic drugs (e.g., cyclosporine, tacrolimus) which might cause additive nephrotoxic effects. Monitoring BP and renal function is recommended for long-term concomitant use of NSAIDs and ACEIs, especially if they are combined with diuretics. Swapping NSAIDs with paracetamol is also advised (if possible) (15, 16). An increased risk of deterioration in renal function appears to occur rarely with a combination of aspirin and ACEIs (1).

Increased lithium toxicity

ACEIs can raise lithium plasma levels. Lithium toxicity has been reported in patients given captopril, enalapril or lisinopril (or possibly perindopril) (1, 15). Risk factors for this DDI seem to be poor renal function, heart failure, volume depletion, increased age, and use of some other drugs (e.g., diuretics, NSAIDs). Patients should be aware of the symptoms of lithium toxicity: increased nausea, weakness, fine tremor, drowsiness, and lethargy (29).

Hepatotoxicity

Hepatotoxicity may be induced by concomitant use of ACEIs and leflunomide or other potentially hepatotoxic drugs (16). ACEIs may demonstrate their own hepatotoxic effects, which are usually cholestatic in nature and which have been reported with captopril, enalapril, lisinopril, ramipril and fosinopril (30–32).

CONCLUSIONS

Searching different data sources on DDIs for potentially clinically significant (contraindicated or those that necessitate close monitoring) DDIs with ACEIs, we found mainly pharmacodynamic DDIs concerning BP reduction, hyperkalemia, nephrotoxicity and hepatotoxicity. There is some evidence linking ACEIs with the induction of lithium toxicity and with severe hypersensitivity reactions in patients undergoing parenteral application of iron compounds or concomitant allopurinol therapy. The prevalence and clinical importance of adverse drug reactions due to DDIs with ACEIs should be evaluated in Slovenia; no such study has been undertaken till now.

Table 2: *Potentially clinically significant drug–drug interactions with angiotensin-converting enzyme inhibitors*

Severity level of ACEI	Clinical evidence	Mechanism(s)	Management
Allopurinol S (!) L (D) DIC (major)	• 3 cases: Stevens–Johnson syndrome • 2 cases: hypersensitivity • 1 case: anaphylaxis • Possibility of increased risk of leukopenia and serious infections	• Incompletely understood	• Close monitoring for any signs of hypersensitivity • White blood cell count
Aspirin (doses >300 mg) S (?) L (C) DIC (moderate)	• Several clinical studies: reduced hypotensive effect • Many studies with no evidence of DDIs	• Inhibition of prostaglandin synthesis leading to reduced hypotensive effects	• Monitoring of blood pressure
Azathioprine S (!) L (C) DIC (/)	• 3 studies with ≈10 patients: anemia (especially in the kidney transplant patients and in dialysis patients) • >3 cases: leukopenia	• Anemia: mechanism is incompletely understood, there are several hypothesis: an ACEI could decrease production of erythropoietin and consequently reduce plasma erythropoietin levels • Leukopenia: unknown	• Monitoring blood cell counts
Cyclosporine S (!) L (D) DIC (moderate)	• 5 cases: acute renal failure • Hyperkalemia	• Most probably cyclosporine causes reduced renal blood flow due to constriction of afferent vessels. This increases the kidney's reliance on angiotensin II to maintain adequate perfusion	• Monitor for increased signs and symptoms of nephrotoxicity • Adequate hydration
Antacids (+ captopril, fosinopril) S (!) L (D) DIC (minor)	• According to the manufacturers, reduced bioavailability of fosinopril by about one-third (also several cases with captopril)	• Incompletely understood, possibly adsorption in the gastrointestinal tract	• Administration of antacids ≥2 h before or after administration of ACEIs • No clinical evidence for this interaction in medical practice
Heparin S (!) L (/) DIC (major)	• Theoretically, hyperkalemia	• Heparin inhibits the secretion of aldosterone, which can cause hyperkalemia	• Monitoring of serum potassium
Iron compounds (only intravenous application, especially iron dextran) S * L (D) DIC (major)	• Some case reports on anaphylactic-type reactions • In a very large clinical study, there was no increase in the incidence of such reactions	• The exact mechanism is incompletely understood, but may be associated with the kinin system (which mediates systemic reactions from parenteral iron therapy in response to iron-catalyzed generation of toxic free radicals). ACEIs reduce the breakdown of kinins	• Close monitoring of patients during and after administration of iron dextran
Lanthanum carbonate S (/) L (D) DIC (moderate)	• Theoretically, reduced bioavailability	• Adsorption of ACEIs in the gastrointestinal tract	• Administration of lanthanum carbonate ≥2 h before or after administration of ACEIs
Leflunomide S (/) L (/) DIC (major)	• Theoretically, possible induction of hepatotoxicity	• Leflunomide may cause hepatotoxicity, which may be induced by ACEIs	• Regular measurements of the activities of liver enzymes

