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COMPUTER SIMULATION OF THE COMBINED USE OF AZATHIOPRINE WITH METHYLPREDNISOLONE UNDER THE CONDITIONS OF PHARMACOTHERAPY OF MYASTHENIA GRAVIS

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The combined use of physiologically active compounds is aimed at optimizing their combined pharmacotherapeutic effect, which provides for reducing adverse reactions of ingredients, reducing their doses under conditions of potential synergism of the used components and increasing the convenience of taking ready-made medicinal forms. The purpose of this study was to assess the possibility of combined use, effectiveness and safety of azathioprine and methylprednisolone in the treatment of myasthenia gravis. Possible chemical reactions of the compounds were predicted based on the presence and reactivity of the functional groups included in their structure. The analysis of the acid-base properties of the compounds was carried out using the ACD/pK_aDB and ChemAxon programs. Analysis of physicochemical properties and data on the interaction with enzyme systems for methylprednisolone and azathioprine suggests the absence of possible interactions between these drugs at the chemical and pharmacokinetic levels (with the need to adjust dosage regimens). At the pharmacological level, the combined therapeutic effect of methylprednisolone and azathioprine is expected to contribute to more effective treatment of multiple sclerosis by inhibiting the development and course of inflammatory reactions.

Key words: myasthenia gravis, computer modelling, pharmacotherapy, combined effect, methylprednisolone, azathioprine, treatment.

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КОМП'ЮТЕРНЕ МОДЕЛЮВАННЯ СУМІСНОГО ВИКОРИСТАННЯ АЗАТІОПРИНУ З МЕТИЛПРЕДНІЗОЛОНОМ ЗА УМОВ ФАРМАКОТЕРАПІЇ МІАСТЕНІЇ

Сумісне використання фізіологічно активних сполук направлене на оптимізацію їх сумісного фармакотерапевтичного ефекту, що передбачає ослаблення побічних реакцій інгредієнтів, зменшення їх доз за умов потенційного синергізму використовуваних компонентів і збільшення зручності прийому готових лікарських форм. Метою даної роботи була оцінка можливості комбінованого застосування, ефективності та безпечності азатіоприну та метилпреднізолону при лікуванні міастенії. Можливі хімічні реакції сполук було спрогнозовано на підставі наявності та реакційної здатності функціональних груп, які входять до їх структури. Аналіз кислото-лужних властивостей сполук здійснювався за допомогою програм ACD/pK_aDB та ChemAxon. Аналіз фізико-хімічних властивостей та даних про взаємодію з ферментними системами для метилпреднізолону та азатіоприну дозволяє припустити відсутність можливих взаємодій між цими препаратами як на хімічному, так у на фармакокінетичному рівні (з необхідністю корекції режимів дозування). На фармакологічному рівні сукупна терапевтична дія метилпреднізолону та азатіоприну очікувано сприятиме більш ефективному лікуванню розсіяного склерозу за рахунок пригнічення процесів розвитку та перебігу запальних реакцій.

Ключові слова: міастенія, комп'ютерне моделювання, фармакотерапія, комбінований вплив, метилпреднізолон, азатіоприн, лікування.

The study is a fragment of the research project "Disorders of the nervous system in paroxysmal, neuroimmunological and cerebrovascular diseases", state registration No. 0119U104025.

Myasthenia gravis is the most frequent autoimmune disease of the neuromuscular synapse, leading to pathological fatigue and weakness of the striated muscles [3–6].

Over the past decades, the trend of a gradual increase in the incidence and prevalence of myasthenia has been maintained in most countries. This is due to the improvement of the diagnosis of the disease, the progress of the effectiveness of treatment and the increase in the life expectancy of patients suffering from

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myasthenia gravis. Thus, the prevalence of myasthenia gravis varies in different countries from 17 to 300 cases per 1 million population per year [5, 6].

