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POTENTIAL RISKS OF SULFAMETOXAZOLE / TRIMETOPRIM

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Abstract

Aim: analysis of possible side reactions (SR), features of the mechanisms of their occurrence, conditions for reducing the risks associated with sulfomethoxazole / trimethoprim.

Materials and methods. Data search on Google and PubMed. The information was collected on the basis of reviews of clinical cases of possible OL, the probable mechanisms of their occurrence with the use of sulfamethoxazole / trimethoprim.

Results. The article analyzes and systematizes the possible SR, their probable mechanisms of occurrence, options for eliminating or reducing the risks associated with the use of sulfamethoxazole / trimethoprim.

Conclusions. Despite the widespread use and many years of experience in the use of sulfamethoxazole / trimethoprim in clinical medicine, the conditions of its use should be monitored to avoid or reduce the development of OL. The article considers important PR, possible mechanisms of their occurrence and conditions of their reduction or elimination. Physicians and pharmacists should be aware of both the positive and negative consequences of prescribing sulfamethoxazole / trimethoprim

Keywords: *sulfanilamides, sulfamethoxazole / trimethoprim, aseptic meningitis, hyperkalemia, hyponatremia, hypoglycemia, hypersensitivity reactions, pregnancy, renal failure.*

Sulfonamides (SA) were the first broad-spectrum chemotherapeutic antibacterial agents to be used in practical medicine. To date, SAs remain a relevant therapeutic option for the treatment of various infectious diseases. These drugs are divided into two groups - antimicrobial and non-antimicrobial drugs. All SAs contain a fragment of $NH_2 – SO_2$; however, sulfanilamide antimicrobials also contain arylamine (-Ar-NH_2) at position 4 and a five- or six-membered nitrogen-containing ring at position 1. The arylamine fragment is responsible for the antimicrobial mechanism of action of SA due to the similarity between 4-aminobenzenesulfonamide and para-aminobenzoic acid (PABA), which is necessary for the microbial synthesis of dihydrofolic acid. This similarity provides a dual antimicrobial mechanism of action of SA: competitive inhibition of microbial dihydropteroate synthetase and the inclusion of SA instead of PABA in the "false" intermediate product of metabolism, which can not be converted into dihydrofolate dihydrofolate synthetase [1].

Sulfamethoxazole / trimethoprim (SMX-TMP), the most commonly used sulfonamide drug for the treatment of various infectious diseases, appeared in 1968. This drug has a double blocking effect on the metabolism of bacteria and protozoa. Sulfamethoxazole blocks the inclusion of paraaminobenzoic acid in the metabolism of bacteria and thus disrupts the synthesis of folic acid. Trimethoprim disrupts folic acid synthesis by blocking the enzyme difolate reductase. Thus, SMX-TMP, due to its complex mechanism of action, inhibits two stages of folic acid synthesis in bacterial cells and thus exhibits synergistic antibacterial activity [2]. This SMX-TMP activity is effective for the treatment of infections caused by gram-positive and gram-negative bacteria, as well as for the prevention and treatment of pneumonia caused by Pneumocystis carinii [3], Pneumocystis jiroveci, Toxoplasma gondii, Stenotrophomonas maltophilia and Staphylococcus aureus resistant to methicillin.

Since the first use of SMX-TMP, back in 1968, concerns were expressed about its possible toxicity [2]. PR for SMX-TMP occurs in approximately 1-3% of people in the general population. Despite the high effectiveness of SMX / TMP, doctors often have to cancel it or reduce the dose due to SR, including nausea, vomiting, anorexia and diarrhea, allergic reactions. More serious SR, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, agranulocytosis, and lightning necrosis, are rare, but have been reported in the literature [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 SR: aseptic meningitis, tremor, delirium, gait disturbances; hematological disorders (methemoglobinemia, nicotinamide adenine dinucleotide-dependent methemoglobin reductase 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, crystalluria [5]. Most SAs can cause photosensitization [6]. CA, especially antimicrobials, are often considered to be the cause of many hypersensitivity reactions. Immediate IgE-mediated reactions have been reported in the literature, but they are much less common than delayed skin reactions [7, 8].

