REVIEW ARTICLE

Drug Interactions in Parkinson's Disease: Safety of Pharmacotherapy for Arterial Hypertension

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Abstract

Background Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system, observed in patients aged older than 50 years. In this study, we review interactions between therapies used in PD and selected antihypertensive agents. Moreover, in view of the lack of evidence-based recommendations regarding the pharmacotherapy of arterial hypertension in PD patients, we propose effective and safe therapeutic algorithms for these two coexisting conditions.

Method We used the "Drug interactions" database affiliated with the Ministry of Health, which allows for the identification of interactions between compared active compounds. The database is updated on a monthly basis and all data are consistent with current legislation. For information about interactions, we additionally added data from the British National Formulary, a joint publication of the British Medical Association and the Royal Pharmaceutical Society of Great Britain. In this analysis, we also used data from Micromedex®, Cerner Multum™, Wolters Kluwer™, Lexicomp® and Stockley's®. We analysed the potential interactions between antihypertensive and antiparkinsonian agents included in respective guidelines on the pharmacotherapy of these conditions.

Results Our analysis revealed the lack of clinically relevant interactions between preparations of levodopa and benserazide (used for the treatment of PD) and angiotensin-converting enzyme inhibitors, antagonists of AT_1 receptor for angiotensin II or antagonists of β-adrenoreceptors (β-adrenolytics).

Conclusion To avoid major drug-to-drug interactions, patients receiving preparations of levodopa and benserazide should be prescribed angiotensin-converting enzyme inhibitors, antagonists of AT_1 receptor for angiotensin II, or antagonists of β-adrenoreceptors (β-adrenolytics) as the first-line agents of antihypertensive treatment.

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Key Points

We lack detailed guidelines on the pharmacotherapy of arterial hypertension in patients with Parkinson's disease.

Pharmacotherapy of arterial hypertension in this group should be individualised.

Angiotensin-converting enzyme inhibitors, antagonists of AT_1 receptor for angiotensin II or antagonists of β-adrenoreceptors seem to be the safest option of hypotensive treatment for patients with Parkinson's disease.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system, most frequently observed in patients aged older than 50 years. The

pathomechanism of PD is associated with the death of dopamine-generating cells in the midbrain's substantia nigra. The concomitant degeneration of other neurons is reflected by disorders in the cholinergic, noradrenergic and serotoninergic systems. The death of approximately 80 % of the dopamine-generating cells is reflected by an evident loss of muscular control, which manifests as a slowness of movement, balancing disorders, rigidity and spasticity of muscles, and shaking of the limbs and head. Furthermore, many patients experience orthostatic impairment of circulatory regulation at advanced stages of PD. Orthostatic hypotension is the most frequent cardiovascular condition associated with PD. It is usually defined as a drop in systolic blood pressure by at least 20 mm Hg during the initial 3 min of verticalisation [1–4].

Epidemiological data suggest that about 50 % of patients with PD experience concomitant orthostatic hypotension and arterial hypertension (especially in the supine position). The signs of arterial hypertension and orthostatic hypotension reduce the quality of life of patients and represent an important therapeutic problem [5–9].

Antihypertensive agents can exacerbate the signs of orthostatic hypotension or interact with drugs used in PD, thus aggravating the symptoms of this condition. However, untreated PD-related arterial hypertension can result in left ventricular hypertrophy. Still, there is a lack of evidence-based recommendations regarding the pharmacotherapy of arterial hypertension in PD patients. Therefore, the choice of antihypertensive agents in patients with co-existing PD should be based on a 24-h profile of blood pressure, taking into account the interactions between antihypertensive and anti-parkinsonian agents. Often, improper pharmacotherapy of arterial hypertension can enhance the signs of PD and as a consequence decreasing the quality of a patient's life [10–15].

Because of their clinical importance, drug-to-drug interactions can be classified as major/significant (life threatening), moderate (requiring additional interventions) and minor/insignificant (without clinical consequences). The knowledge of drug-to-drug interactions by clinicians is vitally important as it enables them to predict potential risks associated with prescription of a given agent. However, the effect of a given interaction and its severity may differ significantly from patient to patient. Older individuals constitute a particular risk group for drug-to-drug interactions; this results mostly from the presence of numerous comorbidities and age-related changes in pharmacokinetics [16].