The strategy for the treatment of myasthenia gravis involves 4 main directions: symptomatic treatment (use of anticholinergics), pathogenetic treatment (immunotherapy), short-term therapy for crises (intravenous immunoglobulin or plasmapheresis), surgical treatment (thymectomy) [5]. The prognosis of the course of the disease is primarily determined by pathogenetic therapy [3, 5].

Since the therapeutic effectiveness of drugs in monotherapy is often limited to individual patients, combination therapy is usually used to improve clinical efficacy while reducing side effects and toxicity. Of particular interest is the combination of agents with an additive or synergistic effect.

One combination that has successfully proven itself in the treatment of myasthenia gravis is the combination of methylprednisolone and azathioprine [5]. However, the successful use of drug combinations should be based on an understanding of the effects that occur with their combined use, and taking into account potential interactions at all levels: from physico-chemical to pharmaceutical and pharmacological.

The purpose of the study was to analyze potential interactions in the combination of methylprednisolone and azathioprine in the treatment of myasthenia gravis.

Materials and methods. This study is based on modelling the interactions of methylprednisolone (which belongs to the pharmacological group of glucocorticoids) and azathioprine (which belongs to the pharmacological group of cytostatic drugs). In this combination, azathioprine acts as a "sparing agent" of methylprednisolone and allows to significantly reduce the effective doses of methylprednisolone and reduce the frequency of side effects.

Possible chemical reactions of the compounds were predicted based on the presence and reactivity of the functional groups included in their structure. ACD/pK_aDB programs (v.12.01) were used to analyze the acid-base properties of compounds and ChemAxon (MarvinSketch). Molecular weight, lipophilicity (logP and logD), and solubility were calculated by additive methods using the indicated programs. Types of biotargets (receptors, enzymes, transporters) were obtained from relevant sources and databases: DrugBank, and PubChem [11, 12]. The freely available calculated data on the probability of interaction of compounds with a certain isoform of cytochrome, transporters or pharmacological targets were calculated by the admetSAR program and presented in the public domain on the website https://www.drugbank.ca.

Results of the study and their discussion. Potentially reactive functional groups, which were taken into account when predicting the potential of compounds for chemical interactions and reverse ionization (Fig. 1, 2) for methylprednisolone, primary (1) secondary (2) and tertiary (3) hydroxyl groups, as well as carbonyl groups (4) at positions 16 and 23 (fig. 1). In the azathioprine molecule, in addition to nitrogen atoms capable of reverse protonation (1) or deprotonation (2), it is a sulfur atom (3) and a nitro group (4) (fig. 2).

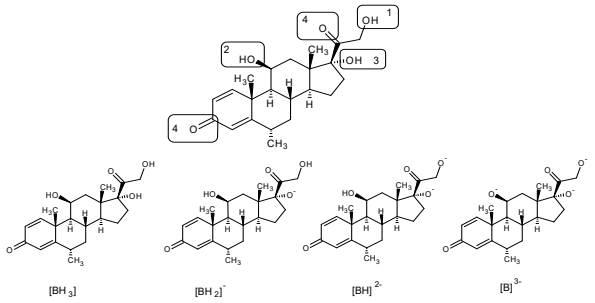

Fig. 1. Reactive functional groups in the methylprednisolone molecule and its potential ionized forms.

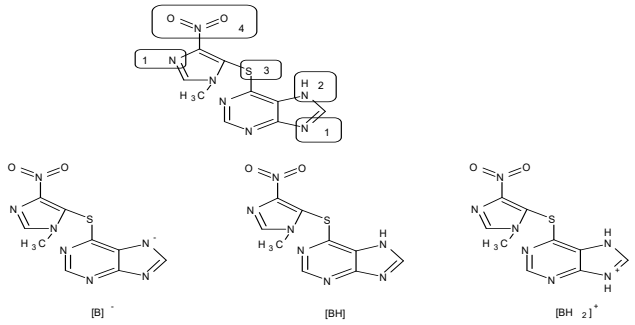

Fig. 2. Reactive functional groups in the azathioprine molecule and its potential ionized forms.