SAs are usually caused by idiosyncratic drug SR (IADR). Although SMX-TMP is considered a safe drug, it is more likely to cause idiosyncratic SR than most other SAs. SMX participates in IADR based on the formation of protein adducts and immune stimulation. But only one SMX cannot explain all IADRs for combined SMX-TMPs, because TMPs (when assigned separately) are also associated with heavy IADRs, but the IADR frequency is higher for SMX-TMPs than for its components. To understand the mechanism of TMP-induced IADR, its potential for covalent binding to proteins after bioactivation and formation of reactive metabolites should be considered. There is evidence that TMP undergoes oxidative bioactivation either through the formation of quinonymine or through O-demethylation followed by the formation of quinone methide. Additional in vitro studies involving human liver microsomes have shown that CYP3A4 is a major enzyme that promotes TMP bioactivation [9, 10].

It is well known that SA causes liver damage. Most often, the damage appears suddenly within one to three weeks after starting therapy, often accompanied by signs of hypersensitivity [11]. The hepatotoxicity of SA may be part of the hypersensitivity spectrum. The severity of liver

damage varies widely, but most SA-related cases are mild to moderate in severity. Thus, SA remains one of the most common causes of acute liver failure caused by drugs. They account for from 5% to 10% of the latter [12].

The literature presents data related to more than 20 reported cases of acute pancreatitis caused by SMX-TMP [13]. Acute interstitial nephritis has also been reported with SMX-TMP [14].

Despite the widespread use of SMX-TMP and many years of experience with this drug, it is important to remain vigilant about its possible SR, especially aseptic meningitis. Among antimicrobial drugs, SMX-TMP was noted as one of the most common components of AM therapy. The probable mechanism of the latter's development is related to its interaction with immune receptors. According to this concept, the drug can stimulate various T-cell responses of type IV [15]. There are also reports of aseptic meningitis the separate use of TMP and SMX [16].

There are reports of hallucinations caused by SMX-TMP [17], one patient after peroral SMX-TMP therapy of the urinary tract developed visual hallucinations and delusions [18]. Another patient developed an acute psychotic attack with convulsions after six doses of SMX-TMP intravenously [19]. A similar attack occurred in a young man taking SMX-TMP [20]. The risk of acute psychosis increased with increasing daily dose of this drug and in particularly vulnerable patients [21].

The mechanisms by which SAs cause abrupt changes in behavior leave many questions. The literature indicates a link between glutathione deficiency and increased toxicity of SMX-TMP. The antioxidant properties of glutathione usually prevent the formation of unstable SA metabolites, which are responsible for SMX-TMP. Thus, glutathione deficiency has been shown to increase the risk of toxic metabolites of SMX-TMP. Another mechanism that is likely to contribute to this toxicity is the intervention of SA in the synthesis of tetrahydrobiopterin, which is used in the synthesis of dopamine and serotonin, and a deficiency of these neurotransmitters can potentially contribute to the emergence of CNS [22].

SMX-TMP is often prescribed for community-acquired methicillin-resistant Staphylococcus aureus infections, especially in the treatment of the urinary tract and respiratory tract. However, physicians in these cases should be aware of SR in the form of life-threatening thrombocytopenia when using this drug, and the low platelet count associated with SMX-TMP carries potentially life-threatening complications. When used in therapeutic doses of SMX-TMP for adults, the expected increased risk of this SR is 38% [23] [24]. Reduction of signs of thrombocytopenia in patients begins within 1-2 days after drug withdrawal. In most cases, it is enough to stop taking the drug that causes this SR [25].

Information on the toxic effects of SMX on white blood cell counts is limited and suggests that this SR is rare and associated with idiosyncratic and dose-dependent toxic effects of SMX-TMP [26].

It is also known that the use of SMX / TMP can lead to methemoglobinemia: it accelerates the production of methemoglobin to the level when the process of inhibition of repair enzymes in red blood cells begins [27, 28]. Therefore, 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.

One of the undesirable effects of SMX-TMP is hypoglycemia. SMX can cause hypoglycemia because it contains the same structural group of CA as oral hypoglycemic agents, sulfonylurea derivatives. SMX can mimic the effects of sulfonylureas on the pancreas by acting as a stimulant of insulin secretion. This hypothesis is confirmed by an increase in insulin levels in patients taking SMX-TMP. The latter is metabolized in the liver, and most of it can be excreted unchanged in the urine. Renal failure increases the risk of hypoglycaemia due to an increase in the half-life of SMX-TMP, which can be up to 20-50 hours in patients with this pathology. 5 days of use will promote the accumulation of the drug, and prolonged hypoglycemia, which is observed after, will correspond to the dose-dependent PR SMX-TMP [29].

