

Considerations when prescribing trimethoprim-sulfamethoxazole

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Introduced in 1968, trimethoprim-sulfamethoxazole remains a popular antibiotic because of its low cost, effectiveness and familiarity among clinicians. It is the most frequently prescribed antibiotic for urinary tract infections in Canada.¹ Other indications include treatment of infections caused by *Pneumocystis jiroveci*, *Toxoplasma gondii*, *Stenotrophomonas maltophilia* and community-associated methicillin-resistant *Staphylococcus aureus*. In addition, among patients with depressed CD4 counts from infection with HIV, the use of low-dose trimethoprim-sulfamethoxazole for prophylaxis against *P. jiroveci* and *T. gondii* is associated with decreased mortality caused by opportunistic infections.² With up to 4000 prescriptions for trimethoprim-sulfamethoxazole dispensed each week in Ontario,³ this drug is used by hundreds of thousands of Canadians each year.

More than 40 years of widespread use has provided ample opportunity to identify the many adverse events associated with trimethoprim-sulfamethoxazole. Although this drug is well tolerated by many patients, it is associated with several potentially serious adverse reactions. Most of these associations are supported only by case reports and case series, but some have been the subject of volunteer studies and observational studies. Many of these adverse effects are rare, however others are predictable and several can be life-threatening. Here we provide an overview of the various toxicities associated with the use of trimethoprim-sulfamethoxazole and offer a simple mnemonic — “NOT RISKY?” — to help clinicians recall the various toxicities associated with this drug (Table 1).

Literature review

We performed a search using MEDLINE (1950 to August 2011) and Embase (1980 to 2011), along with a manual review of relevant bibliographies. We used the permuted index search tool in Ovid to search MEDLINE with the term “trimethoprim-sulfamethoxazole combination” and the subheadings “adverse effects” and “toxicity.” Using the keyword search, we searched for the terms “cotri-

mazole” and “trimethoprim-sulfamethoxazole combination,” and then combined each term with each of the following terms: “cytochrome P450,” “hyperkalemia,” “hypoglycemia,” “hematologic,” “anemia,” “neutropenia,” “thrombocytopenia,” “hemolysis,” “hypersensitivity,” “drug interaction,” “renal” and “methemoglobinemia.” We used a similar search strategy for the Embase database.

We included all types of reports (case reports, volunteer studies, observational studies and randomized trials), and we excluded articles that were not available in English, were conducted in animals or did not include information about the safety of trimethoprim-sulfamethoxazole.

We identified 925 publications that described adverse events involving trimethoprim-sulfamethoxazole. After we assessed the citations for eligibility, 88 articles were reviewed and 70 were included in this review. J.H. reviewed all citations for eligibility and full-text articles for quality. D.J. reviewed selected articles for quality. Conflicts were resolved by consensus.

N: Neurologic effects

Trimethoprim-sulfamethoxazole readily crosses the blood-brain barrier⁴⁰ and is associated with various adverse neurologic events, all of which have been described only in case reports. Numerous instances of aseptic meningitis (involving high doses of trimethoprim alone or trimethoprim-sulfamethoxazole) have been reported, many of them involving patients with pre-existing autoim-

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KEY POINTS

- Trimethoprim-sulfamethoxazole is an effective antimicrobial, but it has numerous adverse effects, some of which can be severe.
- Important drug-drug interactions include the development of hyperkalemia with renin-angiotensin system blocking agents or drugs that inhibit kaliuresis, and hypoglycemia with the concomitant use of some hypoglycemic agents.
- Hyperkalemia in conjunction with use of trimethoprim-sulfamethoxazole can also occur in patients with impaired renal function, diabetes, older age or AIDS.
- Other toxicities include neurologic, renal and reproductive abnormalities, decreased oxygen-carrying capacity and other hematologic effects, and drug hypersensitivity syndromes.