Calculating specific physicochemical indicators of the corresponding protonated or deprotonated forms was also carried out depending on the pH of the medium (table 1).

Based on pKa values, the percentage ratio between different protonated forms of methylprednisolone (fig. 3) and azathioprine (fig. 4) was calculated.

The ability of methylprednisolone and azathioprine to interact with significant transport and metabolic enzyme systems was assessed using the admetSAR program (https://www.drugbank.ca/). Pharmacokinetic parameters of methylprednisolone and azathioprine were obtained from literature data: the leading indicators of mass transfer – absorption and elimination constants (for an individual starting substance), time to reach the maximum concentration, the volume of distribution, clearance, degree of binding to blood plasma proteins and bioavailability (Table 2).

Table 1

Calculated physicochemical parameters of protolytic forms of methylprednisolone and azathioprine

Protolytic form	Physical and chemical parameters				
	pKa	logP (logD)	Solubility, g/L	Proton donors	Proton acceptors
Methylprednisolone					
$[BH_3]$	-	1.9±0.54	0.13	3	2
$[BH_2]^-$	12.48±0.7	-//-	-//-	2	3
$[BH]^{2-}$	12.98±0.1	-//-	-//-	1	4
$[B]^{3-}$	14.59±0.7	-//-	-//-	0	5
Azathioprine					
[BH]	-	0.67±1.1	0.038	1	7
$[B]^-$	7.73±0.27	-1.8±1.0	~10	0	8
$[BH_2]^+$	1.32±0.45	-1.8±1.0	-//-	2	6

In the methylprednisolone molecule, the functional groups are three hydroxyl groups (primary, secondary, and tertiary groups, respectively, with increased reactivity). Under the conditions of acid catalysis, hydroxyl groups are able to enter into esterification reactions, but this process is shifted towards the formation of starter compound, as well as the formation of hemiacetals or acetals, and in the mild conditions of storage or use of methylprednisolone, they have no place; and in conditions of either the dosage form or when used together, their probability is minimal.

Oxidation of the secondary hydroxyl group practically requires the presence of strong oxidizing agents or specific enzymes (localized in different tissues).

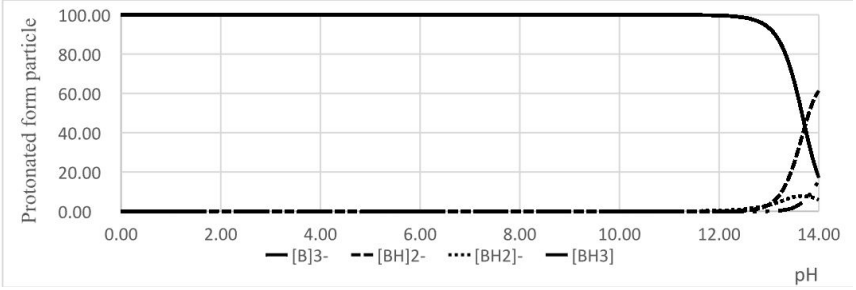

Fig. 3. Percentage ratio between protonated forms of methylprednisolone depending on the pH value.

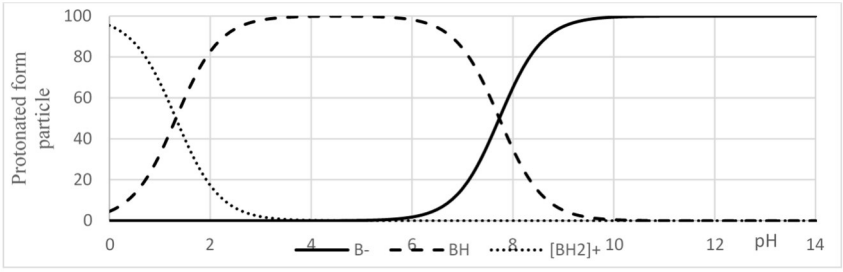

Fig. 4. Percentage ratio between protonated forms of azathioprine depending on the pH value.

