Medicines Adverse Reactions Committee

<table>
<tr><td>Meeting date</td><td>13/06/2019</td><td>Agenda item</td><td>3.2.1</td></tr>
<tr><td>Title</td><td colspan="3">Use of trimethoprim in the 65 years or older population</td></tr>
<tr><td>Submitted by</td><td>Medsafe Pharmacovigilance Team</td><td>Paper type</td><td>For advice</td></tr>
<tr><td>Active ingredient</td><td colspan="2">Product name</td><td>Sponsor</td></tr>
<tr><td>Trimethoprim</td><td colspan="2">TMP</td><td>Mylan</td></tr>
<tr><td>Trimethoprim + sulfamethoxazole</td><td colspan="2">Trisul</td><td>Mylan</td></tr>
<tr><td></td><td colspan="2">Deprim</td><td>AFT Pharmaceuticals</td></tr>
<tr><td></td><td colspan="2">DBL Sulfamethoxazole and Trimethoprim Concentrate injection BP</td><td>Pfizer</td></tr>
<tr><td>PHARMAC funding</td><td colspan="3">Funded without restriction</td></tr>
<tr><td>Previous MARC meetings</td><td colspan="3">None</td></tr>
<tr><td>International action</td><td colspan="3">None</td></tr>
<tr><td>Prescriber Update</td><td colspan="3">None</td></tr>
<tr><td>Classification</td><td colspan="3">Prescription medicine except when supplied by an authorised pharmacist.</td></tr>
<tr><td>Usage data (age ≥65; estimated from Qlik)</td><td colspan="3">Measure: Number of people who received a prescription at least once in the calendar year
<table>
<tr><th>Year</th><th>Total</th><th>Trimethoprim only</th><th>Trimethoprim + sulfamethoxazole</th></tr>
<tr><td>2018</td><td>65,802</td><td>47,921</td><td>20,544</td></tr>
<tr><td>2017</td><td>63,608</td><td>47,112</td><td>19,020</td></tr>
<tr><td>2016</td><td>62,920</td><td>47,140</td><td>18,164</td></tr>
<tr><td>2015</td><td>62,981</td><td>46,872</td><td>18,473</td></tr>
<tr><td>2014</td><td>61,581</td><td>45,719</td><td>18,258</td></tr>
</table></td></tr>
<tr><td>Advice sought</td><td colspan="3">The Committee is asked to advise:
If there is evidence of a changed/increased risk of adverse outcomes from trimethoprim in the elderly (≥65 years) population
What specific adverse reactions (if any) have a changed/increased risk in the elderly population
If any changes to the data sheet are required
If further communication outside of MARC's Remarks in Prescriber Update are required.</td></tr>
</table>

Table of Contents

1 PURPOSE

The *British Medical Journal* recently published a study by Crellin et al (Annex 1), describing an association between trimethoprim and an increased risk of acute injury and hyperkalaemia in patients aged 65 and older, compared with other antibiotics used to treat urinary tract infections (UTIs). The results were considered potentially significant by Medsafe, which triggered further investigation into the safety of trimethoprim in the elderly population. For the purpose of this paper, the elderly population is considered all people aged 65 years and older.

Trimethoprim is one of the most commonly used antibiotics as a treatment for UTIs, and has a high usage in the elderly population. The medicine has been previously associated with adverse effects such as hyperkalaemia, acute kidney injury (AKI) and sudden death, notably when used in combination with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Product information for trimethoprim products is limited on specific warnings for these outcomes, especially in the context of the elderly.

The purpose of this paper is to review the results of the Crellin et al study alongside previous studies, product information, and adverse drug reaction reports, and to assess whether there is a change in the risk of adverse outcomes (specific or as a whole) in the elderly population.

2 BACKGROUND

2.1 Trimethoprim

Trimethoprim is an antibiotic indicated for the treatment of urinary tract infections and long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following sterilisation of the urine. Trimethoprim binds to dihydrofolate reductase (DHFR) to inhibit the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). The affinity to bacterial DHFR is approximately 50,000 times stronger than that to human DHFR. This inhibition prevents bacterial DNA synthesis, which produces trimethoprim's medicinal effect. Depending on the conditions, the effect may be bactericidal or bacteriostatic (1). It is commonly used concomitantly (usually as a combination product) with sulfamethoxazole, an inhibitor of dihydropteroate synthase – which is an enzyme further upstream in the same pathway. The effects are considered synergistic (2). The combination product is commonly referred to as co-trimoxazole.

Trimethoprim has inhibitory activity against most gram-positive cocci and some gram-negative aerobic bacilli. However, resistance may develop from a chromosomal mutation which results in the production of a DHFR enzyme that is less vulnerable to trimethoprim inhibition (2).

Trimethoprim (with or without sulfamethoxazole) has activity against multiple pathogenic bacteria. This includes:

- *Escheria coli*
- *Proteus mirabilis*
- *Klebsiella pneumoniae*
- *Enterobacter* spp.
- Coagulase-negative *Staphylococcus* spp.
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Pneumocystis jirovecii*

Trimethoprim is lipophilic and a weak base. Higher concentrations are generally found in the lungs and kidneys, and adequate concentrations for an inhibitory effect occur in other body tissues. Approximately 50% of trimethoprim in plasma is protein bound. The half-life in humans is in the range of 8.6 to 12 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in the elderly compared with younger adult patients (1).

Excretion of trimethoprim is primarily by the kidneys through glomerular filtration and tubular secretion. Urine concentrations are considerably higher than in the blood. After oral administration 50-60% of trimethoprim is excreted in the urine within 24 hours. Within 2 hours of any therapeutic dose, the concentrations achieved are greatly in excess of the minimum inhibitory concentration (MIC) for most pathogenic bacteria responsible for urinary tract infections. High concentrations usually persist in the urine for 24 hours or more after a single dose. Even in patients undergoing chronic haemodialysis, levels of trimethoprim achieved in the urine exceed the MIC for most of the urinary tract pathogens (1).

2.1.1 Safety concerns

The use of co-trimoxazole has been associated with an increased risk of sudden death among people taking renin-angiotensin system blockers (3, 4). This could be owing to acute kidney injury (5) or fatal cardiac arrhythmias as a result of hyperkalaemia (6-9). These studies have explicitly shown these risks to be apparent for elderly patients. However, the studies evaluating these adverse outcomes have only looked at co-trimoxazole, a combination product of trimethoprim and sulfamethoxazole, rather than a trimethoprim-only product. It is therefore difficult to prove causality from the trimethoprim component. Additionally, the combination product is often used for patients with more severe infections, therefore the observed association may be due to confounding when comparing this product to antibiotics used for less severe infections. The adverse outcomes have also only been associated with patients concomitantly taking specific medicines, such as renin-angiotensin system blockers. Therefore, it is not clear if there is a true association between trimethoprim and these adverse outcomes.

Trimethoprim has structural similarities to the potassium-sparing (antikaliuretic) diuretic amiloride, and reduces urinary potassium excretion by up to 40% (10, 11). The structural similarity gives weight to the hypothesis that hyperkalaemia (and potential subsequent sudden death) associated with co-trimoxazole may be caused by the trimethoprim component.

For a full description of the safety profile, refer to the data sheet summary in section 2.6.

2.1.2 Pharmacokinetics in the elderly

The pharmacokinetics of co-trimoxazole has been evaluated in the elderly through a comparison of six young adults (mean 29.3 years) to six elderly people (mean 78.6 years) (12). Following oral administration of a single dose (total 160mg trimethoprim), the C_{max} of trimethoprim was greater and its area under the curve was larger in elderly people than in young subjects (Figure 1). Total clearance of trimethoprim normalised to body weight was not significantly different between the two groups. There was no significant difference in the protein binding of trimethoprim. Urinary excretion of trimethoprim was reduced by about 50% in the elderly compared to the young subjects (Figure 2). Renal clearance of trimethoprim was significantly lower in the elderly. Measured pharmacokinetic parameters are shown in Table 1. Plasma concentrations in the elderly subjects showed that steady state was reached after 3 days of treatment and that plasma drug concentrations were about two to three times higher than those observed after a single dose (12).

Figure 1: Mean ± s.e. mean plasma concentration vs time of trimethoprim (TMP), sulfamethoxazole (SMZ) and N_4-acetylsuplhamethoxazole (N_4SMZ) in six young adults (○) and six elderly subjects (●) after oral administration of a single dose of TMP 160 mg and SMZ 800 mg (12)

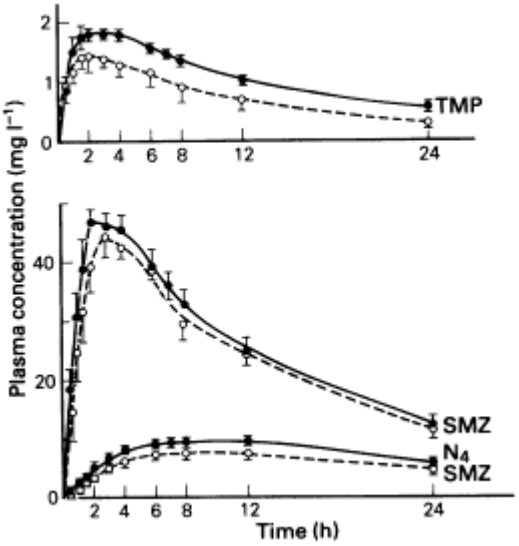


Figure 2: Cumulative urinary excretion of trimethoprim (TMP), sulfamethoxazole (SMZ) and N_4-acetylsulfamethoxazole (N_4SMZ) in six young adults (○) and six elderly subjects (●) after oral administration of a single dose of TMP 160 mg and SMZ 800 mg. Points represent mean ± s.e. mean values (12)

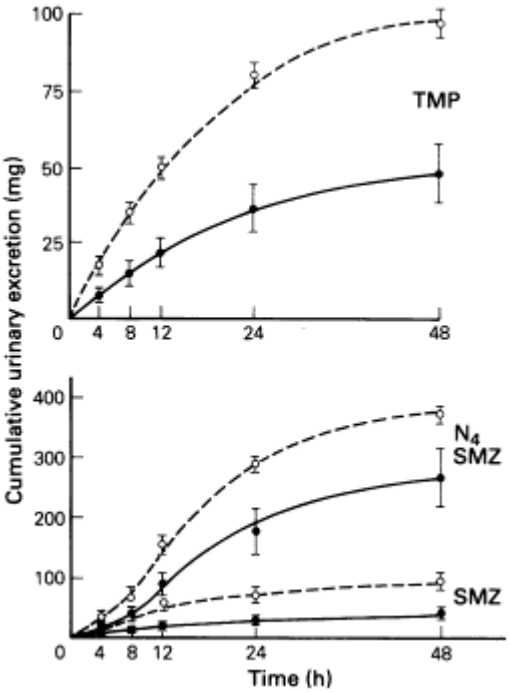


Table 1: Pharmacokinetic values of trimethoprim after oral administration of 160 mg to six young and six elderly subjects (12)