Aim of the Study

The aim of this study was to analyse the interactions between selected anti-parkinsonian and antihypertensive agents in view of international guidelines on the pharmacotherapy of these conditions [17–19]. Moreover, based on this analysis, we aimed to develop recommendations regarding effective and safe therapy of arterial hypertension coexisting with PD. We summarise the risks and benefits of current treatments.

Method

We used the "Drug interactions" database affiliated with the Ministry of Health, Poland, which allows for the identification of interactions between compared active compounds. The database was developed in cooperation with researchers from the Faculty of Pharmacology, Collegium Medicum at Jagiellonian University in Cracow, Poland. The database is updated on a monthly basis and all data are consistent with current legislation. The programme "Drug interactions" allows the analysis of the potential interactions between antihypertensive and anti-parkinsonian agents and the determination of the degree of the clinical gravity of the drug–drug interactions (no interactions, non-significant interactions, significant interactions, very significant interactions).

For information about interactions, we added data from the British National Formulary, a joint publication of the British Medical Association and the Royal Pharmaceutical Society of Great Britain. In this analysis, we also used data from Micromedex®, Cerner Multum™, Wolters Kluwer™, Lexicomp® and Stockley's®.

We analysed the potential interactions between antihypertensive and anti-parkinsonian agents included in respective guidelines on the pharmacotherapy of these conditions.

Results

Diuretics

Diuretics constitute a group of drugs that are inhomogeneous in terms of structure and target site within the nephron. According to the American guidelines (JNC-7 2003), diuretics are recommended as the first-line group of agents in the therapy of arterial hypertension. Diuretics can be classified as thiazides and thiazide-like agents (chlorothiazide, hydrochlorothiazide, trichloromethiazide, bendroflumethiazide, chlorthalidone, indapamide), loop diuretics (furosemide, etacrine acid, piretanide, torasemide) and potassium-sparing diuretics (amiloride, spironolactone, triamterene).

Owing to their mechanism of action, diuretics can be divided into those acting in the proximal tubules

(sulphonamide-acetazolamide), loop diuretics (chlorobenzenesulfonamide and dichlorophenoxyacetic acid derivatives), agents acting in the cortical part of the distal convoluted tubules (thiazides and heterocyclic thiazides), agents acting in the collecting ducts (aldosterone antagonists and agents acting independently of aldosterone), xanthine diuretics and osmotic diuretics [20, 21].

Thiazides and Thiazide-like Agents

Diuretics, especially thiazide (hydrochlorothiazide) and thiazide-like agents (chlorthalidone, indapamide), are the most frequently used antihypertensive drugs. The mechanism of their action is associated with blocking the resorption of sodium ions (Na^+) in the cortical part of the ascending arm of the nephron loop and in the proximal part of the distal tubule. Because they decrease urinary elimination of calcium, thiazides and thiazide-like diuretics can contribute to hypercalcemia. Additionally, similarly to loop diuretics, they increase urinary elimination of potassium and increase blood concentration of uric acid (hyperuricemia) [22–24].

The effects of agents used in PD can be modified as a result of both pharmacokinetic and pharmacodynamic interactions. The interaction between hydrochlorothiazide and anti-parkinsonian agents, such as amantadine and combination of levodopa with benserazide, is significant. Concurrent administration of hydrochlorothiazide and amantadine can cause very significant drug–drug pharmacokinetic interactions. This is reflected by a marked increase in amantadine concentration, resulting from the inhibition of the tubular secretion of this agent by hydrochlorothiazide, and aggravation of its side effects, such as nausea, sleeplessness, vertigo, problems with concentration, orthostatic drop in blood pressure, peripheral edema, memory loss, depression, seizure, heart failure, ocular irritation, hypertension, changes in blood morphology, psychoses, speech disorders, skin hypersensitivity and photophobia. In such cases, a thiazide diuretic should be discontinued and the dose of amantadine should be reduced or replaced with another agent.

Concurrent administration of hydrochlorothiazide and levodopa in combination with benserazide or hydrochlorothiazide, chlorthalidone, indapamide and levodopa in combination with benserazide and entacapone leads to significant drug–drug pharmacokinetic interactions, resulting in an enhanced hypotensive effect. This can be associated with orthostatic hypotension.

Combination of bromocriptine or cabergoline with hydrochlorothiazide leads to a non-significant interaction associated with possible aggravation of the hypotensive effect of the diuretic.

Concurrent use of indapamide and amantadine can be reflected by significant interaction characterised by the aggravation of the side effects of the anti-parkinsonian agent. In such cases, the thiazide diuretic should be withdrawn and the dose of amantadine should be reduced or replaced with another agent.