SMX-TMP is prescribed to treat patients with HIV / AIDS, in whom it sometimes causes severe and prolonged hypoglycaemia when used in high doses [30]. It is known that the prophylactic dose of SMX-TMP can be safely administered to adult patients, however, special attention should be paid to the appointment of SMX-TMP in high doses in the

treatment of pneumonia caused by Pneumocystis jiroveci and patients with comorbidities including renal failure or malnutrition [31]. Malnutrition, especially in depleted patients and in patients with chronic renal failure, high doses of SMX-TMP are risk factors for severe hypoglycemia. [31].

Monitoring of blood glucose levels is recommended when SMX-TMP and antihyperglycemic agents are co-administered to quickly detect and treat potential hypoglycaemia due to excessive insulin secretion, especially in patients with comorbidities [32]. Risk factors for these SRs include old age, renal impairment, prolonged starvation and overdose of SMX-TMP. [33].

Glibenclamide and glipizide (sulfonylureas derivates) are classic hypoglycemic agents [34]. However, their positive effect may be altered by drugs that inhibit CYP2C9 The latter is involved in carbohydrate metabolism. SMX-TMP was found to inhibit CYP2C9 activity. SMX-TMP has been reported to be associated with a sixfold increase in the risk of hospitalization for hypoglycemia in elderly patients taking glibeclamide compared with those taking amoxicillin [35]. The use of SMX-TMP resulted in a 3-fold increase in the chances of hospitalization due to hypoglycaemia in patients taking glipizide compared with those taking cephalexin. In addition, patients with diabetes are more susceptible to infection due to hyperglycemia and impaired immune function [36]. Therefore, SMX-TMP may cause hypoglycaemia, which may be prolonged (approximately 12 hours), especially in patients with risk factors for hypoglycaemia. Common risk factors for the latter include renal impairment, prolonged starvation, malnutrition, and the use of high doses of SMX-TMP [37]. A case of SMX-TMP-associated hypoglycaemia in a patient with Hodgkin's lymphoma has been reported in the literature [38].

Thus, although hypoglycemia is rare, ignoring it can be life-threatening. Therefore, clinicians should be aware of this SR associated with SMX-TMP therapy, especially in patients with renal impairment.

SMX-TMP is indicated for the treatment of kidney and urinary tract infections and is included in the list of essential medicines. TMP has structural and pharmacological similarities to the potassium-sparing diuretic amiloride. TMP causes blockage of epithelial sodium channels in the distal nephron and disrupts potassium excretion by the kidneys [39]. There is a significant dose-dependent risk of hyperkalemia in the elderly receiving SMX-TMP [40]. Approximately 80% of patients receiving SMX-TMP have an increase in serum potassium [41, 42]. Despite reports of SMX-TMP-induced hyperkalemia in AIDS patients and patients with end-stage renal disease and patients receiving high doses of SMX-TMP, there are other reports that hyperkalemia may occur even in patients with when using a standard dose of SMX-TMP [43, 44]. Severe hyperkaliemia may mimic atrioventricular block [45]. Therefore, electrolyte disturbances, especially hyperkaliemia and hyposodemia [46], may be detected in patients taking SMX-TMP. These disorders are more common in patients receiving high doses, but may also be detected after taking low doses [47, 48, 49, 50].

Increased serum creatinine is secondary to the well-known mechanism associated with the TMP, which competitively inhibits renal tubular creatinine secretion [51]. SMX-TMP is often used in HIV-infected patients with elevated creatinine and hyperkalemia [52]. However, hyperkalemia requiring pharmacological correction is more common in patients receiving high doses of SMX-TMP [53].