Table 1: Summary of the adverse effects associated with the use of trimethoprim–sulfamethoxazole

Adverse effect	Manifestation	Postulated risk factor	Frequency
N Neurologic effects	Aseptic meningitis ⁴	Autoimmune disease and HIV ⁴	Uncommon
	Tremor ⁵		Rare
	Delirium ^{5,6}	Older age, previous neurologic injury, infection, metabolic disturbances ^{5,6}	Relatively uncommon
	Gait disturbances ^{5,6}		Rare
O Decreased oxygen-carrying capacity and other hematologic abnormalities	Methemoglobinemia ^{7,8}	<ul style="list-style-type: none"> • Neonates less than 6 weeks of age • Nicotinamide adenine dinucleotide–dependent methemoglobin reductase (also known as cytochrome-<i>b</i>₅ reductase) deficiency 	Rare
	Blood dyscrasia ^{9,10}	<ul style="list-style-type: none"> • Malnutrition, specifically folic acid deficiency • Glucose-6-phosphate dehydrogenase deficiency 	Uncommon
T Toxic epidermal necrolysis and other hypersensitivity reactions	Drug hypersensitivity (fever, rash and internal organ involvement, such as blood dyscrasia, hepatitis and acute interstitial nephritis) ^{11–16}	Previous or family history of drug hypersensitivity syndrome	Uncommon
	Simply exanthema or fixed drug eruption ¹⁷		Common
R Reproductive toxicity	Structural malformations (neural tube, cardiovascular and possible oral cleft and urinary system) ¹⁸	<ul style="list-style-type: none"> • Low levels of folic acid¹⁹ • Exposure during the first trimester²⁰ 	Uncommon
	Small-for-gestational-age ²¹	Exposure during the second and third trimesters ²¹	Uncommon
	Hyperbilirubinemia ²⁰	Exposure after 32 weeks' gestation ²⁰	Rare
I Interactions with other drugs	<ul style="list-style-type: none"> • Inhibition of the cytochrome P450 system (2C8 and 2C9)²² • Renal drug transporter inhibition (organic cation transporter and organic anion transporter)^{23,24} 	Polypharmacy	Common
S Sugar	Hypoglycemia ^{25–30}	<ul style="list-style-type: none"> • Renal insufficiency²⁵ • High-dose trimethoprim–sulfamethoxazole²⁵ • Concomitant use of sulphonylureas or meglitinides^{26–30} 	Common as a drug–drug interaction; rare when trimethoprim–sulfamethoxazole is used in isolation
K Hyperkalemia and other kidney effects	Hyperkalemia ^{31–37}	<ul style="list-style-type: none"> • Renal insufficiency^{34,35} • High-dose trimethoprim–sulfamethoxazole^{32,35} • Older age³⁴ • Diabetes³⁴ • AIDS³⁹ • Concomitant use of ACE inhibitors, angiotensin receptor blockers, spironolactone or NSAIDs^{36,37} 	Common
	Acute interstitial nephritis ¹⁵		Uncommon
	Obstructive tubulopathy ³⁸		Uncommon
	Hyponatremia ^{31,35}		Uncommon
Y? Why not consider an alternate antimicrobial?			

Note: ACE = angiotensin-converting enzyme, NSAID = nonsteroidal anti-inflammatory drug.

immune disease or HIV infection.⁴ The mechanism of toxicity is not well defined, but an immunologic process is suggested.⁴ Clinically, drug-induced meningitis is indistinguishable from other causes of aseptic meningitis, and the diagnosis is suggested by negative results of microbiologic testing, temporal association with drug initiation, prompt improvement following discontinuation of the offending drug and the absence of another identifiable cause.

Other rare adverse neurologic effects include delirium and milder effects such as tremor,⁵ which typically occurs in the first week of therapy, and gait disturbances.^{5,6} In general, neurologic symptoms occur within days of continuous treatment and resolve following discontinuation of trimethoprim–sulfamethoxazole.

O: Decreased oxygen-carrying capacity and other hematologic abnormalities

Several case reports describe methemoglobinemia in patients taking trimethoprim–sulfamethoxazole.^{7,8} Although this adverse effect is rare, the sulfamethoxazole component can induce methemoglobinemia, which occurs when more than 1% of heme iron exists in the ferric (Fe^{3+}) redox state, rather than the usual ferrous (Fe^{2+}) state. Methemoglobin cannot bind oxygen, resulting in functional anemia and bluish-brown discoloration of the skin.