Hydroxyl groups can exhibit the properties of acids (dissociate with forming various protolytic forms depending on pH) with corresponding ionization constants (pKa, table 1, fig. 3). However, the high values of the calculated pKa values allow us to conclude that methylprednisolone under physiological conditions exists in the form of an uncharged molecule ($[BH_3]$), and the reactivity of functional groups excludes the possibility of potential chemical interactions.

Functional groups in the azathioprine molecule are represented by nitrogen atoms (1) (fig. 2), which exhibit basic properties, as well as the NH group (2), which is capable of dissociation. In general, these groups determine the acid-base properties of azathioprine and the existence of at least three protonated forms (table 1, fig. 4). Protonated form $[BH_2]^+$ however, is represented in significant amounts only at low pH values (<1.5), (acidic stomach environment). In the conditions of the body's internal environment (pH 7.4), azathioprine exists both in the non-ionized form and in the form of an anion (NH group (2) exhibits weak acid properties, pKa = 7.73, table 1). The sulfur atom (3) is usually prone to oxidation. Therefore, forming corresponding sulfoxides or sulfones is possible in the presence of oxidizing agents. However, a reductive cleavage reaction is more likely, which occurs in the presence of sulfhydryl compounds (for example, glutathione) in the body and leads to the formation of the active metabolite of azathioprine 6-mercaptopurine.

The reduction reaction is also characteristic of the nitro group (4), but it requires the presence of strong reducing agents, or in the conditions of the body, it takes place with the participation of specific enzymes.

Methylprednisolone in a wide pH range is represented by a non-ionized form with high lipophilicity and low solubility in water. On the contrary, due to deprotonation, azathioprine exists both in

a neutral form and as an anion (table 1, fig. 4) under the conditions of the body. Although the number of proton acceptors changes slightly (from 7 to 8), existence in a charged form not only reduces lipophilicity (logD=-1.8±1.0) but also increases its solubility in water (~10 g/L) which generally increases the ability of the substance to overcome blood-tissue barriers. In particular, this result is that methylprednisolone can be equally absorbed in different parts of the gastrointestinal tract, while azathioprine is more effectively absorbed in parts with a neutral or slightly alkaline pH (duodenum).

Table 2

Predicted properties of azathioprine and methylprednisolone about the interaction with the main enzyme systems and the main pharmacokinetic parameters of the compounds

Nature of interaction with the enzyme	Methylprednisolone		Azathioprine	
	Value	Probability	Value	Probability
P-glycoprotein substrate	Substrate	0.7812	Not a substrate	0.7766
P-glycoprotein inhibitor I	Not an inhibitor	0.7489	Not an inhibitor	0.8049
P-glycoprotein inhibitor II	Not an inhibitor	0.604	Not an inhibitor	0.6683
Renal transporter of organic cations	Not an inhibitor	0.769	Not an inhibitor	0.8493
CYP450 2C9 Substrate	Not a substrate	0.8415	Not a substrate	0.7861
CYP450 2D6 Substrate	Not a substrate	0.9115	Not a substrate	0.8273
CYP450 3A4 Substrate	substrate	0.7582	Not a substrate	0.5944
CYP450 1A2 Substrate	Not an inhibitor	0.9473	Not an inhibitor	0.9046
CYP450 2C9 inhibitor	Not an inhibitor	0.907	Not an inhibitor	0.907
CYP450 2D6 inhibitor	Not an inhibitor	0.9513	Not an inhibitor	0.9231
CYP450 2C19 inhibitor	Not an inhibitor	0.9026	Not an inhibitor	0.9025
CYP450 3A4 inhibitor	Not an inhibitor	0.8309	Not an inhibitor	0.9733
	Pharmacokinetic parameters			
Normal dose, mg	2-32		25-50	
Elimination constant, $hours^{-1}$	0.29±0.05		2.14	
Time to reach the maximum concentration, T_{max}, hours	1.45±0.44		1-2	
Elimination half-life, hours	1.78±0.30		0.5-1.5 3-5 (metabolites)	
Volume of distribution, L/kg	1.28±0.20		5.56	
Degree of binding to blood plasma proteins, %	78		20–30	
Clearance, l/hours· kg	0.414±0.77		3.1	
Bioavailability, %	82±11		47.4	