Hyposodemia in combination with hyperkaliemia has been reported in publications using SMX-TMP [54]. The high incidence (72.3%) of hyponatremia among hospitalized patients is associated with the use of high doses of SMX-TMP [55]. Severe hyponatremia can lead to cerebral edema, seizures, coma, and eventually death. Regarding the mechanism of hyponatremia with SMX-TMP treatment, it has been suggested that aldosterone-mediated SMX-TMP blocks sodium reabsorption in collecting tubules, causing a decrease in serum sodium. Because, a component of SMX-TMP is TMP, which is structurally similar to potassium-sparing diuretics, which inhibit sodium reabsorption in the distal nephron, leading to hyposodemia and / or hyperkalemia [57]. Given the above, SMX-TMP is considered the optimal antibacterial agent, but monitoring of electrolyte disturbances, especially serum sodium, is necessary, especially in the elderly and those with renal dysfunction throughout SMX-TMP therapy to prevent potentially life-threatening hyposodemia.

Adverse drug reactions are often the cause of morbidity and mortality worldwide [58]. Studies have shown that HIV-infected people are a hundred times more susceptible to adverse drug reactions than other patients, and progressive immunodeficiency creates an even greater risk of SR [59].

The number of SRs associated with SMX-TMP and other SAs has recently increased from approximately 2-8% in the general population to 43% among HIV-infected people and to 69% among people living with AIDS [60]. One possible cause of SMX-TMP PR is systemic glutathione deficiency in these patients, which increases the likelihood of circulating toxic intermediates such as hydroxylamine derivatives, which play a key role in initiating SR drugs [61]. In addition, mutations were found to be associated with hypersensitivity to SMX [62].

SMX-TMP is generally well tolerated by patients uninfected with immunodeficiency virus (HIV), and severe SR occurs in approximately 3-5%. However, there are reports of severe systemic reactions, similar to septic shock, after administration of SMX-TMP. The mechanism of the shock caused by SMX-TMP remains unclear. It is currently unknown whether this PR is a form of immune activation, cellular toxicity or nonspecific immune response. There is evidence that the shock induced by SMX-TMP is probably not a traditional anaphylactic reaction [63]. Therefore, SMX-TMP can cause unusual but serious complications, such as renal and electrolyte disturbances and rare life-threatening reactions (for example, Stevens-Johnson syndrome). [64].

Stephen-Johnson syndrome and toxic epidermal necrolysis are considered as a single spectrum of diseases characterized by exfoliation of dead epidermis and erosion of mucous membranes, along with a positive sign of Nikolsky [65]. Among the most common sulfonamide drugs that cause this reaction is SMX-TMP, which accounted for about 20% of cases [66, 67]. There are data when the development of Stephen-Johnson syndrome and toxic epidermal necrolysis due to the use of SMX-TMP was observed [68, 69]. Therefore, to prevent these PRs, physicians should be aware that SMX-TMP and TMP may be the cause of Stephen-Johnson syndrome or toxic epidermal necrolysis [70, 71, 72], taking into account their patient's family history of the symptom when prescribing.

The negative effects of SMX-TMP on the fetus in early pregnancy are associated with an increased risk of miscarriage. TMP has the ability to cross the placenta and affect folic acid metabolism in trophoblast cells by inhibiting dihydrofolate reductase, which can lead to miscarriage due to disruption of DNA synthesis [72,73]. About 3.2% of women take SMX-TMP during pregnancy [74]. It has been reported that taking SMX-TMP in early pregnancy leads to fetal malformations (nervous system damage and cardiovascular disease) [75]. SMX-TMP inhibits folic acid synthesis, but daily folic acid intake may reduce its teratogenic effects [76]. Therefore, the benefits of SMX-TMP, as with any drug during pregnancy, should be weighed against its potential risks.

Thus, SMX-TMP is an effective antibacterial agent, has prophylactic and chemotherapeutic effects, but there is a risk of frequent PR: hyponatremia; hyperkalemia; hypoglycemia; lesions of the nervous system and changes in mental status; hepato-, hemo- and nephrotoxicity; reproductive anomalies; Hypersensitivity syndrome, etc. Therefore, it is necessary to be aware of the potential consequences of SMX-TMP, especially in patients with renal impairment, diabetes, the elderly or infected with HIV / AIDS. Serum creatinine and potassium should be monitored in patients receiving high doses of SMX-TMP. Careful monitoring of total blood cell counts, including platelet counts, before and during SMX-TMP therapy; electrolyte monitoring for several days after initiation of therapy for hyperkalaemia or hyponatraemia. Despite the widespread use and many years of experience in the use of SMX-TMP in modern pharmacotherapy, vigilance should be maintained to prevent the development of adverse events.

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