Administration of indapamide along with levodopa in combination with benserazide can significantly enhance the hypotensive effect, which, similarly to interaction with hydrochlorothiazide, leads to orthostatic hypotension.

Indapamide in combination with biperiden leads to insignificant interaction associated with the stimulation of the diuretic effect, resulting from its faster absorption from the alimentary tract.

Data sources include Micromedex®, updated May 6th, 2014, Cerner Multum™, updated June 16th, 2014 and Wolters Kluwer™, updated June 12th, 2014.

Table 1 presents the interactions between thiazide and thiazide-like agents most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Loop Diuretics

Loop diuretics (furosemide, etacrine acid, piretanide, torasemide) exert stronger hypotensive effect than thiazide diuretics. They act in the ascending part of the loop of Henle. About 30 % of the glomerular load of Na^+ and Cl^- is absorbed in this part of the nephron, along with K^+, and large amounts of Ca^{2+} and Mg^{2+}. Loop diuretics inhibit the Na^{+2}–Cl–K^+ co-transporter, enabling the inflow of Na^+ into the tubular cells. These agents show maximal efficacy because up to 30 % of the glomerular load of Na^+ is eliminated with urine as a result of their action. Translocation of large amounts of Na^+ and K^+ ions into the distal parts of the nephron stimulates exchange of Na^+ to H^+ or K^+, potentially contributing to kaliuresis and hypokalemia. Moreover, loop diuretics block resorption of Ca^{2+} and Mg^{2+}, leading to enhanced urinary elimination of these elements, and contribute to hyperuricemia owing to enhanced renal resorption of uric acid [25, 26].

Significant interaction between furosemide and amantadine, increasing the risk of QT segment prolongation and a *torsade de pointes* (TdP) type of arrhythmia, should be considered when choosing loop diuretics as antihypertensive agents in individuals with PD. Amantadine and furosemide are both drugs with a conditional risk for TdP. This means that the risk of developing TdP highly depends on other risk factors for this condition (e.g. age, presence of concomitant cardiovascular pathologies, potassium level and renal function). Potassium supplementation can be advised in the case of hypokalemia, but should be accompanied by appropriate monitoring of the potassium

Table 1 The interactions between thiazide and thiazide-like agents most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Hydrochlorothiazide	Chlorthalidone	Indapamide
Levodopa preparations			
Levodopa + benserazide	3	1	3
Levodopa + carbidopa	1	1	1
Levodopa + carbidopa + entacapone	3	3	3
Dopamine receptor agonists			
Cabergoline	1	1	2
Pramipexole	1	1	1
Bromocriptine	1	1	1
Rotigotine	1	1	1
Ropinirole	1	1	1
Piribedil	1	1	1
MAO-B inhibitors			
Selegiline	1	1	1
Rasagiline	1	1	1
Amantadine	4	1	3
Cholinolytic agents			
Pridinol	1	1	1
Biperidene	1	1	2
COMT inhibitors			
Tolcapon	1	1	1
Entacapone	1	1	1

COMT catechol-O-methyl transferase, MAO-B monoamine oxidase B, 1 No interactions, 2 non-significant interactions, 3 significant interactions, 4 very significant interactions

level. Furthermore, amantadine should not be prescribed concomitantly to drugs that prolong the QT interval. Furthermore, this agent is known to escalate the effect of neurostimulatory drugs, thus increasing the risk of neurological side effects (e.g. restlessness, nervousness and sleeplessness) and arrhythmia. We used the "Drug interactions" database affiliated with the Ministry of Health, Poland. Such information was not given in Micromedex®, Cerner Multum™ and Wolters Kluwer™.

Administration of furosemide or torasemide along with levodopa combined with benserazide or entacapone can significantly enhance the hypotensive effect, which, similarly to the interaction between hydrochlorothiazide and indapamide, aggravates the orthostatic hypotension.

Table 2 presents the interactions between loop diuretics most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Potassium-Sparing Diuretics

Antikaliuretic diuretics act in the distal part of the nephron (aldosterone antagonists and agents acting independently from aldosterone). They block the sodium channels of collecting tubules involved in the exchange of sodium ions Na^+ and potassium ions K^+, which are further eliminated with urine. Spironolactone is a representative of this group [27].