Subjects	*Age (years)*	*Weight (kg)*	*Sex*	*Lag time (h)*	C_{max} *(mg l^{-1})*	t_{max} *(h)*	$t_{½,z}$ *(h)*	*AUC (mg l^{-1} h)*	*CL/F (ml h^{-1} kg^{-1})*	*fe (48)*	CL_R *(ml h^{-1} kg^{-1})*
Young subjects											
1	27	54	F	0.13	1.92	2.0	9.9	29.47	101	0.66	51
2	26	60	M	0.12	1.58	1.5	8.5	20.42	130	0.66	72
3	35	75	M	0.48	1.26	4.0	11.2	22.40	95	0.56	47
4	27	75	M	0	1.12	1.5	13.3	20.43	114	0.51	42
5	35	50	F	0.48	1.80	2.0	8.8	25.26	128	0.61	73
6	26	75	M	0	1.75	1.5	11.0	25.34	84	0.64	45
Mean	29.3	65		0.20	1.57	2.1	10.5	23.87	107	0.61	55
s.d.	4.4	13		0.22	0.32	—	1.7	3.82	17	0.07	14
Elderly subjects											
1	68	58	F	0.26	2.00	1.5	7.4	23.22	118	0.14	12
2	80	46	F	0	2.65	1.0	8.5	31.36	110	0.39	32
3	86	51	F	0	1.96	3.0	9.7	31.39	99	0.26	24
4	74	72	M	0.28	1.80	3.0	12.3	39.86	57	0.15	6
5	84	56	F	0.80	2.08	1.5	13.7	42.03	68	0.58	30
6	80	60	F	0.23	1.91	1.5	13.5	37.95	70	0.33	14
Mean	78.6	57		0.26	2.06	1.9	10.8	34.30	87	0.31	19
s.d.	6.6	10		0.27	0.29	—	2.7	6.98	24	0.17	10
P				NS	< 0.01		NS	< 0.001	NS	< 0.01	< 0.001

2.2 Susceptibility

The Institute of Environmental Science and Research (ESR) are responsible for generating annual reports on antimicrobial susceptibility/resistance collected from both hospital and community laboratories. This is gathered from routine diagnostic susceptibility testing and includes a range of organisms and antibiotics. Table 2 through Table 6 shows the sensitivity data over five years (2012-2016). Figure 3 summarises the trends in susceptibility for uropathogenic *E. coli* over the same time period for multiple antibiotics. Note the change in reporting from percent resistance to percent susceptible in 2016.

Table 2: Antimicrobial resistance data from hospital and community laboratories, 2012 (13)

	Percent resistance (number tested [2])															
	amikacin	ampicillin	cefepime	ceftazidime	ceftriaxone/cefotaxime	cefuroxime/cefamandole	cephalothin	co-amoxiclav	co-trimoxazole	fluoroquinolone	gentamicin	imipenem/meropenem	nitrofurantoin	piperacillin-tazobactam	ticarcillin-clavulanic acid	tobramycin	trimethoprim
Acinetobacter species				7.4 (421)					7.8 (500)	2.7 (587)	4.0 (594)	1.9 (367)		7.4 (242)		3.4 (267)	
Citrobacter freundii [3]	0.0 (104)				23.2 (306)				11.1 (270)	3.6 (415)	7.1 (392)	0.4 (280)				3.6 (112)	
Enterobacter species [3]	0.7 (865)				28.7 (1835)				10.8 (1878)	2.7 (2372)	4.9 (2212)	0.3 (1591)				3.3 (584)	
Escherichia coli from bacteraemia	0.0 (787)	57.9 (1546)	2.8 (785)		4.5 [4] (1592)	6.9 (1504)	22.8 (644)	14.0 (1746)		8.3 (1739)	5.5 (1754)	0.0 (1416)				2.9 (611)	
E. coli urinary	0.0 (5991)	50.1 (102932)			3.2 [4] (57100)	4.6 (17253)	27.5 (10820)	7.4 (111490)	23.8 (15670)	7.6 (72687)	2.4 (64834)		1.1 (111753)			2.1 (3234)	24.8 (111734)
Klebsiella species from bacteraemia	0.0 (236)		4.1 (269)		14.9 [4] (368)	13.7 (473)	22.6 (195)	7.6 (498)		8.4 (512)	12.0 (515)	1.5 (332)				3.6 (169)	
Morganella morganii [3]	0.0 (222)				8.4 (465)				20.1 (418)	8.5 (577)	15.6 (507)	0.6 (358)				5.9 (152)	
Proteus mirabilis	0.0 (719)	12.7 (3811)			0.8 (2055)	2.2 (1874)	6.0 (1052)	1.9 (3985)	8.6 (1909)	1.7 (2344)	1.9 (2520)	0.6 (1348)				0.6 (667)	
Pseudomonas aeruginosa	5.6 (1232)		2.6 (3440)	2.5 (10823)						6.7 (12985)	6.0 (10969)	4.8 (5892)		1.4 (8160)	7.7 (2501)	1.6 (3669)	
Serratia species [3]	0.6 (328)				16.2 (773)				6.9 (813)	9.1 (999)	0.9 (870)	0.4 (687)				3.1 (225)	

Table 3: Antimicrobial resistance data from hospital and community laboratories, 2013 (14)

	Percent resistance (number tested [2])																
	amikacin	ampicillin	cefepime	ceftazidime	ceftriaxone/cefotaxime	cefuroxime/cefamandole	cephalothin	co-amoxiclav	co-trimoxazole	fluoroquinolone	gentamicin	imipenem/meropenem	nitrofurantoin	piperacillin-tazobactam	ticarcillin-clavulanic acid	tobramycin	trimethoprim
Acinetobacter species	2.1 (189)			7.2 (559)					7.2 (598)	2.5 (640)	1.9 (618)	2.3 (440)		4.6 (373)		1.4 (296)	
Citrobacter freundii [3]	0.0 (140)				26.6 (320)				12.9 (271)	4.2 (404)	7.1 (407)	1.1 (280)				5.0 (161)	
Enterobacter species[3]	0.1 (705)				29.3 (1491)				9.6 (1514)	2.2 (1993)	4.1 (1860)	0.4 (1348)				2.7 (739)	
Escherichia coli from bacteraemia	0.1 (759)	59.7 (1476)	6.7 (568)		6.2[4] (1148)	9.1 (1332)	26.7 (802)	14.8 (1442)		11.5 (1533)	8.5 (1686)	0.3 (1340)				3.9 (773)	
E. coli urinary	0.0 (10952)	50.3 (98683)			3.8[4] (55351)	5.8 (14188)	24.2 (9518)	7.7 (98489)	24.5 (13684)	7.9 (67758)	4.6 (29399)		1.3 (99411)			2.1 (8962)	26.2 (98127)
Klebsiella species from bacteraemia	0.0 (234)		11.4 (193)		17.2[4] (366)	20.3 (300)	29.9 (221)	13.4 (373)		8.4 (383)	12.5 (375)	0.0 (335)				4.3 (231)	
Morganella morganii [3]	0.0 (209)				7.8 (437)				20.7 (440)	7.6 (582)	16.3 (571)	0.3[5] (332)				4.2 (213)	
Proteus mirabilis	0.3 (640)	12.4 (3282)			1.5 (1309)	2.6 (1283)	4.0 (1277)	1.6 (3409)	12.3 (1312)	1.7 (1797)	3.5 (1876)	0.1[5] (1001)				1.5 (671)	
Pseudomonas aeruginosa	1.9 (1685)		1.4 (2655)	2.4 (8909)						6.9 (9589)	5.4 (8971)	5.3 (7388)		1.9 (6614)	12.5 (1323)	2.1 (3454)	
Serratia species[3]	0.3 (314)				10.2 (625)				5.6 (834)	6.9 (926)	1.5 (926)	0.2 (566)				3.4 (298)	

Table 4: Antimicrobial resistance data from hospital and community laboratories, 2014 (15)

	Percent resistance (number tested [2])																
	amikacin	ampicillin	cefepime	ceftazidime	ceftriaxone/cefotaxime	cefuroxime/cefamandole	cephalothin	co-amoxiclav	co-trimoxazole	fluoroquinolone	gentamicin	imipenem/meropenem	nitrofurantoin	piperacillin-tazobactam	ticarcillin-clavulanic acid	tobramycin	trimethoprim
Acinetobacter species	0.7 (149)			5.6 (429)					7.2 (667)	2.6 (739)	3.1 (703)	0.7 (455)		2.8 (288)		2.2 (318)	
Citrobacter freundii [3]	0.9 (106)				37.9 (182)				10.4 (183)	3.3 (299)	6.3 (240)	0.4 (238)					
Enterobacter species[3]	0.0 (764)				31.8 (1633)				10.6 (1905)	1.3 (2179)	3.4 (2055)	0.6 (1564)				2.3 (345)	
Escherichia coli from bacteraemia	0.2 (823)	57.2 (1746)	5.5 (910)		7.1[4] (1629)	7.1 (1417)	22.3 (870)	17.9 (1870)		10.1 (1653)	6.7 (1765)	0.2 (1588)				3.6 (640)	
E. coli urinary	0.1 (8170)	49.3 (99337)			4.9[4] (13559)	6.2 (10979)	22.6 (7241)	9.6 (107503)	24.8 (12011)	8.0 (66807)	4.8 (21009)		1.2 (107474)			1.6 (4496)	26.1 (102798)
Klebsiella species from bacteraemia	0.0 (203)		10.6 (207)		22.0[4] (387)	19.6 (312)	27.1 (225)	15.8 (417)		8.4 (382)	12.2 (384)	0.0 (390)				7.9 (101)	
Morganella morganii [3]	0.4 (242)				5.9 (456)				19.4 (454)	7.9 (631)	15.0 (545)	0.0[5] (354)					
Proteus mirabilis	0.0 (689)	13.9 (3625)			1.5 (1210)	3.3 (1158)	8.3 (629)	2.2 (4039)	11.8 (1199)	1.9 (2633)	3.4 (1982)	1.3[5] (1046)				0.6 (337)	
Pseudomonas aeruginosa	2.5 (3220)		3.4 (4439)	2.9 (11257)						6.2 (11023)	6.6 (10900)	4.6 (7629)		2.2 (8650)	9.4 (1209)	2.2 (4649)	
Serratia species[3]	0.0 (360)				8.8 (717)				4.7 (889)	6.4 (963)	0.8 (927)	0.0 (613)				1.2 (169)	