No chemical interactions are expected for methylprednisolone or azathioprine according to their functional groups, which could lead to changes in their chemical structure and even salt formation, which allows us to conclude that there is no possibility of chemical interactions between them.

Interaction at the pharmacokinetic level. No active transport systems were found for methylprednisolone and azathioprine, and their absorption occurs due to passive diffusion from the intestinal cavity. However, as can be seen from the data on the predicted ability to interact with various enzyme systems (table 2), methylprednisolone is highly likely (0.78) to be a substrate of the P-gp system, which carries out the reverse transport of mainly lipophilic compounds from cells to the outside. Methylprednisolone is easily absorbed in the duodenum, while in the lower parts of the intestines (jejunum and ileum), the overall absorption process is reduced due to reverse transport. On the contrary, azathioprine is well absorbed throughout the gastrointestinal tract, mainly in the upper parts. Therefore, these compounds are not expected to affect each other's absorption processes at the absorption stage.

Regarding the metabolism of compounds, the metabolism of methylprednisolone, as a steroid, is specifically mediated by the activity of 11β-hydroxysteroid dehydrogenase and 20-ketosteroid reductase [7]. However, oxidation under the influence of CYP 3A4 is also possible (with a probability of 0.75, table 2), for which a large number of compounds act as substrates.

According to the predicted properties, azathioprine is not a substrate of any enzyme systems (Table 2). As a prodrug, it forms an active metabolite 6-mercaptopurine in a non-enzymatic way. The resulting 6-mercaptopurine is further oxidized to thiouric acid under the influence of xanthine oxidase or converted to nucleosides, which excludes the participation of the most common enzyme systems in this process.

Accordingly, the possibility of interaction between azathioprine and methylprednisolone can also be excluded at the metabolic stage.

As a result of different lipophilicity, the compounds bind to blood plasma proteins to varying degrees (table 2). Lipophilic methylprednisolone is almost 78% protein-bound in blood plasma. At the same time, azathioprine is present as a non-ionized form (which binds to proteins) and as an anion that dissolves in water. Also, potential interactions between azathioprine and methylprednisolone should not be expected at the distribution stage.

The drugs have a relatively similar recommended dose for administration (table 2), but azathioprine shows a quite fast elimination. However, 6-mercaptopurine has a much longer retention time in the body. Methylprednisolone is almost entirely bound to blood plasma proteins, while azathioprine and its metabolites penetrate the tissues intensively, which leads to an increasing in its volume of distribution (5.56 L/kg). However, the time to reach these drugs' maximum concentration is comparable, mainly due to similar absorption processes. In general, methylprednisolone remains in the body for a longer time (total clearance 0.414±0.77 L/hours ·kg) than azathioprine; what should be taken into account when using their combined dosage regimen (increasing the intervals of taking methylprednisolone) to prevent the accumulation effect.

Thus, specific pharmacokinetic parameters of methylprednisolone and azathioprine allow combined use with appropriate adjustment of methylprednisolone administration intervals.

The combined pharmacological effect of the combined use of methylprednisolone and azathioprine is due to the impact of each of these drugs.