Significant interaction between spironolactone and levodopa combined with benserazide or entacapone should be considered before the administration of potassium-sparing diuretics as antihypertensive agents in individuals with co-existing PD. Such interaction can enhance hypotensive effect, thus aggravating the orthostatic hypotension. Data sources include Micromedex®, updated May 6th, 2014, Cerner Multum™, updated June 16th, 2014 and Wolters Kluwer™, updated June 12th, 2014. It is noteworthy that this interaction is not included in Lexicomp® and Stockley's® databases.

Table 3 presents the interactions between potassium-sparing diuretics most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Angiotensin-Converting Enzyme Inhibitors

According to the 2011 recommendations of the Polish Society for Arterial Hypertension, angiotensin-converting enzyme (ACE) inhibitors can be used in non-complicated arterial hypertension. ACE inhibitors are competitive inhibitors of ACE, which is involved in the transformation of angiotensin I (inactive decapeptide) into angiotensin II. Angiotensin II is one of the strongest endogenous vasoconstrictive factors. Moreover, ACE inhibitors also inhibit kininase II, an enzyme catalyzing degradation of bradykinin and other strong vasodilating peptides. This is reflected

Table 2 The interactions between loop diuretics most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Furosemide	Torasemide
Levodopa preparations		
Levodopa + benserazide	3	3
Levodopa + carbidopa	1	1
Levodopa + carbidopa + entacapone	3	3
Dopamine receptor agonists		
Cabergoline	1	1
Pramipexole	1	1
Bromocriptine	1	1
Rotigotine	1	1
Ropinirole	1	1
Piribedil	1	1
MAO-B inhibitors		
Selegiline	1	1
Rasagiline	1	1
Amantadine	3*	1
Cholinolytic agents		
Pridinol	1	1
Biperidene	1	1
COMT inhibitors		
Tolcapon	1	1
Entacapone	1	1

COMT catechol-*O*-methyl transferase, *MAO-B* monoamine oxidase B, *1* No interactions, *2* non-significant interactions, *3* significant interactions, *4* very significant interactions

* No information in Micromedex®, Cerner Multum™ and Wolters Kluwer™

Table 3 The interactions between potassium-sparing diuretics most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Spironolactone
Levodopa preparations	
Levodopa + benserazide	3*
Levodopa + carbidopa	1
Levodopa + carbidopa + entacapone	3*
Dopamine receptor agonists	
Cabergoline	1
Pramipexole	1
Bromocriptine	1
Rotigotine	1
Ropinirole	1
Piribedil	1
MAO-B inhibitors	
Selegiline	1
Rasagiline	1
Amantadine	1
Cholinolytic agents	
Pridinol	1
Biperidene	1
COMT inhibitors	
Tolcapon	1
Entacapone	1

COMT catechol-*O*-methyl transferase, *MAO-B* monoamine oxidase B, *1* No interactions, *2* non-significant interactions, *3* significant interactions, *4* very significant interactions

* No information in Lexicomp® and Stockley's® databases

by increased concentration of bradykinin, which stimulates β_2 receptors, as a result increasing the release of nitrogen oxide (NO) and vasoactive prostaglandins, such as prostaglandin E2 or prostacyclins [28–30].

Although ACE inhibitors are not involved in significant interactions with anti-parkinsonian agents according to the Polish ministerial database, Lexicomp® and Stockley's® databases include significant interactions between monoamine oxidase B (MAO-B) inhibitors and ACE inhibitors (level C in Lexicomp® and monitor level in Stockley's®). Some drugs (captopril, enalapril, benazepril) cause insignificant drug–drug pharmacokinetic interactions manifested by enhanced hypotensive effect of ACE inhibitors, when combined with bromocriptine and cabergoline. This can be associated with orthostatic hypotension. Although most patients tolerate therapy with ACE inhibitors well, the administration of these agents can be associated with adverse effects, such as orthostatic hypotension, dry cough, hyperkalemia, acute renal failure, proteinuria and vasoactive oedema [28–30].

Considering the fact that orthostatic hypotension is the most frequent cardiovascular disorder associated with PD, its occurrence as an adverse effect of ACE inhibitors is undesirable. The signs of hypotonia associated with the use of ACE inhibitors can result from the lack of vascular tone, normally induced by angiotensin II. This is particularly evident in individuals with high plasma activity of renin, in particular following the administration of the initial dose [28–30].