Several uncommon but potentially serious

blood dyscrasias have been reported following the use of trimethoprim–sulfamethoxazole. The incidence of severe hematologic toxicity is unknown, but estimates range up to 1.7–5.5/100 000 prescriptions.^{9,10} Several mechanisms have been implicated and described in case reports (Table 2). Generation of antibodies to the glycoprotein IIb/IIIa complex on platelets can cause immune thrombocytopenia, which is typically observed within the first week of treatment and is generally reversible on discontinuation of the drug.^{47–49}

Although uncommon at therapeutic doses, the inhibition of folate metabolism by trimethoprim can cause dose-related leukopenia and megaloblastosis, both of which are responsive to folinic acid.^{41,42} Periodic monitoring of the complete blood count may be advisable in patients receiving a high dose of trimethoprim–sulfamethoxazole for extended periods.

Finally, oxidative hemolysis has rarely been reported in patients with glucose-6-phosphate dehydrogenase deficiency.^{44–46} Although a few small observational studies have shown that patients with this deficiency often tolerate the drug without difficulty, clinicians should be aware of this potential risk.^{51–53}

T: Toxic epidermal necrolysis and other hypersensitivity reactions

Immune-mediated idiosyncratic reactions are often associated with a reactive metabolite, lead-

Table 2: Hematologic abnormalities associated with the use of trimethoprim–sulfamethoxazole

Hematologic abnormality	Mechanism	Clinical manifestation	Risk factor
Bone marrow suppression	Folate deficiency ^{41,42}	Megaloblastic anemia, thrombocytopenia	Poor nutritional status, concomitant anti-folate drugs (e.g., methotrexate) ⁴³
	Drug hypersensitivity syndrome	Any hematologic abnormality in conjunction with fever and rash, most commonly lymphopenia or lymphocytosis	Family history of drug hypersensitivity
Oxidative hemolysis	Oxidative stress ^{44–46}	Hemolytic anemia	Glucose-6-phosphate dehydrogenase deficiency ^{44–46}
Drug-induced thrombocytopenia	Antibody-mediated destruction of platelets with specificity for the glycoprotein IIb/IIIa complex ^{47–49}	Thrombocytopenia	
Methemoglobinemia	Increase in methemoglobin (iron moiety in the hemoglobin tetramer is in the ferric state [Fe^{3+}] instead of the usual ferrous state [Fe^{2+}]) ^{7,8}	Cyanosis, “chocolate-coloured” blood, and falsely low oxygen saturation on pulse oximetry but a normal oxygen saturation on arterial blood gas measurement (“saturation gap”)	Neonates less than 6 weeks of age, ⁵⁰ nicotinamide adenine dinucleotide–dependent methemoglobin reductase (cytochrome- b_5 reductase) deficiency

ing to drug-specific antibodies or T-lymphocyte activation. Simple exanthems and fixed drug eruptions are some of the most common adverse effects of trimethoprim–sulfamethoxazole, occurring in about 3% of hospital inpatients taking the drug.⁵⁴ Less common is a classic drug hypersensitivity syndrome manifesting with a triad of fever, exanthem and varying degrees of internal organ involvement. Typical manifestations vary in presentation and severity. They include hematologic abnormalities (most commonly lymphopenia or lymphocytosis, but occasionally eosinophilia), cholestatic or hepatocellular hepatitis (which may progress to fulminant hepatic failure), renal dysfunction (including acute interstitial nephritis),^{11–15} Stevens–Johnson syndrome and potentially life-threatening toxic epidermal necrolysis.¹⁶ If there has been no previous exposure to trimethoprim–sulfamethoxazole, these reactions typically begin after at least four or five days of therapy but may occur after several weeks of prolonged therapy. Importantly, the presence of fever can mislead clinicians by suggesting an unresolved infection, thereby delaying discontinuation of trimethoprim–sulfamethoxazole.

R: Reproductive toxicity

Folic acid is important for normal development of the fetus and placenta.¹⁹ Although the inhibitory effect of trimethoprim on dihydrofolate reductase is more selective for the bacterial isozyme than for the human isozyme, the rapid rate of cell division during pregnancy potentiates the drug’s anti-folate effect in humans. A host of

adverse effects have been well described with use of trimethoprim–sulfamethoxazole during pregnancy and the neonatal period.

