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FEATURES OF SIDE EFFECTS OF SULFAMETHOXAZOLE / TRIMETHOPRIM COMBINED PHARMACOTHERAPY

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Abstract

The aim of this review article is to analyze clinical cases of side effects of sulfamethoxazole / trimethoprim combination therapy with angiotensin-converting enzyme (ACE) inhibitors, potassium-sparing diuretics, angiotensin receptor blockers, methontharin and phenytoin, and phenytoin.

Materials and methods. This information was collected based on an analysis of clinical data from Google and PubMed on the side effects of sulfamethoxazole / trimethoprim combination therapy with ACE inhibitors, potassium-sparing diuretics, phenytoin, warfarin and methotrexate.

Results. The article systematizes the peculiarities of the side effects of sulfamethoxazole / trimethoprim combined therapy, presents options for eliminating or reducing the risks of side effects.

Conclusions. Due to the side effects of sulfamethoxazole / trimethoprim combination therapy, measures should be taken to minimize the risks associated with potentially hazardous sulfamethoxazole / trimethoprim combinations. To do this, physicians should be aware of both the positive and negative effects of combination therapy with sulfamethoxazole / trimethoprim with other drugs.

Key words: *sulfanilamides, sulfamethoxazole / trimethoprim, ACE inhibitors, potassium-sparing diuretics, phenytoin, warfarin, methotrexate, drug interactions.*

Introduction

Sulfamethoxazole / trimethoprim (SMX-TMP) is a combined sulfanilamide drug that includes sulfamethoxazole (SMX) and the difolate reductase inhibitor trimethoprim (TMP). According to recommendations published in 2019 by the American Society of Infectious Diseases, SMX-TMP is recommended as an effective treatment for uncomplicated urinary tract infections when the detected bacterial strain is sensitive to this drug [1]. SMX-TMP has been used for more than 50 years and is currently a popular antibacterial agent due to its effectiveness and low cost [2].

Adverse drug reactions of antibacterial drugs complicate the treatment of any infection. SMX-TMP is generally relatively well tolerated by patients who are not infected with immunodeficiency virus (HIV), and severe OL occurs in only about 3-5% of patients. However, there are published data on severe adverse systemic reactions, such as septic shock after administration of SMX-TMP [3]. SMX-TMP can also cause nausea, vomiting, diarrhea, confusion, facial edema, headache, bone marrow depression, elevated serum transaminases, renal and electrolyte disturbances, and rare life-threatening reactions (eg, Stevens-Johnson syndrome) [4]. The effect of SMX-TMP on the synthesis of purine and pyrimidine bases, which are associated with the formation of nucleic acids DNA and RNA, is also the cause of many PR: aseptic meningitis, tremor, delusions, hematological disorders (methemoglobinemia, nicotinamide-adenine-dinucleotide-dependent deficiency; epidermal necrosis; effects on the reproductive system (structural abnormalities of the nervous and cardiovascular, urinary systems); inhibition of the cytochrome P450 system; hypoglycemia, hyperkalemia, hyponatremia, acute interstitial nephritis [2].

Thus, SMX-TMP, although considered a relatively safe and effective drug, but it causes a higher frequency of idiosyncratic side effects (SE) compared to most other sulphonamides (SA) [6, 7].

For SMX-TMP, hepatotoxicity is a classic SE, as virtually all currently used CAs are associated with liver damage. [4]. The nature of this damage varies, is often mixed and can be hepatocellular or cholestatic [8]. Cases of severe cholestasis with SMX-TMP may be prolonged and lead to inflammation of the bile ducts, or cause acute liver failure, especially in cases with rapid onset and hepatocellular increase in serum enzymes [10].

As an etiological factor of drug intoxication are drugs that can lead to aseptic meningitis (AM). The signs and symptoms of this unusual adverse drug reaction may mimic the symptoms of a CNS infection and therefore clinicians should consider this feature primarily if the patient has already been treated on their own [9]. In addition, it is known that the prophylactic use of SMX-TMP in HIV-infected patients increases the likelihood of drug AM [11], especially in female patients and in autoimmune diseases [12].

It is known from literature that paranoid psychosis developed after SMX-TMP therapy was started [13, 14, 15, 16], and one woman developed visual hallucinations and delusions after oral SMX-TMP therapy for urinary tract disease [14], another patient had an acute psychotic seizure after six doses of intravenous SMX-TMP [15]. A similar attack occurred in a young man taking SMX-TMP [16].

The mechanism of SMX-TMP-induced psychosis is not well known, but there is evidence that both components of SMX-TMP inhibit folic acid metabolism, which is associated with neuropsychiatric symptoms [17]. In addition, trimethoprim is known to irreversibly inhibit dihydrofolate reductase (DHFR), thereby limiting the conversion of dihydrofolate to tetrahydrofolate and the active form of folic acid. There is evidence in the literature that DHFR deficiency is associated with mental illness, including schizophrenia [16].