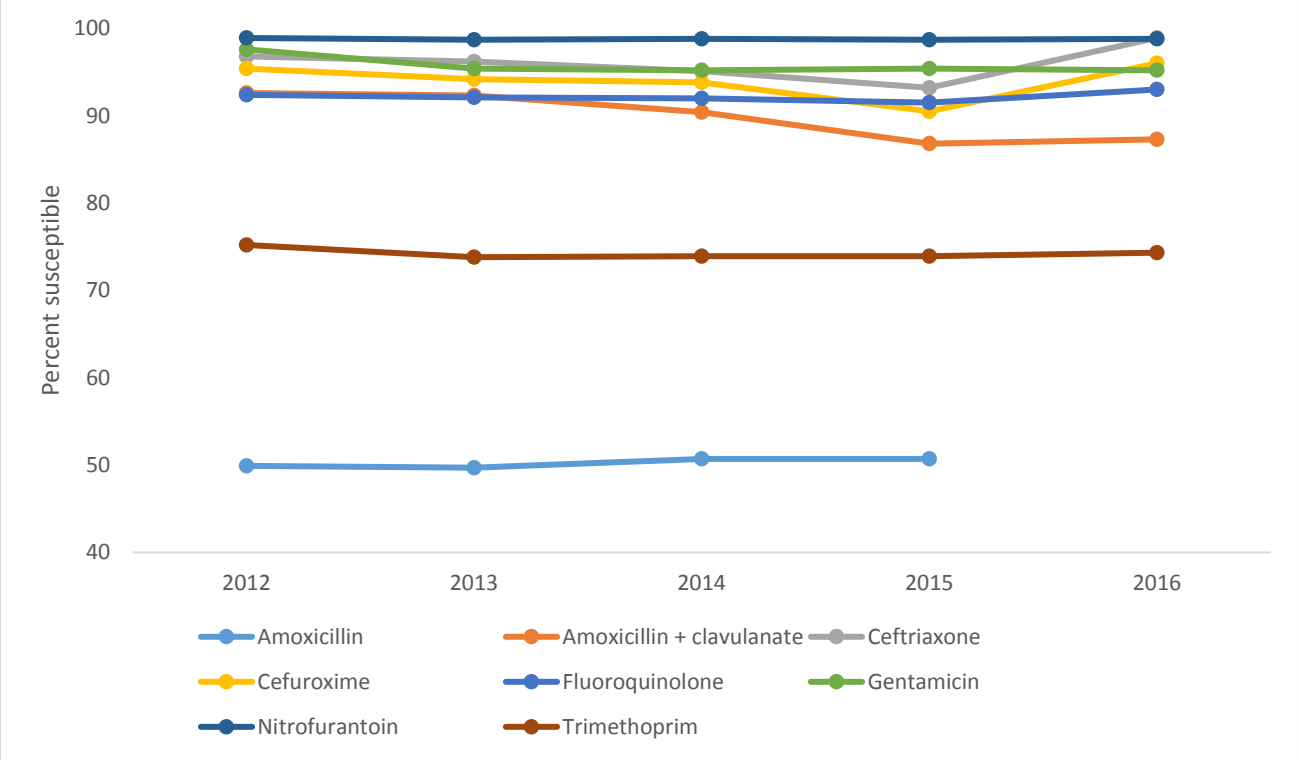
Table 5: Antimicrobial resistance data from hospital and community laboratories, 2015 (16)

	Percent resistance (number tested [2])																
	amikacin	ampicillin	cefepime	ceftazidime	ceftriaxone/cefotaxime	cefuroxime/cefamandole	cephalothin	co-amoxiclav	co-trimoxazole	fluoroquinolone	gentamicin	imipenem/meropenem	nitrofurantoin	piperacillin-tazobactam	ticarcillin-clavulanic acid	tobramycin	trimethoprim
Acinetobacter species	0.9 (219)			5.0 (240)					3.2 (372)	4.0 (550)	3.6 (528)	2.9 (277)		2.4 (125)		2.9 (272)	
Citrobacter freundii [3]	0.8 (241)				35.2 (230)				6.6 (227)	4.2 (336)	5.7 (299)	0.0 (184)					
Enterobacter species[3]	0.1 (1342)				28.2 (1833)				7.7 (1472)	2.1 (2327)	2.4 (2150)	0.8 (1147)				2.6 (387)	
Escherichia coli from bacteraemia	0.1 (862)	56.6 (1828)	6.4 (894)		6.5[4] (1348)	8.0 (1405)	20.8 (443)	23.5 (1927)		10.2 (1572)	6.2 (1605)	0.0 (1441)				4.8 (477)	
E. coli urinary	0.2 (8109)	49.3 (88471)			6.8 (12403)	9.5 (10544)	22.7 (3814)	13.2 (90527)	25.9 (12350)	8.5 (73788)	4.6 (19864)		1.3 (79323)			3.6 (4603)	26.1 (86181)
Klebsiella species from bacteraemia	0.0 (181)		7.8 (192)		13.7[4] (357)	20.2 (321)	23.3 (116)	15.7 (427)		11.0 (337)	9.8 (388)	0.0 (315)					
Morganella morganii [3]	0.2 (465)				5.1 (666)				21.3 (516)	8.7 (909)	12.9 (612)	0.0[5] (412)					
Proteus mirabilis	0.1 (755)	13.9 (3390)			0.7 (1240)	1.7 (1099)	4.4 (481)	1.9 (3354)	13.0 (1175)	2.9 (2741)	3.7 (1740)	0.0[5] (1280)				1.0 (395)	
Pseudomonas aeruginosa	2.5 (4423)		4.2 (4693)	3.8 (9842)						7.0 (9491)	7.4 (9307)	5.1 (6047)		2.3 (8338)		2.2 (4122)	
Serratia species[3]	0.0 (686)				6.8 (1046)				3.5 (881)	6.7 (1167)	0.4 (1214)	0.2 (600)				3.6 (197)	

Table 6: Antimicrobial susceptibility data from hospital and community laboratories, 2016 (17)

	Percent susceptible (number tested [2])																	
	amikacin	amoxicillin-clavulanic acid	ampicillin	cefazolin	cefepime	ceftazidime	ceftriaxone/cefotaxime	cefuroxime/cefamandole	cephalexin	co-trimoxazole	ertapenem	fluoroquinolone	gentamicin	meropenem	nitrofurantoin	piperacillin-tazobactam	tobramycin	trimethoprim
Acinetobacter calcoaceticus-baumannii complex	97.5 (161)					82.4 (159)				91.5 (271)		95.5 (267)	94.3 (261)	97.1 (240)		84.6 (130)	97.8 (139)	
Enterobacter species from bacteraemia	100 (116)						69.5 (151)			91.4 (187)		97.7 (172)	98.4 (189)	100 (142)				
Escherichia coli (non-ESBL[3]) from bacteraemia	98.6 (1011)	73.7[4] (1478)	48.9 (1932)	78.6 (459)	99.7 (1177)		98.6 (1415)	95.9 (1457)			100 (300)	93.5 (1650)	95.3 (1929)	100 (1361)			94.3 (699)	
E. coli (ESBL[3]) from bacteraemia	95.0 (100)	38.7[4] (119)					3.0 (135)				92.5 (120)	41.5 (142)	53.1 (143)	100 (131)				
E. coli (non-ESBL[3]) urinary	98.5 (12329)	87.3[4] (35212)	53.2 (36924)				98.9 (16001)	96.0 (12673)	97.4 (70354)			93.0 (65300)	95.2 (20314)		98.8 (78507)		95.1 (8831)	74.3 (86839)
E. coli (ESBL[3]) urinary	94.9 (2915)	72.3[4] (2674)					1.5 (3291)					37.4 (2917)	64.2 (3024)		95.4 (3303)		58.5 (479)	29.4 (3424)
Klebsiella species (non-ESBL[3]) from bacteraemia	99.6 (266)	93.9[4] (423)		72.7 (121)	99.7 (299)		99.4 (332)	95.9 (343)				96.3 (382)	99.1 (452)	99.7 (330)			99.3 (146)	
Klebsiella species (ESBL[3]) from bacteraemia	80.8 (52)	16.9[4] (59)					0.0 (59)				96.1 (51)	33.3 (60)	38.3 (60)	100 (59)				
Pseudomonas aeruginosa from bacteraemia	95.8 (120)				96.4 (137)	96.3 (214)						93.6 (219)	98.6 (209)	94.3 (176)		94.4 (196)	98.3 (120)	

Figure 3: Comparative summary of ESR susceptibility data for *E. coli* (non-ESBL) to trimethoprim, urinary, 2012-2016



Comment

The susceptibility of *E. coli* to trimethoprim has remained relatively constant over the past five years. However, as it shows a ~25% resistance in *E. coli*, it does not meet the criteria of <20% resistance to be considered a first-line agent (18).

2.3 Usage

Table 7 shows the usage data from 2013 to 2019. Table 8 shows the same data but only for people whom were age 65 or older at the time of the dispensing. For each year, a single person can only be counted once in each column. The difference between NumPpl and the summation of NumTrimethoprim and NumCotrimoxazole can be accounted for by people who received both a prescription for trimethoprim and a prescription for co-trimoxazole in the given year.

The data is sourced from the Pharmaceutical Collections and queried by QlikSense. The data is not a validated statistic and therefore considered unofficial. However, it provides a good estimation of how many people are receiving trimethoprim, and the trends over time.

Table 7: Number of people dispensed a trimethoprim product, 2013 to 2019[†]

Year	NumPpl[a]	NumTrimethoprim[b]	NumCotrimoxazole[c]
2013	233,059	124,589	113,438
2014	235,626	128,312	112,418
2015	237,251	130,792	111,593
2016	235,190	131,777	108,783
2017	232,881	130,447	107,844
2018	235,750	130,902	110,681
2019	56,388	30,178	26,677

[†] Data loaded 12 April 2019

[a] Total number of people who received at least one prescription for any trimethoprim product
[b] Total number of people who received at least one prescription for a trimethoprim-only product
[c] Total number of people who received at least one prescription for a trimethoprim + sulfamethoxazole product