Methylprednisolone is a synthetic glucocorticoid of medium action. It is mainly used as an anti-inflammatory or immunosuppressive agent. The methylprednisolone-glucocorticoid receptor complex binds and blocks the promoter sites of pro-inflammatory genes, promotes the expression of anti-inflammatory gene products, and inhibits the synthesis of inflammatory cytokines, mainly by blocking the function of transcription factors such as nuclear factor-kappa-B (NF-kB).

Methylprednisolone suppresses cell-mediated immunological functions, especially those dependent on lymphocytes. Using methylprednisolone and other glucocorticoids decreases the adhesion of white blood cells to the vascular endothelium and excretion from the blood circulation. Glucocorticoids impair various T-cell functions, and moderate to high doses induce T-cell apoptosis while preserving B-cell function and antibody production [9].

However, like other corticosteroids, methylprednisolone also causes specific side effects: significant undesirable effects of glucocorticoids are the result of their hormonal action, which leads to a clinical picture of iatrogenic Cushing syndrome. Usually, there is rounding of the face, puffiness, fat deposits, and hyperemia (moon face). There is an increased growth of fine hair on the face, thighs and torso. There may be pinpoint pimples caused by steroids, as well as insomnia and increased appetite.

Concomitant use of methylprednisolone increases protein catabolism, redirecting amino acids to produce glucose, which increases the need for insulin and eventually leads to weight gain. Myopathy and muscle wasting may occur, as well as thinning skin with striae and bruises. Hyperglycemia and eventually osteoporosis, as well as diabetes mellitus and aseptic necrosis of the hip, may develop.

Azathioprine is approved by the Food and Drug Administration (FDA) for the symptomatic treatment of active rheumatoid arthritis. It is also approved as an adjunct therapy to prevent kidney transplant rejection [7].

Azathioprine is used off-label for the treatment of inflammatory bowel diseases [14], Churg-Strauss syndrome, autoimmune hepatitis (for supportive treatment together with steroids) [1, 15], lupus nephritis [7] and other diseases associated with a violation of the proper functioning of the immune system.

Azathioprine is a purine analogue that is converted to its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN), by the enzymes hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and thiopurine methyltransferase (TPMT). It then inhibits purine synthesis by incorporating replicating DNA and can also block the de novo purine synthesis pathway. This action is believed to contribute to its relative specificity to lymphocytes due to their lack of a “rescue pathway”. It disrupts the function of T-cell lymphocytes and is more selective for T-lymphocytes than for B-lymphocytes [13]. A recent study further elucidates the efficacy of azathioprine in chronic inflammatory and autoimmune diseases [2, 8]. In particular, in multiple sclerosis, treatment with immunosuppressive and immunomodulatory drugs is used to reduce the frequency of relapses, which are thought to result from local inflammation and consequent loss of the myelin sheath surrounding axons, typically in the central

nervous system. Due to its favorable therapeutic index, azathioprine can be used in monotherapy and combination therapy.

Therefore, given the direction of the pharmacological effects of methylprednisolone and azathioprine, their combination for treating multiple sclerosis may provide advantages over monotherapy with each drug separately.

Conclusion

Analysis of the physicochemical properties of methylprednisolone and azathioprine allows us to conclude that there are no possible interactions between these drugs at the chemical level. Also, taking into account the lack of potential influence on mass transfer systems (since compounds are absorbed by passive diffusion), distribution (lack of active transport systems and competitive binding to blood transport proteins), metabolism (compounds do not have common enzyme systems involved in their transformation) and elimination, we can exclude their interaction at the pharmacokinetic level. However, the difference in some pharmacokinetic parameters (elimination constant, half-life time) implies the need to adjust the dosage of these compounds when used together. At the pharmacological level, the combined therapeutic effect of methylprednisolone and azathioprine is expected to contribute to more effective treatment of myasthenia gravis by inhibiting the development and course of autoimmune reactions.

Prospects for further research. Further research into the combined use of drugs from different pharmacotherapeutic groups at the physicochemical level is promising for their more rational use in the treatment of myasthenia gravis.

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