SMX-TMP even at the recommended doses can lead to thrombocytopenia [18, 19], and a significant decrease in platelet count (≤10x109 / l) can lead to dangerous bleeding. Interestingly, recovery from patients with thrombocytopenia caused by SMX-TMP occurs after drug withdrawal (several days to a week) [20].

Methemoglobinemia and hemolysis develop as a result of deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD), which is the catalyst of the first stage of the pentose phosphate pathway, which uses glucose-6-phosphate to convert nicotinamide adenine dinucleotide to phosphate. In erythrocytes, NADPH is crucial for preventing damage to these cellular structures, and

also acts as a substrate for the formation of the enzyme glutathione reductase [21]. Sulfanilamide, Sulfapyridine, Sulfadiazine, Sulfaguanidine most often cause hemolytic crisis in people with G6PD deficiency [22]. There are cases when the appointment of SMX-TMP led to methemoglobinemia [23, 24]. Physicians should be aware of the risks of SMX / TMP as a possible cause of methemoglobinemia, even if administered to prevent opportunistic infections at reduced doses and intervals..

Renal dysfunction is a risk factor for severe hypoglycemia in patients receiving high doses of SMX-TMP [25]. Hypoglycaemia caused by SMX-TMP is considered secondary to the development of hyperinsulinemia [26], therefore the use of SMX-TMP should be avoided in patients with diabetes mellitus taking glibenclamide or glipizide [27].

In outpatient and inpatient settings, patients are often prescribed two or more drugs, especially in severe conditions and comorbidities, when several organs and systems need to be treated at the same time. Therefore, it is desirable to take into account all aspects related, in particular, in the interaction of SMX-TMP with other drugs, as this can lead to both strengthening and weakening of the therapeutic effect, as well as the development of SE. Identifying the most important and clinically significant drug interactions is important for patient safety. Strategies to reduce the risk of drug interactions include minimizing the number of drugs prescribed at the same time, differential reassessment of complex therapy, consideration of non-pharmacological therapeutic options, monitoring of signs and symptoms of toxicity, adjusting drug doses. Analyzing the above for warfarin, it should be noted that it is a widely used oral anticoagulant, however, has a narrow therapeutic index and many drug interactions, which complicates its safe use [28]. Warfarin has an anticoagulant effect by inhibiting vitamin K-dependent activation of coagulation factors II, VII, IX and X. Excessive hypocoagulation caused by it can cause severe bleeding [29]. Interaction of SMX-TMP with warfarin can also cause bleeding, it was found that SMX-TMP is associated with more than 2-fold increase in the risk of bleeding [30]. SMX-TMP can alter warfarin metabolism by inducing or inhibiting cytochrome P450-2C9, leading to a decrease or enhancement of the anticoagulant effect [31]. The small кфтпуof therapeutic action and multiple drug interactions of warfarin pose a risk of severe bleeding for patients. Therefore, warfarin is dangerous to combine with SMX-TMP.

Repaglinide is a short-acting antidiabetic drug from the group of meglitinides. Trimethoprim inhibits the metabolism of repaglinide by human liver microsomes. SMX-TMP can inhibit the CYP450 isoenzyme, alter protein binding, and reduce vitamin K absorption by altering the intestinal flora [32]. There is evidence in the literature that at normal clinical doses, trimethoprim inhibits CYP2C8-mediated metabolic clearance by approximately 26-80% [33]. It was also found that trimethoprim in therapeutic doses increases plasma concentrations of repaglinide and prolongs its half-life. Because the hypoglycaemic effect of repaglinide is dose-dependent, concomitant use of trimetroprim may potentiate the pharmacological action of repaglinide and thus increase the risk of hypoglycaemia. Renal insufficiency is a significant factor influencing the reduction of blood glucose levels when combined with sulfamethoxazole [34]. Therefore, if a patient starts taking SMX-TMP while taking repaglinide, it is recommended to monitor blood glucose levels and, if necessary, adjust the dose of the latter.

Attention to the interaction of trimethoprim and rosiglitazone is also of clinical importance because trimethoprim is a competitive inhibitor of CYP2C8-mediated rosiglitazone metabolism in vitro (trimethoprim administration increases rosiglitazone plasma concentrations). Patients taking rosiglitazone and trimethoprim may be at greater risk for SE, such as edema, but the most serious PRs associated with thiazolidinediones (rosiglitazone) are: heart failure, pulmonary edema, pleural effusion. However, all these SE depend on the concentration of these drugs [35].

The combination of SMX-TMP with phenytoin doubles the toxicity of the latter. Phenytoin biotransformation is catalyzed by cytochrome P450 2C9, 2C8, and 2C19 enzymes, and concomitant use of drugs that may inhibit these enzymes may cause increase in the risk of phenytoin toxicity in elderly patients. [36].