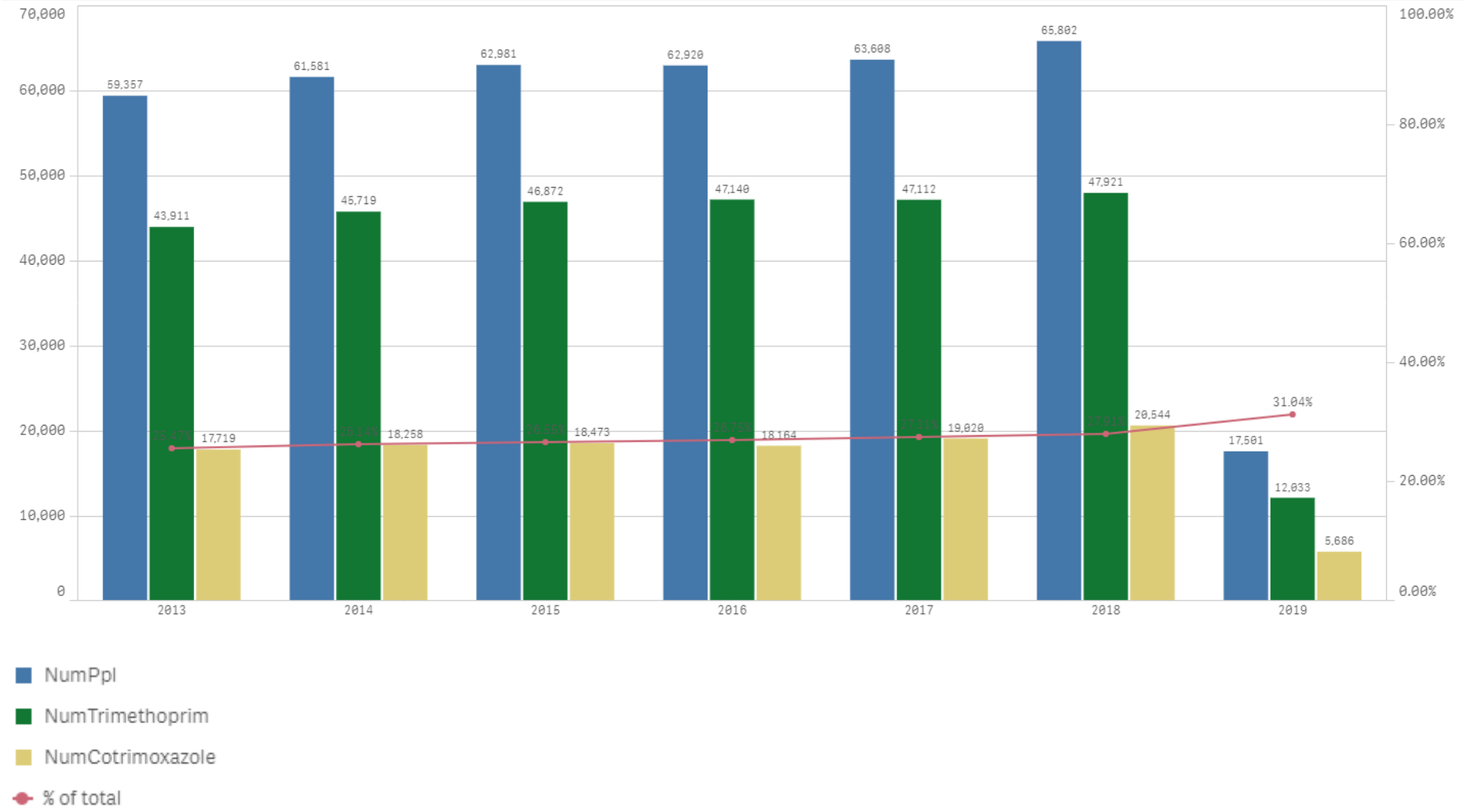
Table 8: Number of people aged >65 years dispensed a trimethoprim product, 2013 to 2019[†]

Year	NumPpl[a]	NumTrimethoprim[b]	NumCotrimoxazole[c]
2013	59,357	43,911	17,719
2014	61,581	45,719	18,258
2015	62,981	46,872	18,473
2016	62,920	47,140	18,164
2017	63,608	47,112	19,020
2018	65,802	47,921	20,544
2019	17,501	12,033	5,686

[†] Data loaded 12 April 2019
[a] Total number of people who received at least one prescription for any trimethoprim product
[b] Total number of people who received at least one prescription for a trimethoprim-only product
[c] Total number of people who received at least one prescription for a trimethoprim + sulfamethoxazole product

Figure 4 summarises the data in Table 8 graphically. Additionally, this figure shows the percentage of the total number of people who received a trimethoprim product in the given year that were aged over 65 years.

Figure 4: Number of people aged >65 years dispensed a trimethoprim product 2013 to 2019†



† Data loaded 12 April 2019

2.4 Classification

Schedule 1, Part 1 of the Medicines Regulations 1984 classifies trimethoprim as follows:

Trimethoprim; except in medicines for oral use containing 300 milligrams or less per dose unit when sold in a pack of 3 solid dosage units to a woman aged 16–65 years for the treatment of an uncomplicated urinary tract infection by a registered pharmacist who has successfully completed the New Zealand College of Pharmacists' training in the treatment of urinary tract infections.

2.4.1 Reclassification to prescription-except-when

At the 47th meeting of the Medicines Classification Committee (MCC) on 1 May 2012, trimethoprim was reclassified to "prescription except when" from "prescription only". The submission was made by Pharmacybrands Limited and proposed to enable accredited pharmacists to sell packs of three tablets to women aged 16 to 70 years for treatment of uncomplicated urinary tract infections.

At the time, the Committee considered the upper age limit of 70 years to be too high. The Committee instead recommended that the upper limit be changed to 65 years of age – this is the same age as other countries described in the submission use as their upper limit.

The Committee's final recommendation was that trimethoprim should be reclassified from prescription medicine to prescription medicine except when supplied in packs of three tablets to women aged 16 to 65 years for uncomplicated urinary tract infection by a pharmacist who has successfully completed the New Zealand College of Pharmacists' training in the treatment of urinary tract infections. Additionally, Medsafe should review and be satisfied with the training materials. The MCC Chair also requested that Medsafe investigates the use of and resistance to trimethoprim following the reclassification (see section 2.4.3) (19).

2.4.2 PSNZ competency requirements

The Pharmaceutical Society of New Zealand (PSNZ) provides a training course for pharmacists to become accredited to provide trimethoprim to treat uncomplicated cystitis in women aged 16 to 65 years.

Accredited pharmacists must:

- understand the legal reclassification of trimethoprim for pharmacist supply
- describe the benefits to the patient of pharmacist-supplied trimethoprim
- understand the pathogenesis of organisms involved with cystitis
- describe the microbiology of bacteria involved in uncomplicated cystitis
- understand issues surrounding antibiotic resistance
- describe the risk factors for uncomplicated cystitis
- understand the various sexually transmitted infections and pyelonephritis
- identify when symptomatic treatment is necessary
- identify when referral to a general practitioner is necessary
- provide appropriate advice to patients relating to cystitis symptoms.

2.4.3 MCC review

As per the recommendations of the 47th MCC meeting, Medsafe reviewed the use and resistance of trimethoprim following the reclassification. This investigation was presented to the MCC at the 60th meeting on 26 April 2018.

The paper noted there had been a small increase in the number of community prescriptions dispensed but this may reflect the increase in population rather than any change in prescribing habits. There also had been a steady increase in the use of nitrofurantoin.

There was no dramatic increase in resistance associated with the wider availability of trimethoprim. The paper concluded that Medsafe did not consider a review of the reclassification of trimethoprim was required at the time.

The Committee noted no significant impact on the resistance of trimethoprim, given the limitations of the data available. The Committee recommended that the classification of trimethoprim should remain unchanged (20).

Comments
Patients over the age of 65 years are not able to access trimethoprim through pharmacists. As the patient population used in the Crellin et al study was aged >65 years, it is unlikely to have any impact on the pharmacist supply of trimethoprim.

2.5 Urinary tract infections

Urinary tract infections (UTIs) include cystitis (infection of the bladder/lower urinary tract) and pyelonephritis (infection of the kidney/upper urinary tract). UTIs can be considered as uncomplicated, if there is no concern the infection has extended beyond the bladder, or complicated, if there is concern that the infection has reached the upper urinary tract and/or kidneys. Bacteriuria is the presence of bacteria in the urine but this is not indicative of a urinary tract infection. Cystitis among women is extremely common, and the risk is much higher than in men (21).

E. coli is the most frequent microbial cause of uncomplicated cystitis (75-95% of cases), with occasional infections caused by other species of Enterobacteriaceae, such as *Klebsiella pneumoniae* and *Proteus mirabilis*. Other gram-negative and gram-positive species are infrequently isolated in cases of uncomplicated cystitis (including *Staphylococcus saprophyticus*). Recent antimicrobial or other health care exposure increases the risk of infection by other gram-negative bacilli (such as *Pseudomonas)*, enterococci and staphylococci (21, 22).

Symptoms of urinary tract infections vary and can often be subtle. The classical manifestation of cystitis consists of dysuria, urinary frequency, urinary urgency and suprapubic pain. In elderly patients, this can be more difficult to identify as chronic dysuria or urinary incontinence are more common even when there is no evidence of a UTI (21). Pyelonephritis is usually associated with symptoms including fever, chills, flank pain, costovertebral angle tenderness, and nausea/vomiting. More severe complications of complicated UTIs include bacteraemia, sepsis, multiple organ dysfunction, shock and acute kidney failure. Elderly patients are at a higher risk of these complications and may also develop delirium in response (22).

2.5.1 Best Practice Advisory Committee (BPAC) antimicrobial guidelines: Cystitis

First choice

Nitrofurantoin: 50 mg, four times daily, for five days (avoid at 36+ weeks in pregnancy, and in patients with creatinine clearance <60 mL/min) (treat for seven days in pregnant women and in males).

Alternatives

Trimethoprim: 300 mg, once daily, for three days (avoid during the first trimester of pregnancy) (treat for seven days in pregnant women and males).

Cefalexin - only if infecting organism known to be susceptible, and resistant to other choices: 500 mg, twice daily, for three days (treat for seven days in pregnant women and males). (23)

2.5.2 Best Practice Advisory Committee (BPAC) antimicrobial guidelines: Pyelonephritis

Empiric therapy

First choice

Trimethoprim + sulfamethoxazole: 960 mg (total 160 mg trimethoprim), twice daily, for ten days.

Alternatives

Amoxicillin clavulanate: 625 mg, three times daily, for ten days.

Cefalexin: 500 mg, twice daily, for ten days.

In most cases, patients with severe infection would be referred to hospital for treatment. If treatment is required in the community, give one dose of IV gentamicin followed by standard oral treatment (23).

2.6 Data sheets

2.6.1 New Zealand (Trimethoprim only) – TMP Tablets

4.2 Dose and method of administration

This product is not able to deliver all approved dose regimens.

Dose

Acute urinary tract infections

Adults and children over 12 years: 300 mg once daily.

This dosage approximates to 6mg/kg bodyweight/day. The recommended duration of treatment will vary according to medical practice in different countries.

Long term prophylaxis of recurrent, or suppression of chronic urinary tract infections following sterilisation of the urine

Adults and children over 12 years: 100 mg once daily.

Treatment may be continued for 3 to 12 months or more as appropriate.

Trimethoprim dose not induce its own metabolism and therefore no dose modification is required on this account during long term treatment.

Special populations

Renal impairment

When a patient is known to have a creatinine clearance below 15 to 20 ml/minute trimethoprim plasma levels should be monitored after approximately 3 days of treatment. When clearance is below 10 ml/minute TMP should not be administered unless plasma concentrations can be estimated regularly and haemodialysis facilities are available.

4.3 Contraindications

TMP should not be given to patients with a history of trimethoprim hypersensitivity, or a hypersensitivity to any of the excipients listed in section 6.1.

Patients with severely impaired renal function (creatinine clearance less than 10 ml/minute) should not be prescribed TMP unless the plasma concentration of trimethoprim is monitored repeatedly during treatment.