Table 4 presents the interactions between ACE inhibitors most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Antagonists of AT_1 Receptor for Angiotensin II

The mechanism behind the hypotensive effect of antagonists of AT_1 receptor for angiotensin II is associated with the binding of the drug to AT_1 receptor for angiotensin II (AT II) in adrenal glands and smooth muscles of the blood vessels. This prevents the vasoconstrictive effect of angiotensin II and aldosterone release. Of note, the

antagonists of AT_1 receptor for angiotensin II do not modulate the metabolism of bradykinin, noradrenalin and substance P [31–34].

Data from the Polish ministerial database suggest that the antagonists of AT_1 receptor for angiotensin II do not interact with anti-parkinsonian agents, apart from an insignificant interaction between sartans and bromocriptine or cabergoline, which is associated with the enhancement of their hypotensive effect [31–34]. In contrast, Lexicomp® and Stockley's® include significant interactions between MAO-B inhibitors and antagonists of AT1 receptor.

Table 5 presents the interactions between the antagonists of AT_1 receptor for angiotensin II most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Calcium Channel Antagonists

Calcium channel antagonists constitute the most popular group of antihypertensive agents. Three groups of drugs are used most often: dihydropyridine derivatives (nifedipine, amlodipine), phenylalkylamines (verapamil) and benzothiazepines (diltiazem). These groups differ in terms of their pharmacological properties and chemical structure. The mechanism underlying the effects of calcium channel antagonists pertains to blocking calcium channels, which results in the inhibition of the intracellular inflow of Ca^{2+} ions. Free intracellular Ca^{2+} ions regulate the tonus of vascular smooth muscles. Therefore, the blockade of the intracellular inflow of Ca^{2+} is reflected by decreased vascular tone, reduced peripheral resistance and subsequent drop in blood pressure [35–38].

There are noteworthy interactions between nifedipine, amlodipine, felodipine, isradipine, nitrendipine, verapamil or diltiazem and anti-parkinsonian agents, such as bromocriptine, ropinirole or levodopa combined with benserazide. Concurrent administration of the abovementioned agents and levodopa combined with benserazide or entacapone can lead to insignificant drug–drug interaction at the pharmacokinetic phase. This can be reflected by the impairment of synaptic transmission by calcium channel antagonists and the weaker effect of levodopa and benserazide. Moreover, the previously mentioned antihypertensive agents can be involved in insignificant interactions with bromocriptine, resulting in the enhanced hypotensive effect. Combining nifedipine, nitrendipine, verapamil or diltiazem with ropinirole is associated with the risk of bradycardia, arrhythmia and excessive decrease in blood pressure; this latter can be also a consequence of the interaction between amlodipine or isradipine and ropinirole. Nifedipine, amlodipine, felodipine, isradipine, nitrendipine, verapamil and diltiazem can also insignificantly interact with cabergoline (with the exception of

Table 4 The interactions between angiotensin-converting enzyme inhibitors most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Captopril	Enalapril	Benazepril	Lisinopril	Ramipril	Imidapril
Levodopa preparations						
Levodopa + benserazide	1	1	1	1	1	1
Levodopa + carbidopa	1	1	1	1	1	1
Levodopa + carbidopa + entacapone	1	1	1	1	1	1
Dopamine receptor agonists						
Cabergoline	2	2	2	2	1	1
Pramipexole	1	1	1	1	1	1
Bromocriptine	2	2	2	1	1	1
Rotigotine	1	1	1	1	1	1
Ropinirole	1	1	1	1	1	1
Piribedil	1	1	1	1	1	1
MAO-B inhibitors						
Selegiline	1	1	1	1	1	1
Rasagiline	1	1	1	1	1	1
Amantadine	1	1	1	1	1	1
Cholinolytic agents						
Pridinol	1	1	1	1	1	1
Biperidene	1	1	1	1	1	1
COMT inhibitors						
Tolcapon	1	1	1	1	1	1
Entacapone	1	1	1	1	1	1

COMT catechol-O-methyl transferase, MAO-B monoamine oxidase B, 1 No interactions, 2 non-significant interactions, 3 significant interactions, 4 very significant interactions