Case–control studies have reported an association between exposure to trimethoprim–sulfamethoxazole during the first trimester and an increased risk of structural malformations. These include defects of the neural tube, cardiovascular system and possibly oral cleft and urinary system.^{18,19,55} The risk of major malformations, however, is reduced with supplementation with folic acid.^{56,57} In patients with first-trimester exposure to trimethoprim–sulfamethoxazole, detailed ultrasonography should be performed at 18–20 weeks’ gestation.²⁰

A recent case–control study reported a 60% increased risk of small-for-gestational-age among the offspring of women exposed to trimethoprim–sulfamethoxazole during the second and third trimesters, compared with those exposed to other urinary antimicrobials.²¹ The use of sulfamethoxazole has classically been discouraged for pregnant women at 32 weeks’ gestation or later because of the risk of hyperbilirubinemia resulting from the drug’s displacement of bilirubin from albumin. Although there are no case reports describing this toxicity in the literature, the use of an alternative antibiotic should be considered in most situations.

Although the overall risk of methemoglobinemia is low with trimethoprim–sulfamethoxazole, it may be increased in neonates younger than six weeks because of lower levels of nicotinamide adenine dinucleotide–dependent methemoglobin reductase activity.⁵⁰ If there is a strong clinical

Table 3: Potential and proven drug interactions involving trimethoprim–sulfamethoxazole		
Drug	Mechanism of interaction	Complication
S-warfarin	CYP450 2C9 inhibition ²²	Increased international normalized ratio and hemorrhage ^{60–62}
Oral hypoglycemic drugs: Sulfonylureas (e.g., glyburide, gliclazide, glimepiride, glipizide) Meglitinides (e.g., repaglinide)	CYP450 2C9 inhibition, CYP450 2C8 inhibition ²²	Hypoglycemia ^{25–30}
Methotrexate	Organic anion transporter inhibition in the renal tubule, ^{23,24} anti-folate effect	Methotrexate toxicity (cytopenia, hepatotoxicity, mucositis) ⁴³
Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, celecoxib, piroxicam)*	CYP450 2C9 inhibition Trimethoprim-induced antikaliuretic effect ³¹	Hypertension, hyperkalemia
Angiotensin receptor blocking agents and angiotensin-converting enzyme inhibitors Spironolactone	Trimethoprim-induced antikaliuretic effect	Hyperkalemia ^{36,37}
Fluvastatin*	CYP450 2C9 inhibition	Myalgia, myositis, rhabdomyolysis
Phenytoin (also metabolized by 2C19)	CYP450 2C9 and 2C8 inhibition	Phenytoin toxicity ^{17,63}

*Potential interaction.

indication for trimethoprim–sulfamethoxazole therapy in a newborn, it is recommended to start the drug after four to six weeks of age.⁵⁸ Although trimethoprim–sulfamethoxazole is detected in breast milk, exposure through breast milk appears to be safe in healthy breastfed infants.⁵⁹

I: Interactions with other drugs

Drug interactions occur when one drug alters the clinical response to another. Several important drug interactions can occur with trimethoprim–sulfamethoxazole (Table 3).

Interactions involving the cytochrome P450 enzyme system

The cytochrome P450 enzyme system is responsible for the oxidative metabolism of hundreds of drugs. Among the various cytochrome P450 enzymes, the 2C8 and 2C9 isoforms are of particular relevance in patients receiving trimethoprim–sulfamethoxazole because the 2C8 isoform is inhibited by trimethoprim and the 2C9 isoform is inhibited by sulfamethoxazole. Consequently, drugs metabolized by cytochrome P450 2C8 or 2C9 can accumulate during treatment with trimethoprim–sulfamethoxazole.²² Whereas several interactions are theoretically possible under this mechanism, two merit particular emphasis: oral hypoglycemic agents and warfarin.