TMP should not be given to patients with severe haematological disorders or documented megaloblastic anaemia due to folate deficiency.

4.4 Special warnings and precautions for use

TMP should be discontinued if a skin rash appears. Regular monthly blood counts are advisable when TMP is given for long periods since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. These changes may be reversed by administration of folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity of trimethoprim.

Special care should be exercised in treating elderly or suspected folate deficient patients; folate supplementation should be considered.

A folate supplement should also be considered when high doses of TMP are administered intravenously (see Interactions).

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

The administration of TMP to patients known or suspected to be at risk of acute porphyria should be avoided as trimethoprim has been associated with clinical exacerbation of porphyria.

Use in renal and hepatic impairment

Exercise caution when treating patients with impaired renal function or severe hepatic parenchymal damage as changes may occur in the absorption and metabolism of trimethoprim.

Use in elderly

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result.

Electrolyte abnormalities

Close monitoring of serum electrolytes is advised in patients at risk of hyperkalaemia. These include older patients, those with renal impairment and those taking other medicines that are known to increase serum potassium (see sections 4.5 and 4.8).

Interference with laboratory tests

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in the overestimation of serum/plasma creatinine of the order of 10%. Functional inhibition of the renal tubular secretion of creatinine may produce a spurious fall in the estimated rate of creatinine clearance.

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay.

4.5 Interaction with other medicines and other forms of interaction

Occasional reports suggest that patients receiving pyrimethamine as malarial prophylaxis at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co-trimoxazole be prescribed concurrently. The same interaction is likely if trimethoprim be prescribed concurrently.

Trimethoprim may potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Careful control of the anticoagulant therapy during treatment with TMP is advisable.

Trimethoprim prolongs the half-life of phenytoin and if co-administered the prescriber should be alert for excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Concurrent use of rifampicin and trimethoprim results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

Reversible deterioration in renal function has been observed in patients treated with trimethoprim and cyclosporin following renal transplantation.

When trimethoprim is administered simultaneously with medicines that form cations at physiological pH, and are also partly excreted by active renal secretion (eg. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the medicines.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

If TMP is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (section 4.4).

Cases of pancytopenia have been reported in patients taking trimethoprim in combination with methotrexate. Most of these patients were on long term methotrexate therapy, and/or predisposed to folate deficiency, and none of them were reported to have received a prophylactic folinic acid supplement (see section 4.4).

Concomitant use of medicines known to increase serum potassium, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and potassium sparing diuretics may results in severe hyperkalaemia.

4.8 Undesirable effects (specific to elderly)

Metabolism and nutrition disorders

Close supervision is recommended when trimethoprim is used in elderly patients, patients with renal impairment or in patients taking high doses as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

2.6.2 New Zealand (Trimethoprim + sulfamethoxazole) – Trisul tablets

4.2 Dose and method of administration

STANDARD DOSAGE – 2 tablets every 12 hours

This dosage approximates to 6mg trimethoprim and 30 mg sulfamethoxazole per kilogram body weight per 24 hours.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evidence after 7 days' therapy, the patient should be reassessed.

As an alternative to STANDARD DOSAGE for acute uncomplicated lower urinary tract infections, short term therapy of 1 to 3 days' duration has been shown to be effective.

Special populations

Hepatic impairment

No data are available relating to dosage in patients with impaired hepatic function

Elderly

See section 4.4. Unless otherwise specified STANDARD DOSAGE applies

Renal impairment

Adults and children over 12 years:

Creatinine clearance (ml/min)	Recommended dosage
> 30	STANDARD DOSAGE
15 – 30	Half the STANDARD DOSAGE
< 15	Not recommended

4.3 Contraindications

Hypersensitivity to the active substances sulfonamides, trimethoprim, co-trimoxazole or to any of the excipients listed in section 6.1.

Contraindicated in patients showing marked liver parenchymal damage.

Contraindicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.

Contraindicated in patients with a history of drug-indicated immune thrombocytopenia with use of trimethoprim and/or sulfonamides.

Contraindicated in patients with acute porphyria.

4.4 Special warnings and precautions for use

Fatalities, although very rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

- Life-threatening cutaneous reactions Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfamethoxazole (one of the active ingredients in TRISUL).
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
- If signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, TRISUL treatment should be discontinued (see section 4.8).
- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS or TEN with the use of sulfamethoxazole or TRISUL, TRISUL must not be re-started in this patient at any time.

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other medicines.

For patients with known renal impairment special measures should be adopted (see section 4.2).

An adequate urinary output should be maintained at all times. Evidence of crystalluria in vivo is rare, although sulfonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

Regular monthly blood counts are advisable when TRISUL is given for long periods, or to folate deficient patients or to the elderly; since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. Supplementation with folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficiency (see section 4.5).

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients, haemolysis may occur.

TRISUL should be given with caution to patients with severe allergy or bronchial asthma.

TRISUL should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci; eradication of these organisms from the oropharynx is less effective than with penicillin

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

The administration of TRISUL to patients known or suspected to be at risk of porphyria should be avoided. Both trimethoprim and sulfonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Close monitoring of serum potassium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

TRISUL has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Except under careful supervision TRISUL should not be given to patients with serious haematological disorders (see section 4.8). Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

The combination of antibiotics in TRISUL should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risk; consideration should be given to the use of a single effective antibacterial agent.

4.5 Interaction with other medicines and other forms of interaction

Interaction with laboratory tests: trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate. If co-trimoxazole is considered appropriate therapy in patients receiving other anti-folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4).

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co-trimoxazole be prescribed concurrently.

Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Lamivudine: administration of trimethoprim/sulfamethoxazole 160 mg / 800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.

Warfarin: co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites in vitro. Careful control of the anticoagulant therapy during treatment with TRISUL is advisable.

Phenytoin: co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels is advisable.

Sulfonylurea hypoglycaemic agents: interaction with sulfonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Rifampicin: concurrent use of rifampicin and co-trimoxazole results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

Drugs that form cations: when trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.

Digoxin: concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Hyperkalaemia: caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) may result in clinically relevant hyperkalaemia.

Repaglinide: trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in Pneumocystis jirovecii pneumonia prophylaxis and treatment.

Contraceptives: oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive, or choose another method of contraception.

Azathioprine: there are conflicting clinical reports of interactions between azathioprine and trimethoprim-sulfamethoxazole, resulting in serious haematological abnormalities.

4.8 Undesirable effects (specific to elderly)

Metabolism and nutrition disorders

Close supervision is recommended when co-trimoxazole is used in elderly patients or in patients taking high doses of co-trimoxazole as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

2.6.3 International product information

No notable differences to the New Zealand data sheets as above.

3 LITERATURE REVIEW

Literature from the past 10 years was searched for studies investigating adverse events in elderly following trimethoprim treatment (combination or single product). Crellin et al (24) is the focus of this paper as it is the most recent evidence and has fewer limitations than previous studies. Other studies provide some background evidence on adverse outcomes, but have not yet resulted in any regulatory action. The major adverse reactions that have been investigated are hyperkalaemia, acute kidney injury, and sudden death, particularly in the context of an interaction between trimethoprim and ACE inhibitors/ARBs. Other adverse reactions in elderly patients noted in the literature are from case reports and have not been formally studied.

3.1 Crellin et al. 2018 (24)

This study triggered the full review of trimethoprim in the elderly that is summarised in this paper. The full paper is in Annex 1.

The study aimed to investigate the association between trimethoprim and acute kidney injury, hyperkalaemia, or sudden death in a cohort of patients aged 65 and over. The analysis was restricted to patients with an antibiotic prescription for only UTIs and examined the risk of adverse outcomes in patients prescribed trimethoprim and four comparison antibiotics (amoxicillin, cefalexin, ciprofloxacin, and nitrofurantoin).

Methods

The design was a cohort study using electronic clinical records from adults attending primary care practices contributing to the UK Clinical Practice Research Datalink (CPRD GOLD) and linked hospital record data from the Hospital Episode Statistics (HES) database. All patients over the age of 65 during the study period (April 1997 to September 2015) were identified. Individuals were eligible for the study by receiving a prescription for an antibiotic for a urinary tract infection after the latest of the following: 65th birthday; data practice reached CPRD quality control standards; or one year after practice registration date. Patients were no longer eligible to

be included from the earliest of the following: date of death; left practice; or last data collection from practice. Patients who developed end stage renal disease before they were eligible for inclusion were excluded.

The date of inclusion was the day of initiation for any of the five antibiotic drugs recorded up to three days after a primary care morbidity code for uncomplicated UTI. A gap of three days between diagnosis and treatment was allowed. If two or more study drugs were prescribed on the same day, the patient was excluded. Prescriptions for co-amoxiclav (amoxicillin plus clavulanic acid) and co-trimoxazole were also excluded. Additional exclusions included any UTI episode where a patient received one or more of the study drugs in the 14 days preceding the UTI and where a code for a non-UTI infection was recorded in the 3 days preceding the antibiotic prescription.

The primary outcomes were acute kidney injury, hyperkalaemia, and death recorded within 14 days of antibiotic initiation for a UTI. Odds ratios were calculated for each outcome comparing each antibiotic drug to amoxicillin, adjusting for potential confounders using logistical regression. Various sensitivity analyses were also conducted.

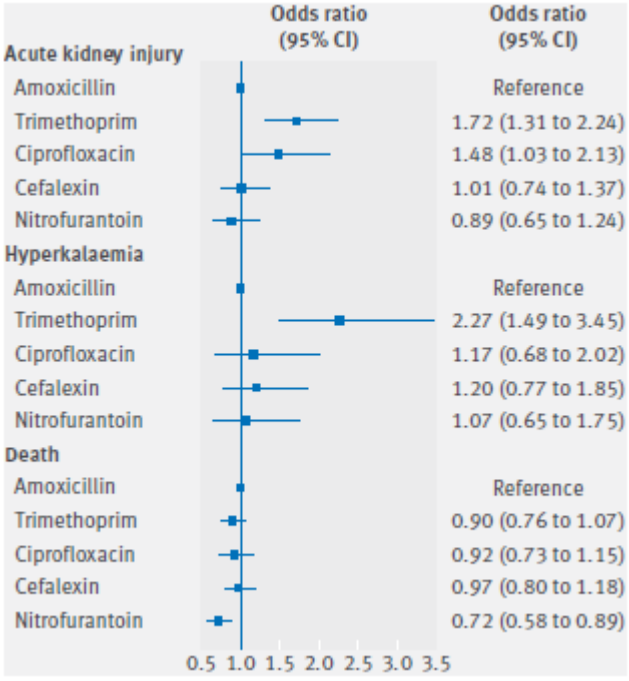
Results

Among a cohort of 1,191,905 eligible patients, 178,238 individuals with at least one UTI treated with antibiotics were identified comprising a total of 422,514 episodes. 59% of episodes were treated with trimethoprim, 5% with amoxicillin, 15% with cefalexin, 15% with nitrofurantoin and 5% with ciprofloxacin. There were a total of 1,345 episodes of acute kidney injury, 648 episodes of hyperkalaemia, and 2,214 deaths within 14 days of antibiotic initiation.