The combined use of SMX-TMP and methotrexate may increase the toxicity of the latter. According to

research, the concentration of free methotrexate in the blood when co-administered with SMX-TMP increases by approximately 60% [37]. The second report on the toxicity of methotrexate in its interaction with SMX-TMP states that the negative manifestations of this combination are pancytopenia, acute megaloblastic anemia, stomatitis and nephrotoxicity [38]. It is also known that the combination of methotrexate and SMX-TMP leads to ulcers of the skin and mucous membranes, leukopenia and renal failure [39]. Severe pancytopenia with subsequent bacterial sepsis may develop with concomitant use of SMX-TMP and methotrexate [40]. Even low doses of TMP when co-administered with methotrexate increase the toxicity of the latter. This may be due to the synergistic mechanism of action of methotrexate and SMX-TMP, such as competition for tubular secretion. Therefore, the pharmacokinetic properties of the components of this combination may play an important role in the interaction of SMX-TMP with methotrexate [41]. In addition, it is known that after oral administration, methotrexate is rapidly absorbed, excreted by the kidneys by 80-90%, and liver enzymes metabolize the amount that remains. A positive correlation was observed between methotrexate clearance and creatinine clearance, so it is possible that renal impairment may provoke methotrexate toxicity. After glomerular filtration, it undergoes both secretion and reabsorption, and during these processes methotrexate competes with other drugs, including SMX-TMP. Its primary metabolite is 90% bound to plasma proteins and may cause significant drug interactions. Given the above, the combination of methotrexate and SMX-TMP should be avoided, as it can lead to adverse IY, and even possibly death [42].

Co-administration of SMX-TMP with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers results in a sevenfold increase in the risk of hospitalization with hyperkalaemia compared with those receiving amoxicillin instead of SMX-TMP [43]. The association between SMX-TMP and the development of hyperkalaemia is the mechanism of action of trimethoprim, which is similar to that of potassium-sparing amiloride: blockade of epithelial sodium channels in the distal nephron, impaired renal elimination of potassium [44]. Physicians should be aware of this risk and constantly monitor serum potassium in elderly patients taking SMX-TMP with ACE inhibitors. [45].

In view of the above, SMC-TMP combination pharmacotherapy regimens have recently focused on assessing the effects of concomitant medications (ACE inhibitors, spironolactone and beta-blockers), which may lead to severe hyperkalaemia, which may result in the risk of sudden SM death. and the above drugs, especially in elderly patients [46]. Renal insufficiency in combination with ACE inhibitors, angiotensin receptor blockers is a major risk factor for hyperkalaemia, which can be caused by combination with SMX-TMP and even at low doses of the latter [47].

Doubts about the rational use of SMX-TMP in elderly patients treated with spironolactone have been associated with a significant increase in the risk of hyperkalemia, and this risk far outweighed the risk of other widely used chemotherapeutic agents for urinary tract infections [48]. Thus, compared with amoxicillin, the appointment of SMX-TMP was associated with more than a 12-fold increased risk of hospitalization for hyperkalemia in elderly patients taking enalapril and spironolactone [49, 50, 51, 52, 53]. It has been established that as a result of drug interaction of SMX-TMP with spironolactone, the patient may even die due to the development of hyperkalemia. The mechanism of hyperkalemia on the background of SMX-TMP and spironolactone is associated with amyloride-like inhibition of sodium channels in the membrane of the distal tubules, which leads to impaired potassium secretion and sodium reabsorption [54]. The structural similarity of trimethoprim with potassium-sparing diuretics may lead not only to hyperkalemia but also to hyponataemia.

Thus, hyperkalaemia is a common electrolyte disturbance associated with the use of SMX-TMP, especially in patients with renal insufficiency or in persons taking concomitant drugs that may increase serum potassium [55].

Propylene glycol (PG) is a widely used solvent for pharmaceuticals. Although it is considered safe, large intravenous doses over a short period of time can be toxic. Renal failure and hepatic impairment increase the risk of PG toxicity [56]. As a solvent, GHG is also used for SMX-TMP, which is metabolized in the liver to lactic acid. There is information in the literature on a case of severe lactic acidosis after a 3-

day course of SMX-TMP with a presumably safe amount of PG [57]. Although GHG-associated lactoacidosis is well recognized, clinicians should keep in mind that SMX-TMP also contains PG, and toxic effects of PG should be suspected in patients who develop unexplained metabolic acidosis with SMX-TMP, even in the recommended dosage. In this case, immediate discontinuation of SMX-TMP is crucial to prevent the development of increasing multiorgan failure.

Thus, the analysis of the features of combination therapy with the inclusion of SMX-TMP indicates the mandatory observance of rational conditions of its use. Concomitant use of warfarin, methotrexate, phenytoin and SMX-TMP should be avoided whenever possible; adhere to rational conditions when combining the latter with oral hypoglycemic agents (repaglinide, rosiglitazone), ACE inhibitors, potassium-sparing diuretics. Therefore, objective and sound reliable knowledge of the pharmacological features of SMX-TMP is necessary for the safe and effective use of CA in the treatment of patients.

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