Table 5 The interactions between the antagonists of AT_1 receptor for angiotensin II most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Eprosartan	Irbesartan	Losartan	Telmisartan	Valsartan
Levodopa preparations					
Levodopa + benserazide	1	1	1	1	1
Levodopa + carbidopa	1	1	1	1	1
Levodopa + carbidopa + entacapone	1	1	1	1	1
Dopamine receptor agonists					
Cabergoline	2	2	2	2	2
Pramipexole	1	1	1	1	1
Bromocriptine	2	2	2	2	2
Rotigotine	1	1	1	1	1
Ropinirole	1	1	1	1	1
Piribedil	1	1	1	1	1
MAO-B inhibitors					
Selegiline	1*	1*	1*	1*	1*
Rasagiline	1*	1*	1*	1*	1*
Amantadine	1	1	1	1	1
Cholinolytic agents					
Pridinol	1	1	1	1	1
Biperidene	1	1	1	1	1
COMT inhibitors					
Tolcapon	1	1	1	1	1
Entacapone	1	1	1	1	1

COMT catechol-*O*-methyl transferase, *MAO-B* monoamine oxidase B, *1* No interactions, *2* non-significant interactions, *3* significant interactions, *4* very significant interactions

* Lexicomp® and Stockley's® include significant interactions between MAO-B inhibitors and AT_1 receptor

verapamil, which shows a significant interaction), leading to the enhancement of the hypotensive effect of these agents. It should be noted that, contrary to the Polish database, Lexicomp® and Stockley's® databases include significant interactions between MAO-B inhibitors and calcium channel antagonists. Data from: Micromedex®, Cerner Multum™ and Wolters Kluwer™ also include significant interactions between MAO-B inhibitors and calcium channel antagonists. For example, selegiline and amlodipineine may have additive effects in lowering a patient's blood pressure.

Table 6 presents the interactions between calcium channel antagonists most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Antagonists of β-Adrenoreceptors (β-Adrenolytics)

Antagonists of β-adrenoreceptors bind selectively to β-adrenergic receptors and cause competitive reversible antagonism of β-adrenergic stimulation of various organs. The mechanism of their action is variable and not completely understood as suggested by differences in the effects of various drugs from this group.

β-Adrenolytic agents are classified into several categories; namely, non-selective and selective antagonists of β-adrenoreceptors. Non-selective β-adrenolytics causing competitive blockade of β_1 and β_2 receptors with intrinsic sympathomimetic activity include nadolol, propranolol, tymolol and sotalol, while the group of agents without such activity encompasses pindolol, carteolol, penbutolol, oxprenolol and alprenolol. Similarly, there are selective β-adrenolytics with intrinsic sympathomimetic activity, such as atenolol, bisoprolol, metoprolol and betaxolol, or without such activity, e.g. acebutolol. Moreover, there is a group of α- and β-adrenolytics that act as peripheral vasodilators by blocking α_1-adrenergic receptor (labetalol, carvedilol, bucindolol) [39–42].

Interactions between agents such as acebutolol, bisoprolol, propranolol and metoprolol and such anti-parkinsonian agents as bromocriptine, selegiline or ropinirole should be considered. Concurrent administration of the abovementioned β-adrenolytics and selegiline is reflected by very significant interaction associated with the risk of bradycardia and potentially dangerous reversal of β-receptor blockade.

Moreover, a significant interaction between such active compounds as acebutolol, atenolol, bisoprolol, carvedilol, metoprolol, nebivolol or pindolol and ropinirole can occur, with subsequent risk of bradycardia, arrhythmia and excessive drop in blood pressure. The abovementioned β-adrenolytics also insignificantly interact with bromocriptine and cabergoline (and also, in the case of carvedilol,

Table 6 The interactions between calcium channel antagonists most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Nifedipine	Amlodipine	Felodipine	Isradipine	Lacidipine	Nitrendipina	Verapamil	Diltiazem
Levodopa preparations								
Levodopa + benserazide	2	2	2	2	1	2	2	2
Levodopa + carbidopa	1	1	1	1	1	1	1	1
Levodopa + carbidopa + entacapone	2	2	2	2	1	2	2	2
Dopamine receptor agonists								
Cabergoline	2	2	2	2	1	2	3	2
Pramipexole	1	1	1	1	1	1	1	1
Bromocriptine	2	2	2	2	1	2	2	2
Rotigotine	1	1	1	1	1	1	1	1
Ropinirole	3	3	1	3	1	3	3	3
Piribedil	1	1	1	1	1	1	1	1
MAO-B inhibitors								
Selegiline	1*	1*	1*	1*	1*	1*	1*	1*
Rasagiline	1*	1*	1*	1*	1*	1*	1*	1*
Amantadine	1	1	1	1	1	1	1	1
Cholinolytic agents								
Pridinol	1	1	1	1	1	1	1	1
Biperidene	1	1	1	1	1	1	1	1
COMT inhibitors								
Tolcapon	1	1	1	1	1	1	1	1
Entacapone	1	1	1	1	1	1	1	1