Trimethoprim was associated with the highest odds of acute kidney injury (adjusted odds ratio 1.72, 95% CI 1.31-2.24) and hyperkalaemia (2.27, 1.49-3.45). Ciprofloxacin was also associated with an increased odds of acute kidney injury (1.48, 1.03-2.13) but not of hyperkalaemia (1.17, 0.68-2.02). Cefalexin and nitrofurantoin were not associated with an increased odds of acute kidney injury or hyperkalaemia compared with amoxicillin. The odds of death were similar to amoxicillin for trimethoprim (0.90, 0.76-1.07) and the other antibiotics. These results are summarised in Figure 5.

Minimal differences were observed from the sensitivity analyses. Of note, redefining exposure as antibiotic prescription for any indication increased the observed effect size of the association between trimethoprim and acute kidney injury (2.36, 2.22-2.51).

Figure 5: Summary of primary outcomes from Crellin et al



Strengths

This is the first study to quantify the association of trimethoprim with these outcomes, for an unselected general population cohort after a UTI. The study used a large number of routine, prospectively collected clinical records from a UK general practice database that is broadly representative of the UK population. The results are therefore generalizable to all patients aged 65 and over, in contrast to previous research restricted to select populations. As the effect of trimethoprim alone was investigated, it can be clear about the likely causative agent compared with research on the combination product.

Limitations

While the study only attempted to capture simple UTIs, in the main analyses, patients with underlying urinary tract disorders or other infections may have been included. Since different classes of antibiotic drugs are prescribed for different clinical scenarios, some degree of confounding by indication is unavoidable. However, confounding was able to be reduced by robustly defining and adjusting for variables that may have influenced the choice of antibiotic drug prescribed such as baseline renal function. As trimethoprim was less frequently prescribed for patients with urological pathology, this would likely have led to underestimating the odds of adverse outcomes, particularly acute kidney injury, for trimethoprim compared with the true result. Similarly, clinicians may have been cautious in prescribing trimethoprim to those at highest risk of acute kidney injury and hyperkalaemia, again leading to underestimation of the true risk of adverse outcomes. However, the strongest evidence of adverse outcomes in association with trimethoprim use for those taking renin-angiotensin system blockers was only published towards the end of the period of this study.

The assessment of antibiotic exposure was based on prescriptions alone and patients may not have collected or taken their medicine. This may have led to differential misclassification owing to the severity of the infection, with resulting over or under estimation of the true effect size. However, it was attempted to mitigate for this by limiting the study to simple UTIs and adjusting, in particular, for history of renal or urological disease.

The outcomes may have also been misclassified. Trimethoprim reduces tubular secretion of creatinine causing apparent renal impairment, although glomerular filtration rate does not fall. Lack of awareness of this physiological effect may have led clinicians to incorrectly diagnose acute kidney injury among the trimethoprim treated group, particularly given the current focus on creatinine based definitions of acute kidney injury. However, the definition of acute kidney injury relied on clinical coding of hospital admissions. In general, this leads to under ascertainment compared with analyses of serial creatinine tests but disproportionately captures more severe acute kidney injury. In addition, the increased risk of acute kidney injury dated back to 2001-04, before creatinine based definitions of acute kidney injury were in common use. It is also possible that there was a bias towards testing for or recording acute kidney injury or hyperkalaemia among patients taking trimethoprim if clinicians were aware of a potential association which would have led to an overestimation of the true risk of adverse outcomes.

3.2 Acute kidney injury

3.2.1 Gentry & Nguyen. 2013

Aims: To describe hyperkalaemia and acute renal injury associated with high-dose co-trimoxazole.

Methods: An electronic medical record database retrospective study conducted of outpatients from Oklahoma City Veterans Affairs Medical Centre receiving high-dose or low-dose co-trimoxazole comparing the incidences of hyperkalaemia and acute renal injury.

Results: Of 6,162 patients, more developed hyperkalaemia (3.06% vs 1.05%, P<0.0001) or acute renal injury (1.99% vs 0.700%, P=0.0001) in the high dose co-trimoxazole group. Variables independently associated with hyperkalaemia includes age >58 years (OR 3.44, 95% CI 1.86-7.0; P<0.0001), concomitant receipt of an NSAID (1.71, 1.02-2.79, P=0.044) or an ACE inhibitor (3.27, 2.06-5.14, P<0.0001), high dose co-trimoxazole prescribed (2.92, 1.85-4.60, P<0.0001) and baseline elevated serum creatinine (45.1; 21.7-93.2, P<0.0001). Variables

independently associated with acute renal injury included concomitant receipt of an ACE inhibitor (2.36, 1.01-5.24, P=0.048) or a potassium supplement (41.9, 1.45-10.1, P=0.010), high dose co-trimoxazole prescribed (3.70, 1.70-8.12, P=0.0012), and baseline elevated serum creatinine (2110, 724-7890, P<0.0001). Results are summarised in Table 9 and Table 10 (9).

Table 9: Frequency of laboratory adverse reactions during TMP-SMX therapy

Adverse Reaction	High Dose No. of Patients (%) n=491	Standard-dose No. of Patients (%) n=491	p-value
Electrolyte disturbances	25 (5.09)	8 (1.63)	0.0021
Hyperkalemia	17 (3.46)	4 (0.81)	0.0066
Hypokalemia	2 (0.41)	3 (0.61)	1.00
Hyponatremia	10 (2.04)	3 (0.61)	0.045
Renal (acute renal injury)	18 (3.67)	8 (1.63)	0.044
Hepatic (increased LFT)	1 (0.20)	0	0.24
Hematologic	5 (1.02)	3 (0.61)	0.48
Anemia	2 (0.41)	2 (0.41)	1.00
Thrombocytopenia	1 (0.20)	1 (0.20)	1.00
Increased INR	2 (0.41)	0	0.096
Metabolic	5 (1.02)	1 (0.20)	0.087
Rhabdomyolysis	0	1 (0.20)	0.24
Hypoglycemia	3 (0.61)	0	0.041
Hyperglycemia	2 (0.41)	0	0.096

Table 10: Variable found to be statistically significant to any laboratory ADR and hyperkalaemia

	ADR Present	ADR Absent	p-Value
Any laboratory ADR	**n=59**	**n=423**	
Mean age (SD)	60.2 ± 13.7	57.0 ± 14.4	0.047
High-dose TMP-SMX, n (%)	38 (64.4)	21 (5.0)	0.017
Concomitant potassium supplement, n (%)	9 (15.2)	27 (6.38)	0.028
Hyperkalemia	**n=15**	**n=467**	
Mean age (SD)	67.5 ± 12.0	57.1 ± 14.3	0.002
High-dose TMP-SMX, n (%)	13 (86.7)	2 (13.3)	0.007
Concomitant ACE inhibitor, n (%)	7 (46.7)	107 (22.9)	0.048

* ADR = Adverse drug reaction.

Comments

Indicates a possible dose-related effect and shows that older age groups are more commonly associated with hyperkalaemia and AKI adverse effects. However, does not associate the outcomes to the trimethoprim component only.

3.2.2 Fraser et al. 2012

Aims: To systematically study the adverse renal effects of co-trimoxazole in a middle-aged veteran population.

Methods: A review of complete electronic records for all patients from the Michael E. DeBakey Veterans Affairs Medical Centre who, during a 3 year period, had received ≥6 days of treatment with co-trimoxazole, and for whom a baseline and follow-up determination of serum creatinine and blood urea nitrogen (BUN) were available. The likelihood of the AKI being caused by co-trimoxazole was based on the extent of the underlying

disease states which may affect serum creatinine or BUN (e.g. pre-existing CKD would mean AKI was unlikely to be related to co-trimoxazole).

Results: Of 736 patients who met inclusion criteria, 64 (11.2%) had increases in both serum creatinine and BUN that met predetermined criteria for acute kidney injury (AKI): in 33 (5.8%), AKI was judged likely due to co-trimoxazole; in 28 (4.9%), possibly due to co-trimoxazole; and in 3 (0.52%), unrelated to co-trimoxazole. In nearly all cases likely due to co-trimoxazole, AKI resolved promptly after discontinuation of therapy, but one patient required dialysis. Patients with hypertension and diabetes mellitus had increased risks for renal insufficiency. Results are summarised in Table 11 and Table 12 (5).

Table 11: Classification of AKI based on likelihood of causation by co-trimoxazole

Classification of AKI	Number of patients
Likely to be caused by trimethoprim/sulfamethoxazole	33
Possibly caused by trimethoprim/sulfamethoxazole	28
medications	8
comorbidities	3
intravenous contrast	4
pre-renal	3
post-renal	0
multiple causes	10
Unlikely to be caused by trimethoprim/sulfamethoxazole	3

Table 12: Urinalysis findings after documentation of AKI

Study findings	Number of patients
≥5 WBCs/HPF	12 (32.4)
≥5 RBCs/HPF	11 (29.7)
Urine pH ≥6	14 (37.8)
Urine crystals	4 (10.8)
Calcium oxalate	2 (5.4)
Uric acid	2 (5.4)
Sulpha	0 (0)
RBC casts	0 (0)
WBC casts	0 (0)
Coarse granular casts	0 (0)
Renal epithelial cells	0 (0)
Urine eosinophils[a]	0 (0)

Comments

The mean ages of patients in AKI and non-AKI groups were 63.8 and 62.4 respectively; the population used in this study is not reflective of the elderly population (>65 years). Additionally, the study uses co-trimoxazole rather than a trimethoprim-only product.

Design of the study only allowed for descriptive analysis without odds ratios, which has limited use. The study is more like a case series analysis and, therefore, cannot confirm an association between AKI and co-trimoxazole.

3.3 Hyperkalaemia

3.3.1 Chan et al. 2017

Aims: To investigate changes in serum potassium in patients without acute infections, and the influence of concomitant antikaliuretic drugs on this effect.

Methods: Post-hoc analysis of a randomised controlled trial in 181 patients from England and Wales with interstitial lung disease who were randomly assigned to placebo plus folic acid, or 960 mg co-trimoxazole twice daily plus folic acid. Serum potassium and creatinine concentrations were measured at baseline, 6 weeks, and 6, 9 and 12 months. The primary outcome was the difference in mean serum potassium concentrations between co-trimoxazole and placebo at 6 weeks.

As a secondary outcome, the same analysis was done for serum creatinine.

Results: Co-trimoxazole significantly increased mean serum potassium levels at 6 weeks, with a difference between means compared with placebo of 0.21 mmol/L (95% CI 0.09-0.34; P=0.001). A difference was observed at all other time points recorded (Figure 6). This significant increase was detectable even after exclusion of patients on antikaliuretic drugs. There were 5 (5.7%) patients on co-trimoxazole whose serum potassium concentrations reach ≥5.5 mmol/L during the study period.