Sulfonylurea agents (e.g., glyburide, gliclazide, glimepiride and glipizide) are metabolized by cytochrome P450 2C9, whereas repaglinide, a meglitinide, is metabolized by cytochrome P450 2C8.⁶⁴ Pharmacokinetic studies have shown that trimethoprim–sulfamethoxazole increases plasma levels of sulfonylureas⁶⁵ and repaglinide,²⁶ leading to an increased release of pancreatic insulin and symptomatic hypoglycemia.^{27,28} The clinical consequences of the interaction between trimethoprim–sulfamethoxazole and sulfonylureas have been described in case reports and observational studies, which have reported four- to sixfold increases in the risk of hospital admission for hypoglycemia following the addition of trimethoprim–sulfamethoxazole to regimens containing a sulfonylurea.^{28–30}

Warfarin also has the potential to interact with trimethoprim–sulfamethoxazole. Commercially available warfarin exists as two enantiomers, R- and S-warfarin. Of these, the latter is roughly five times more biologically active and is metabolized by cytochrome P450 2C9.^{66,67} Co-prescription of trimethoprim–sulfamethoxazole increases S-warfarin levels in most patients.⁶⁰ Two recent population-based studies have shown that among patients receiving warfarin, the use of

trimethoprim–sulfamethoxazole is associated with a two- to threefold increased risk of gastrointestinal hemorrhage relative to other antibiotics.^{61,62}

Interactions involving drug transporters

Trimethoprim also inhibits the renal organic cation transporter and sulfamethoxazole inhibits the organic anion transporter,^{68,69} transport systems that normally facilitate the renal elimination of several drugs. In children receiving methotrexate, treatment with trimethoprim–sulfamethoxazole decreases organic anion transporter–mediated renal clearance of methotrexate by 40%,^{23,24} increasing the risk of methotrexate toxicity (including cytopenia, mucositis, hepatotoxicity and gastrointestinal symptoms). The anti-folate effect of trimethoprim may also contribute to this interaction, as documented in several case reports and one observational study.⁴³ Consequently, the Canadian 3E Initiative in Rheumatology⁷⁰ has formally recommended against the use of trimethoprim–sulfamethoxazole by patients receiving methotrexate.

S: Sugar (hypoglycemia)

In patients taking trimethoprim–sulfamethoxazole, the most common reason for hypoglycemia is the potentiation of concomitant sulfonylurea or repaglinide therapy.^{26–30,65} However, sulfamethoxazole itself can directly cause pancreatic insulin release, particularly at higher doses and in patients with renal impairment.²⁵ This likely reflects the drug's structural similarity to the sulfonylureas. Hypoglycemia typically develops shortly after the patient begins to receive trimethoprim–sulfamethoxazole, and resolution may be delayed in patients with renal failure. To minimize the risk of hypoglycemia, reduction of dosage should be considered in patients with a creatinine clearance of less than 30 mL/min.

K: Hyperkalemia and other kidney effects

Trimethoprim–sulfamethoxazole can influence kidney function in several ways, which can result in hyperkalemia and hyponatremia, among other kidney effects.

Hyperkalemia

Hyperkalemia was first recognized during high-dose trimethoprim–sulfamethoxazole therapy for *P. jiroveci*, but it is increasingly appreciated as a potential complication at doses usually prescribed. This is a predictable and potentially fatal adverse effect of treatment with trimethoprim–

sulfamethoxazole. Structurally similar to the potassium-sparing diuretic amiloride, trimethoprim inhibits potassium elimination in the distal nephron.³¹ In a randomized controlled trial involving 97 outpatients taking trimethoprim–sulfamethoxazole, 6% of patients experienced hyperkalemia (serum potassium level > 5.5 mmol/L) and most patients (81.5%) experienced an increase in serum potassium level.³⁹ Among observational studies of patients in hospital, the incidence of hyperkalemia (serum potassium level > 5.0 mmol/L) has been reported to exceed 20%.^{32–34}

Hyperkalemia tends to develop after several days of therapy,^{32,34} and the risk factors predictably include diabetes,³⁴ renal insufficiency,^{34,35} older age,³⁴ AIDS,³⁹ higher doses of trimethoprim^{32,35} and treatment with other drugs that inhibit kaliuresis such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers³⁶ and spironolactone.³⁷ A recent population-based case–control study involving 439 677 patients taking ACE inhibitors or angiotensin receptor blockers

found a sevenfold increased risk of hospital admission for hyperkalemia among those taking trimethoprim–sulfamethoxazole compared with those taking other antibiotics used for urinary tract infections.³⁶ We suggest that physicians monitor patients for hyperkalemia following a few days of trimethoprim–sulfamethoxazole treatment at a standard dose, especially patients with impaired renal function, which may include older patients, those with diabetes or AIDS, and those also taking ACE inhibitors, angiotensin receptor blockers or spironolactone.

