Canterbury District Health Board
Te Poari Hauora o Waitaha

Antimicrobial Stewardship Bulletin

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Trimethoprim and trimethoprim/sulfamethoxazole

Drug-drug interactions and tips for safe prescribing

- Trimethoprim and sulfamethoxazole inhibit different steps in the folate pathway and, when used together, their antibacterial effects against susceptible organisms are synergistic.
- Trimethoprim has its niche in the treatment of urinary tract infections. Trimethoprim/sulfamethoxazole is used less frequently due to the availability of more active agents with fewer adverse effects. It is included in some CDHB adult antimicrobial guidelines including MRSA soft tissue infections, pertussis, prostatitis and some gastrointestinal infections eg. *Salmonella* spp. (Pink Book, 2015).
- This bulletin outlines some of the significant drug interactions that may occur with these agents **(column 1)**, and provides some advice for safe prescribing and administration **(column 2)**. General discussion on adverse reactions is beyond the scope of this bulletin.

INTERACTIONS

TRIMETHOPRIM AND POTASSIUM-SPARING DRUGS

Trimethoprim is structurally similar to the potassium-sparing diuretic, amiloride. Both agents impair the elimination of potassium in the distal nephron, which may result in its accumulation in blood. Most patients (~80%) receiving standard trimethoprim doses experience an increase in serum potassium of ≥ 0.4 mmol/L during a short course. Significant hyperkalaemia (> 5.4 mmol/L) occurs in ~6% of cases[1].

Predictably, risk factors for hyperkalaemia (see box below) increase risk with trimethoprim. For example, use of trimethoprim/sulfamethoxazole in older patients (> 65 years) on an ACE inhibitor or angiotensin receptor antagonist was associated with a 7-fold increased risk of hyperkalaemia-related hospital admission, compared with amoxicillin[2]. If multiple risk factors exist, trimethoprim should be avoided. If a suitable alternative is not available, potassium must be monitored closely to help prevent cardiac events.

Risk factors for hyperkalaemia with trimethoprim

- Co-administration with agents that cause hyperkalaemia, eg.
  - ACE inhibitors
  - Angiotensin II receptor antagonists
  - Potassium sparing diuretics
  - Potassium supplements/salt substitutes containing potassium
  - NSAIDs
- Renal dysfunction
- Diabetes
- Advanced age

INHIBITION OF CYTOCHROME P450 2C8/9 (CYP2C8/9)

Trimethoprim and sulfamethoxazole inhibit cytochrome P450 2C8 and 2C9, respectively, and may delay elimination of substrate drugs. This is most relevant for agents with a narrow therapeutic index such as phenytoin and warfarin (Pink Book 2015, p196). For example, older patients on warfarin had a 2- to 3-fold increased risk of gastrointestinal haemorrhage with trimethoprim/sulfamethoxazole relative to other antibiotics[4,5]. Trimethoprim alone can be prescribed with warfarin, with the usual increased frequency of INR monitoring that is required with "low risk" antimicrobials.

POTENTIATED MYELOSUPPRESSION WITH METHOTREXATE

Avoid prescribing trimethoprim ± sulfamethoxazole with methotrexate due to risk of severe myelosuppression resulting from folate depletion. Trimethoprim may also reduce methotrexate elimination via transporter pathways. Antimicrobials that are safer with methotrexate include nitrofurantoin, doxycycline and macrolides.

Contact your ward pharmacist or drug information (ext. 80900) for more information about these and other drug interactions.

TRIMETHOPRIM/SULFAMETHOXAZOLE

Combination products require extra care with prescribing

AVOID ABBREVIATING THE NAME

- Trimethoprim/sulfamethoxazole is the approved name at CDHB.
- Use of the full generic name helps minimise the risk of:
  - incorrect product selection for dispensing or administration,
  - administration to a patient with a history of adverse reaction to either of the components.
- Do **not** use abbreviations like "TMP-SMX" or "co-trimoxazole" as they increase the risk of error.

CHECK THE DOSE CAREFULLY

- Dosing guidelines vary and may refer to:
  - milligrams (mg) of the trimethoprim component only,
  - milligrams (mg) of trimethoprim plus sulfamethoxazole,
  - millilitres (mL) of the oral liquid or injection (see below),
  - number of tablets per dose.
- Errors can occur with dose calculation – check carefully.

PAEDIATRIC DOSING – A SPECIAL CASE

- CDHB's paediatric department now prescribe trimethoprim/sulfamethoxazole 8 mg/40 mg per mL oral liquid using millilitres (mL) **not** milligrams (mg).
- For example, urinary tract infections are treated with:
  - 0.5 mL per kilogram twice daily (equals trimethoprim 4 mg and sulfamethoxazole 20 mg per kilogram per dose).
- This is an exception to the usual method of dosing in milligrams per kilogram (mg/kg), and is thought to have reduced the frequency of dosing error.

"Sulfur allergy"

- This term causes confusion as it may refer to sulfonamides (eg. sulfamethoxazole), sulfites or sulfates.
- Patient implications vary with the type of agent and reaction involved.
- It is important to understand the different types of allergies and to document them clearly, when able.
- Refer to the "Sulfur allergy" bulletin (April 2013, No. 006/13) on the Clinical Pharmacology intranet page for further information.

Trimethoprim/sulfamethoxazole formulations in NZ

Formulation	Amount of trimethoprim/sulfamethoxazole
Oral liquid	8 mg/40 mg per mL (also known as 40 mg/200 mg per 5 mL, or 240 mg per 5 mL)
Tablet	80 mg/400 mg per tablet (also known as 480 mg per tablet)
Injection	16 mg/80 mg per mL, 5 mL ampoule (also known as 80 mg/400 mg per 5 mL, or 480 mg per 5 mL)

References:
1. Alappan R et al., Am J Nephrol 1999;19:389. 2. Antoniou T et al., Arch Intern Med 2010;170:1045. 3. Fralick M et al., BMJ 2014;349:g6196.
4. Schelleman H et al., Clin Pharmacol Ther 2008;84:581. 5. Fischer HD et al., Arch Intern Med 2010;170:617.