COMT catechol-*O*-methyl transferase, *MAO-B* monoamine oxidase B, *1* No interaction, *2* non-significant interactions, *3* significant interactions, *4* very significant interactions

* Lexicomp®, Stockley's®, Micromedex®, Cerner Multum™, Wolters Kluwer™ include significant interactions between MAO-B inhibitors and calcium channel antagonists

with biperiden), which can be reflected by the enhancement of their hypotensive effect.

Data sources include Micromedex®, updated May 6th, 2014, Cerner Multum™, updated June 16th, 2014 and Wolters Kluwer™, updated June 12th, 2014.

Table 7 presents the interactions between antagonists of β-adrenoreceptors most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance.

Discussion

At present, we lack detailed guidelines regarding the pharmacotherapy of arterial hypertension and the choice of hypotensive agents for patients with PD. Pharmacotherapy of arterial hypertension in individuals with PD has to be individualised. Achieving the desired effect of hypotensive agents and avoiding adverse effects associated with their interaction with anti-parkinsonian agents constitute prerequisites of efficacious antihypertensive therapy [43–45].

To avoid potential adverse effects, pharmacotherapy of arterial hypertension should begin with the lowest possible dose of the antihypertensive agent. If the results are unsatisfactory, the dose of the single agent should be increased. If monotherapy is unsuccessful, a combination of drugs, preferably originating from various classes and characterised by different modes of action, is recommended. Blood pressure in older patients should be decreased gradually to reduce the incidence of adverse events [46–48].

According to the international guidelines, in the cases where monotherapy with a small dose of antihypertensive agent is insufficient to reduce blood pressure, it should be replaced with another agent at a low dose, its initial dose should be increased or combined therapy should be implemented.

Consideration of a patient's preferences and potential interactions with agents used in the treatment of comorbidities constitutes a prerequisite of successful therapy [46–48].

In view of existing guidelines and evidence of potential interactions between antihypertensive and anti-

Table 7 The interactions between antagonists of β-adrenoreceptors most frequently used in the treatment of arterial hypertension and anti-parkinsonian agents, stratified according to their significance

Drugs	Acebutolol	Atenolol	Bisoprolol	Carvedilol	Metoprolol	Nebiwolol	Pindolol	Propranolol
Levodopa preparations								
Levodopa + benserazide	1	1	1	1	1	1	1	1
Levodopa + carbidopa	1	1	1	1	1	1	1	1
Levodopa + carbidopa + entacapone	1	1	1	1	1	1	1	1
Dopamine receptor agonists								
Cabergoline	2	2	2	2	2	2	2	2
Pramipexole	1	1	1	1	1	1	1	1
Bromocriptine	2	2	2	2	2	2	2	1
Rotigotine	1	1	1	1	1	1	1	1
Ropinirole	3	3	3	3	3	3	3	1
Piribedil	1	1	1	1	1	1	1	1
MAO-B inhibitors								
Selegiline	4	1	4	1	4	1	1	4
Rasagiline	1	1	1	1	1	1	1	1
Amantadine	1	1	1	1	1	1	1	1
Cholinolytic agents								
Pridinol	1	1	1	1	1	1	1	1
Biperidene	1	1	1	2	1	1	1	1
COMT inhibitors								
Tolcapon	1	1	1	1	1	1	1	1
Entacapone	1	1	1	1	1	1	1	1

COMT catechol-*O*-methyl transferase, *MAO-B* monoamine oxidase B, *1* No interactions, *2* non-significant interactions, *3* significant interactions, *4* very significant interactions

parkinsonian agents, individualised hypotensive therapy comprising drugs currently used by the patient should be proposed [43–45].

Because of the lack of interactions, patients in whom preparations of levodopa and benserazide were implemented owing to co-existing PD and arterial hypertension should be prescribed ACE inhibitors, antagonists of AT_1 receptor for angiotensin II or antagonists of β-adrenoreceptors (β-adrenolytics) as the first-line agents of antihypertensive treatment.

Although most patients tolerate the therapy with ACE inhibitors well, in the case of patients with PD, special attention should be paid to the potential occurrence of orthostatic hypotension, a potential adverse event. In such an event, withdrawal of ACE inhibitors and replacement with antagonists of AT_1 receptor for angiotensin II or β-adrenoreceptor antagonists should be considered.