Other kidney effects

Although not as common as hyperkalemia, trimethoprim-mediated blockade of epithelial sodium channels in the distal nephron may also increase the risk of hyponatremia.^{31,35}

Patients with chronic renal insufficiency are at increased risk of adverse effects associated with use of trimethoprim–sulfamethoxazole.^{25,34,35} Although uncommon, this drug can also cause renal injury in otherwise healthy patients. This adverse effect generally manifests as a form of drug hypersensitivity syndrome, most commonly acute interstitial nephritis.²⁹ The classic findings include fever, rash and an elevated creatinine level. If present, eosinophilia and eosinophiluria support the diagnosis, but their absence does not exclude it.

A much less common mechanism by which trimethoprim–sulfamethoxazole may cause acute kidney injury is obstructive tubulopathy resulting from the intraluminal precipitation of sulfamethoxazole. This phenomenon has been described in one case report but is more typically associated with older sulfonamide antibiotics.³⁸

Box 1: Applying the results of this review to a fictional case in clinical practice

A 67-year-old woman presents to her family physician with a nonspecific complaint of weakness and an unwell feeling. She recently completed a seven-day course of trimethoprim–sulfamethoxazole for a urinary tract infection. Her longstanding medications include ramipril for hypertension and metformin for type 2 diabetes. Her physical examination is unremarkable. Results of routine blood tests show hyperkalemia (serum potassium level 6.9 [normal 3.5–5.0] mmol/L) and are otherwise normal.

Hyperkalemia developed because of the potassium-sparing effect of trimethoprim on the distal tubule of the kidney, which was exacerbated by diabetes and the concomitant use of ramipril. Symptomatic treatment of hyperkalemia is started and ramipril is temporarily withheld. The patient's condition improves without consequence.

Box 2: Suggestions for reducing the risks of prescribing trimethoprim–sulfamethoxazole, based on the results of our literature review

When prescribing trimethoprim–sulfamethoxazole, consider the following:

- Prescribing an alternative antibiotic if clinically indicated, particularly for pregnant patients in the first trimester, patients with glucose-6-phosphate dehydrogenase deficiency or patients taking methotrexate.
- Monitoring electrolytes within a few days of starting therapy to identify hyperkalemia or hyponatremia in specific patient groups, including those with reduced renal function, diabetes, older age and AIDS. Electrolytes should also be monitored in those taking higher doses of trimethoprim–sulfamethoxazole and those also taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or spironolactone.
- Monitoring the international normalized ratio within three to four days of starting therapy in patients taking warfarin.
- Monitoring for hypoglycemia within a few days of starting therapy for patients taking oral hypoglycemic agents (e.g., sulfonylureas and meglitinides).

Y: Why not consider an alternate antimicrobial?

Although trimethoprim–sulfamethoxazole has numerous benefits, particularly in the care of patients with HIV and methicillin-resistant *S. aureus*, it is associated with multiple toxicities. However, all drugs carry adverse effects. When considering other antimicrobials, clinicians should remember that areas of uncertainty remain, particularly with newer agents.

Gaps in knowledge

Although trimethoprim–sulfamethoxazole is a popular, effective and inexpensive drug with a long history of use, it is associated with a range of adverse effects, some with fatal outcomes. Box 1 provides a fictional example of a drug–drug

interaction with trimethoprim–sulfamethoxazole. The exact mechanisms of toxicity and occurrence for some of the adverse effects of trimethoprim–sulfamethoxazole have yet to be defined. In addition, more studies are needed to understand the influence of pharmacogenomics on the safety profile of trimethoprim–sulfamethoxazole.

Clinicians should be cognizant of the potential consequences of prescribing trimethoprim–sulfamethoxazole, monitor patients for adverse events during therapy or use an alternate antibiotic when appropriate. Box 2 provides suggestions for reducing the risks associated with trimethoprim–sulfamethoxazole.

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