Severity level of ACEI	Clinical evidence	Mechanism(s)	Management
Lithium S (!) L (D) DIC (moderate)	• Many case reports and results from retrospective studies: ACEIs can raise lithium levels; in some individuals 2–4-fold increases have occurred	• Not certain: several possible mechanisms. For example, lower levels of angiotensin II lead to lower circulating levels of aldosterone. Subsequently, excretion of sodium and water increase, possibly causing greater renal retention of the lithium ion	• Monitoring serum concentrations of lithium for ≥4–6 weeks after changes in ACEI treatment
NSAID S (?) L (C) DIC (moderate)	• Several clinical studies have shown reduced hypotensive effects and nephrotoxicity	• Inhibition of prostaglandin synthesis leads to reduced hypotensive effects and nephrotoxicity	• Monitoring of blood pressure • Dosage management • Monitoring renal function
Potassium-sparing diuretics, potassium S (!) L (C) DIC (major)	• Several clinical studies: hyperkalemia, particularly in the presence of other risk factors (e.g., advanced age, diabetes, daily doses of spironolactone >25 mg and, in particular, renal impairment) • Increased hypotensive effects	• Additive effect in potassium retention	• Dosage adjustment, • Monitoring of serum potassium
Procainamide S (!) L (/) DIC (/)	• According to the manufacturers, an increased risk of leukopenia, especially in patients with renal impairment	• Incompletely understood	• Monitoring of white blood cell counts before concurrent use of ACEIs every 2 weeks during the first 3 months of administration and then periodically after
Rituximab S (/) L (D) DIC (/)	• Theoretically, excessive hypotensive reactions	• Rituximab has hypotensive effects but the exact mechanisms are not known	• Temporarily withholding ACEIs for 12 h before rituximab infusion
Sodium phosphates (doses >20 g) S (/) L (D) DIC (/)	• Several case reports and results from retrospective studies: enhanced nephrotoxic effects	• Incompletely understood	• Temporarily suspending treatment with ACEIs or find alternatives to sodium phosphates
Tacrolimus S (!) L (/) DIC (/)	• Theoretically, nephrotoxicity and hyperkalemia	• Tacrolimus may cause nephrotoxicity and hyperkalemia, which may be additive with the effects of ACEIs	• Monitor serum potassium and look for increased signs and symptoms of nephrotoxicity
Tizanidine S (/) L (C) DIC (major)	• Theoretically, hypotension	• Tizanidine has hypotensive effects which can potentiate the effect of ACEIs	• Lower initial dosage and cautious dosage titration of tizanidine

ACEI = angiotensin-converting enzyme inhibitor; DIC = Drug Interaction Checker; DDI = drug–drug interaction; L, Lexi-Interact; NSAID = non-steroidal anti-inflammatory drug; *S = Stockley's Drug Interactions Pocket Companion; ! = caution, close monitoring or modification of therapy; ? = some doubt about the outcome of concurrent use and/or consider some type of monitoring; C = monitoring; D = caution, close monitoring or modification of therapy; / = not found; Major = usually contraindicated; Minor = minimally clinically significant; Moderate = caution, monitoring or modification of therapy needed; * = not included in Stockley's Drug Interactions Pocket Companion and hence severity level not marked*

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