At the 6-week follow-up, the mean serum creatinine concentration in the treatment group (105.79 ± 33.43 mmol/L) was significantly higher than in the placebo group (89.81 ± 18.10 mmol/L), which represents a difference between means of 15.99 (95% CI 7.88-24.09) mmol/L (P = 0.005). The elevation in creatinine was persistent at further follow-up measurements (Figure 7). A moderate positive correlation between the change from baseline in potassium and creatinine concentrations at 6 weeks (r(168) = 0.383; P < 0.0005) (25).

Figure 6: Mean serum potassium in the co-trimoxazole and placebo arms of the study. The illustrated error bars depict the standard error for each measurement

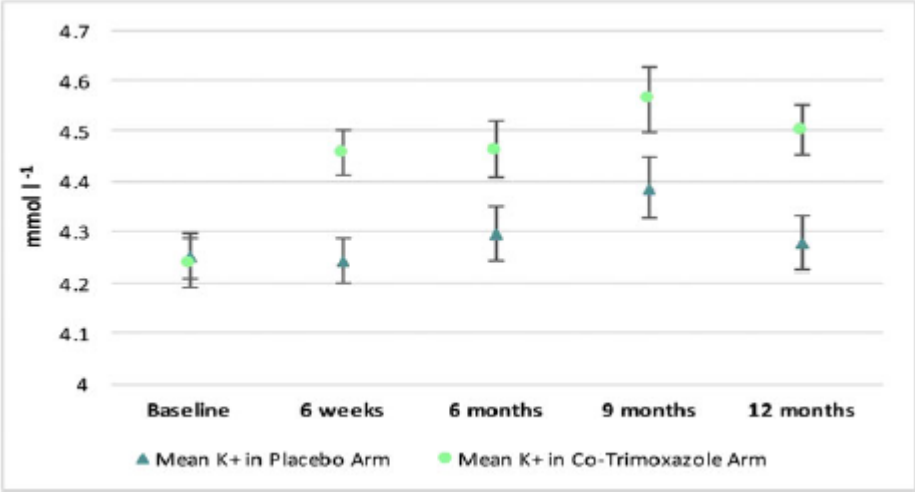
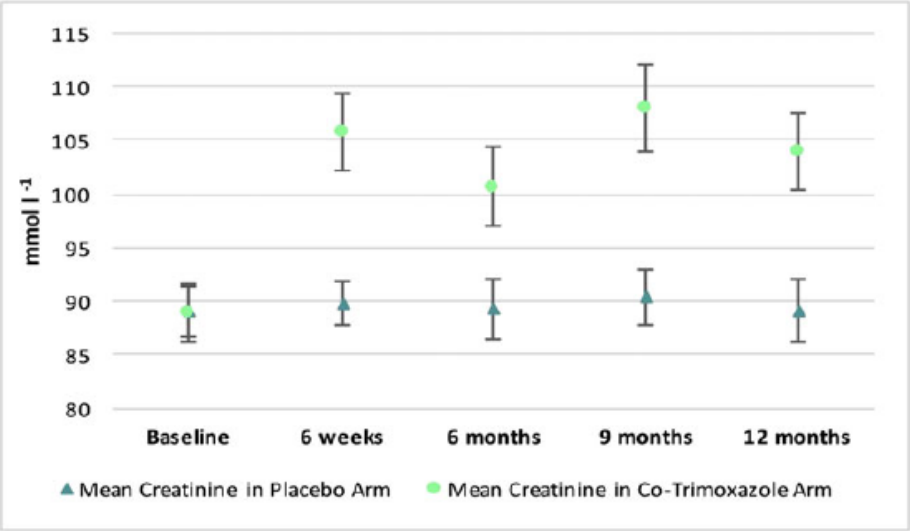


Figure 7: Mean serum creatinine in co-trimoxazole and placebo arms. The illustrated error bars depict the standard error for each measurement



Comments

The study does not show that hyperkalaemia can occur within the 3-14 day duration of a typical course of antibiotic treatment for a UTI; most other studies observe outcomes within 14 days of taking the antibiotic. The population used in this study were across all ages and results may be different for the elderly. Additionally, the study uses co-trimoxazole rather than a trimethoprim-only product.

3.3.2 Antoniou et al. 2010

Aims: To characterise the risk of hyperkalaemia-associated hospitalisation in elderly patients who were being treated with trimethoprim-sulfamethoxazole with either an ACE inhibitor or an ARB.

Methods: Population-based, nested case-control study of a cohort of elderly patients 66 years or older who were residents of Ontario, Canada, and who were receiving continuous therapy with either an ACE inhibitor or an ARB. Case patients were those with a hyperkalaemia-associated hospitalisation within 14 days of receiving a prescription for co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. For each case, up to 4 control patients were identified from the same cohort matched for age, sex, and presence or absence of chronic renal disease and diabetes. Odds ratios were determined for the association between hyperkalaemia-associated hospitalisation and previous antibiotic use.

Results: During the 14-year study period, 4,148 admissions involving hyperkalaemia were identified, 371 of which occurred within 14 days of antibiotic exposure. Compared with amoxicillin, the use of co-trimoxazole was associated with a nearly 7-fold increased risk of hyperkalaemia-associated hospitalisation (adjusted odds ratio 6.7, 95% confidence interval 4.5-10.0). No such risk was found with the use of comparator antibiotics. Results are summarised in Table 13 (7).

Table 13: Association between hospital admission involving hyperkalaemia and recent antibiotic use

Antibiotic	No. (%) Cases	No. (%) Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Primary analysis				
14-Day exposure window				
Total	**367**	**1417**		
Trimethoprim-sulfamethoxazole	204 (55.6)	323 (22.8)	6.2 (4.3-9.1)	6.7 (4.5-10.0)
Norfloxacin	20 (5.4)	163 (11.5)	0.8 (0.5-1.5)	0.8 (0.4-1.5)
Ciprofloxacin	76 (20.7)	413 (29.1)	1.5 (1.0-2.3)	1.4 (0.9-2.2)
Nitrofurantoin	18 (4.9)	129 (9.1)	1.2 (0.6-2.1)	1.1 (0.6-2.0)
Amoxicillin[a]	49 (13.4)	389 (27.5)	1 [Reference]	1 [Reference]
Secondary analysis				
7-Day exposure window				
Total	**213**	**809**		
Trimethoprim-sulfamethoxazole	112 (52.6)	143 (17.7)	6.2 (3.9-9.9)	6.8 (4.1-11.3)
Norfloxacin	8 (3.8)	96 (11.9)	0.7 (0.3-1.7)	0.7 (0.3-1.8)
Ciprofloxacin	52 (24.4)	222 (27.4)	1.9 (1.1-3.1)	1.5 (0.9-2.6)
Nitrofurantoin	10 (4.7)	90 (11.1)	1.0 (0.5-2.1)	0.9 (0.4-2.1)
Amoxicillin[a]	31 (14.6)	258 (31.9)	1 [Reference]	1 [Reference]
21-Day exposure window				
Total	**368**	**1193**		
Trimethoprim-sulfamethoxazole	204 (55.4)	236 (19.8)	6.1 (4.2-8.9)	6.5 (4.3-9.9)
Norfloxacin	21 (5.7)	154 (12.9)	0.8 (0.5-1.5)	0.8 (0.4-1.5)
Ciprofloxacin	76 (20.6)	346 (29.0)	1.5 (1.0-2.3)	1.5 (1.0-2.4)
Nitrofurantoin	18 (4.9)	110 (9.2)	1.2 (0.6-2.2)	1.2 (0.6-2.2)
Amoxicillin[a]	49 (13.3)	347 (29.1)	1 [Reference]	1 [Reference]

Comments

The study uses co-trimoxazole rather than a trimethoprim-only product.

3.3.3 Antoniou et al. 2011

Aims: To characterise the risk of admission to hospital for hyperkalaemia in elderly patients treated with co-trimoxazole in combination with spironolactone.

Methods: Population based nested-case control study in Ontario, Canada, from 1 April 1992 to 1 March 2010. Cases were residents of Ontario aged 66 years or above receiving chronic treatment with spironolactone and admitted to hospital with hyperkalaemia within 14 days of receiving a prescription for either co-trimoxazole, amoxicillin, norfloxacin, or nitrofurantoin. Up to four controls for each case were identified from the same cohort, matched on age, sex, and presence or absence of chronic kidney disease and diabetes, and required to have received one of the study antibiotics within 13 days before the case's index date. Adjusted odds ratios for association between admission to hospital with hyperkalaemia and receipt of a study antibiotic in the preceding 14 days were calculated.

Results: During the 18 year study period, 6,903 admissions for hyperkalaemia were identified, 306 of which occurred within 14 days of antibiotic use. 10.8% of spironolactone users received at least one prescription for co-trimoxazole. Compared with amoxicillin, prescription of co-trimoxazole was associated with a marked increase in the risk of admission to hospital for hyperkalaemia (adjusted OR 12.4, 95% CI 7.1-21.6). The population attributable fraction was 59.7%, suggesting that approximately 60% of all cases of hyperkalaemia in older patients taking spironolactone and treated with an antibiotic for a urinary tract infection could be avoided if co-trimoxazole was not prescribed. Treatment with nitrofurantoin was also associated with an increased risk of hyperkalaemia (2.4, 1.3-4.6) but no risk was found with norfloxacin (1.6, 0.8-3.4). Results are summarised in Table 14 (8).

Table 14: Association between hospital admission involving hyperkalaemia and recent antibiotic use

Use of antibiotic in preceding 14 days	No (%) cases (n=248)	No (%) controls (n=783)	Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
TMP-SMX	161 (65)	162 (21)	11.0 (6.8 to 17.8)	12.4 (7.1 to 21.6)
Nitrofurantoin	34 (14)	159 (20)	2.5 (1.4 to 4.4)	2.4 (1.3 to 4.6)
Norfloxacin	17 (7)	137 (17)	1.5 (0.8 to 2.9)	1.6 (0.8 to 3.4)
Amoxicillin	36 (15)	325 (42)	1.0 (reference)	1.0 (reference)

Comments

The study uses co-trimoxazole rather than a trimethoprim-only product.

3.4 Sudden death

3.4.1 Fralick et al. 2014

Aims: To determine whether the prescription of co-trimoxazole with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker is associated with sudden death.