The adverse effects of β-adrenoreceptor antagonists result from their influence on the central nervous system and include fatigue, headache, sleeping disorders, sleeplessness, "living dreams" and depression (rarer in the case of hydrophilic β-adrenolytics). Moreover, β-adrenolytics can cause or enhance impotence or loss of libido in some patients. As this type of adverse events is also

characteristic for PD, discontinuation of β-adrenolytics is recommended if evidence for the enhancement of their severity is present.

However, it should be remembered that sudden withdrawal of β-adrenolytics after long-term use can be reflected by "withdrawal syndrome", presenting with arrhythmia, arterial hypertension and exacerbation of angina pectoris.

The results of previous clinical trials suggest that antagonists of AT_1 receptor for angiotensin II are characterised by a lower incidence of adverse events; additionally, their advantages include long-term hypotensive effect and mild onset of action. Therefore, they seem to be the most beneficial antihypertensive agents for individuals with co-existing PD.

Patients receiving dopamine agonists can be prescribed loop diuretics or potassium-sparing diuretics as antihypertensive therapy because of the lack of interaction between these two groups of drugs. In the case of other antihypertensive agents, one should consider their potential interactions with various dopamine agonists and determine whether the patient is receiving combined anti-parkinsonian therapy, including drugs that could potentially interact with those used to treat arterial hypertension.

Table 8 The occurrence of the interactions between various groups of anti-parkinsonian agents and antihypertensive drugs

Grupa leków	Thiazides and thiazide-like agents	Loop diuretics	Potassium-sparing diuretics	Angiotensin-converting enzyme inhibitors	Antagonists of AT_1 receptor for angiotensin II	Calcium channel antagonists	Antagonists of β-adrenoreceptors (β-adrenolytics)
Levodopa preparations	−	−	−[a]	+	+	−	+
Dopamine receptor agonists	−	+	+	−	−	−	−
MAO-B inhibitors	+	+	+	+	+[b]	+[c]	−
Amantadine	−	−[d]	+	+	+	+	+
Cholinolytic agents	−	+	+	+	+	+	−
COMT inhibitors	+	+	+	+	+	+	+

COMT catechol-*O*-methyl transferase, *MAO-B* monoamine oxidase B

+ No interactions, − interactions

[a] No information in Lexicomp® and Stockley's® databases

[b] Lexicomp® and Stockley's® include significant interactions between MAO-B inhibitors and AT_1 receptor for AT II

[c] Lexicomp®,Stockley's® Micromedex®, Cerner Multum™ and Wolters Kluwer™ include significant interactions between MAO-B inhibitors and calcium channel antagonists

[d] No information in Micromedex®, Cerner Multum™ and Wolters Kluwer™

Dopamine agonists should not be prescribed to patients with dementia, signs of psychosis or mental confusion. Moreover, existing arrhythmia or its history, peripheral circulatory disorders or orthostatic hypotension constitute indications to use these agents with caution.

The dose of dopamine agonists should be increased gradually and blood pressure should be measured on a regular basis. Other groups of anti-parkinsonian agents should be considered for individuals with co-existing hypertension.

MAO-B inhibitors and catechol-*O*-methyl transferase inhibitors can be safely combined with all antihypertensive agents (the only exceptions include concurrent use of acebutolol, bisoprolol, propranolol, or metoprolol and selegiline).

Cholinolytic agents can be safely used with loop diuretics, potassium-sparing diuretics, ACE inhibitors, antagonists of AT_1 receptor for angiotensin II and calcium channel antagonists, as they do not interact with these antihypertensive agents.

The occurrence of the interactions between various groups of anti-parkinsonian agents and antihypertensive drugs is summarised in Table 8.

Conclusion

At present, we lack detailed guidelines regarding the pharmacotherapy of arterial hypertension and the choice of hypotensive agents for patients with PD. Pharmacotherapy of arterial hypertension in individuals with PD has to be individualised. Achieving the desired effect of hypotensive agents and avoiding adverse effects associated with their interaction with anti-parkinsonian agents constitute prerequisites of efficacious antihypertensive therapy.

The differences between British, Polish, and American databases are very interesting. We believe that this information should be taken into account for the patient's well-being.

Clinicians working with patients with PD need to know the significance of these interactions to properly advise patients and prevent therapeutic problems.

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