Methods: A population based nested case-control study in Ontario, Canada, from 1 April 1994 to 1 January 2012. Residents aged 66 years or older treated with an angiotensin converting enzyme inhibitor or angiotensin receptor blocker were included. Cases were those who died suddenly shortly after receiving an outpatient prescription for one of co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. Each case was matched with up to four controls on age, sex, chronic kidney disease, and diabetes. The main outcome was the association between sudden death and exposure to each antibiotic relative to amoxicillin (after adjustment)

Results: Of 39,879 sudden deaths, 1,027 occurred within seven days of exposure to an antibiotic and were matched to 3,733 controls. Relative to amoxicillin, co-trimoxazole was associated with an increased risk of sudden death (adjusted odds ratio 1.38, 95% CI 1.09-1.76). The risk was marginally higher at 14 days (1.54, 1.29-1.84). This corresponds to approximately three sudden deaths within 14 days per 1,000 co-trimoxazole prescriptions. Ciprofloxacin was also associated with an increased risk of sudden death (1.29, 1.03-1.62), but no such risk was observed with nitrofurantoin or norfloxacin. Results are summarised in Table 15 (3).

Table 15: Antibiotic use and risk of sudden death within seven days

Antibiotic use	No (%) cases	No (%) controls	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Amoxicillin (reference)	226 (22.0)	1098 (29.4)	1.0 (reference)	1.0 (reference)
Co-trimoxazole	288 (28.0)	734 (19.7)	1.83 (1.50 to 2.24)	1.38 (1.09 to 1.76)
Ciprofloxacin	340 (33.1)	964 (25.8)	1.66 (1.37 to 2.00)	1.29 (1.03 to 1.62)
Norfloxacin	79 (7.7)	455 (12.2)	0.81 (0.61 to 1.08)	0.74 (0.53 to 1.02)
Nitrofurantoin	94 (9.2)	482 (12.9)	0.87 (0.66 to 1.15)	0.64 (0.46 to 0.88)

Comments

The study uses co-trimoxazole rather than a trimethoprim-only product.

3.4.2 Antoniou et al. 2015

Aims: To examine whether the combination of trimethoprim and spironolactone is associated with an increased risk of sudden death, a consequence of hyperkalaemia.

Methods: Population-based nested case-control study involving Ontario residents aged 66 years or older who received spironolactone between 1 April 1994 and 31 December 2011. Within this group, cases were identified

as patients who died of sudden death within 14 days after receiving a prescription for co-trimoxazole or one of the other study antibiotics (amoxicillin, ciprofloxacin, norfloxacin or nitrofurantoin). For each case, up to 4 controls were matched by age and sex. The adjusted odds ratio for the association between sudden death and exposure to each antibiotic relative to amoxicillin was calculated.

Results: Of the 11,968 patients who died of sudden death while receiving spironolactone, 328 whose death occurred within 14 days after antibiotic exposure were identified. Compared with amoxicillin, co-trimoxazole was associated with a more than twofold increase in the risk of sudden death (adjusted OR 2.46, 95% CI 1.55-3.90). Ciprofloxacin (1.55, 1.02-2.38) and nitrofurantoin (1.70, 1.03-2.79) were also associated with an increased risk of sudden death, although the risk with nitrofurantoin was not apparent in a sensitivity analysis. Results are summarised in Table 16 (4).

Table 16: Association between sudden death and recent antibiotic use

	No. (%) of patients		OR (95% CI)	
Antibiotic	Cases *n* = 328	Controls *n* = 1171	Unadjusted	Adjusted†
TMP/SMX	86 (26.2)	189 (16.1)	2.45 (1.67–3.61)	2.46 (1.55–3.90)
Nitrofurantoin	49 (14.9)	202 (17.3)	1.32 (0.86–2.02)	1.70 (1.03–2.79)
Norfloxacin	27 (8.2)	162 (13.8)	0.84 (0.51–0.39)	0.86 (0.47–1.58)
Ciprofloxacin	105 (32.0)	289 (24.7)	1.99 (1.38–2.87)	1.55 (1.02–2.38)
Amoxicillin	61 (18.6)	329 (28.1)	1.00 (ref)	1.00 (ref)

Note: CI = confidence interval, OR = odds ratio, ref = reference group, TMP/SMX = trimethoprim–sulfamethoxazole.
*Antibiotic use in preceding 14 d.
†Adjusted for disease risk index (covariates in Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140816/-/DC1) and duration of spironolactone use.

Comments

The study uses co-trimoxazole rather than a trimethoprim-only product.

3.5 Other reactions

3.5.1 Hypoglycaemia

Case report describing an 85-year-old man with diabetes mellitus who attended the emergency room with severe hypoglycaemia that persisted despite multiple intravenous bolus doses and a continuous infusion of glucose. He needed hospital admission to stabilize. The patient, a nursing home resident, was being treated with co-trimoxazole for an uncomplicated urinary tract infection, but was also taking multiple additional drugs for his co-morbidities. After co-trimoxazole was discontinued, plasma glucose levels slowly stabilized within the normal range. A diagnosis of prolonged and refractory hypoglycaemia induced mainly by the antimicrobial agent was made, with additional contribution from multiple other drugs. No further episodes of hypoglycaemia occurred during the next 6 months of follow-up (26).

Comments

Trisul Datasheet: Section 4.8 – Hypoglycaemia is listed as a very rare adverse event.

3.5.2 Circulating anti-neutrophil cytoplasmic antibody-positive (ANCA) small vessel vasculitis

Case report of an 83-year-old woman with a history of polycythaemia vera, recurrent thrombosis, pulmonary embolism and lumbar compression fractures who suffered ANCA-positive vasculitis induced by co-trimoxazole. Symptoms began two days after initiation of co-trimoxazole (960 mg twice daily) for an infection at the inguinal catheterization site for an inferior vena cava filter placement (27).

3.5.3 Hyponatraemia

Case report of a 71-year-old female who developed hyponatraemia following completion of a 7 day course of co-trimoxazole at a dose of 960 mg twice daily. The patient's serum sodium concentrations increased to baseline in the following 7 days. She was again treated with co-trimoxazole several months later for a urinary tract infection. Again, within 7 days, she developed hyponatraemia (28).

Comments

Trisul Datasheet: Section 4.8 – Hypoglycaemia is listed as a very rare adverse event.

3.5.4 Hallucinations

Case report of an 86-year-old Caucasian immune-competent female with major depressive disorder and insomnia who developed hallucinations when treated with co-trimoxazole at a dose of 960 mg twice daily for a lower urinary tract infection. Symptoms significantly improved after switching to nitrofurantoin and using risperidone (29).

Comments

Trisul Datasheet: Section 4.8 – Hallucinations are listed as a very rare adverse event.

3.5.5 Higher-level gait disorder and nocturnal delirium

Case report of an 82-year-old male with a recent history of depression who was on 960 mg of co-trimoxazole, increased up to 1920 mg, twice daily for aspiration pneumonia. Within one month, the patient developed high-level gait disorder (HLGD) with gait ignition failure, poor balance, and frequent falls. His other medications at the time were thiamine 100 mg daily, multivitamin 1 tablet daily, omeprazole 20 mg twice daily and modified release venlafaxine 150 mg daily. Investigation did not reveal any cause for his acute gait disturbance. Co-trimoxazole was stopped and within 3 days the patient's gait had returned to normal (30).

3.6 CARM data

There are 1003 case reports for trimethoprim in the Centre for Adverse Reactions Monitoring (CARM) database. Of these, 31.7% (318) are for people aged 65 years or older – shown in Table 17, grouped into 5-year age bands. The number of reactions (534) within each System Organ Class is shown in Table 18.

See Annex 2 for a line listing of these 318 cases. Note that from 1985 onwards, the data only includes trimethoprim-only products and does not include co-trimoxazole.

Comments

The usage data (27.9% of all people were elderly) is similar to the proportion of ADR reports from elderly (31.7%). Therefore, based on the usage data, this number of reports could be considered expected.

Table 17: Number of reports in 5 year age bands, separated by gender, in the CARM database for trimethoprim in patients aged 65 years and older (n=318).

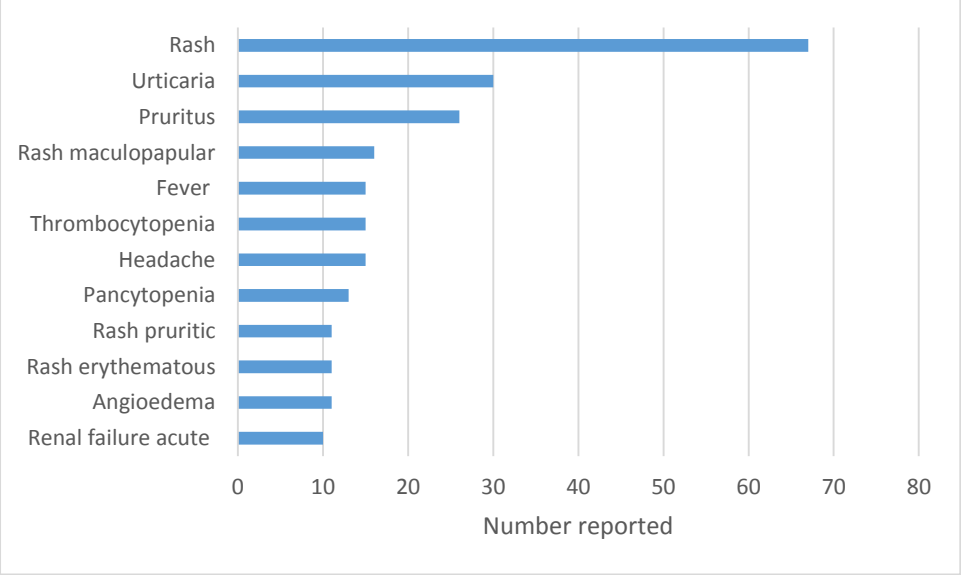
Age Group	Female	Male	Total
65 – 69 years	49	16	65
70 – 74 years	45	18	63
75 – 79 years	49	26	75
80 – 84years	54	10	64
85 – 89 years	28	7	35
90 plus years	14	2	16
Total	239	79	318

Table 18: Reactions grouped by System Organ Class, separated by gender, in the CARM database for trimethoprim in patients aged 65 years and older (n=534)

System Organ Class	Female	Male	Total
Alimentary	52	7	59
Cardiovascular	21	3	24
Endocrine/Metabolic	11	2	13
Haematological	39	23	62
Liver	6	8	14
Musculoskeletal	8	1	9
Nervous System	27	2	29
Others	42	7	49
Psychiatric Changes	17	2	19
Reproductive Disorder	1		1
Resistance Mechanism Disorders		1	1
Respiratory	13	3	16
Skin and Appendages	165	51	216
Special Senses	3		3
Urinary	13	6	19
Total	**418** 78%	**116** 22%	**534**

Figure 8 shows the 12 most commonly reported reactions. These are also the only reactions reported 10 or more times. Notably of absence are hyperkalaemia (n=4) and hyponatraemia (n=4). All case reports for hyperkalaemia also included renal terms (renal impairment, renal failure acute, renal tubular disorder, blood creatinine increased).

Figure 8: Top 12 most commonly reported reactions in the CARM database for trimethoprim in patients aged 65 years and older



There are 15 reports where the drug was considered possibly contributory:

- 8 in the haematological SOC

- 3 in skin and appendages
- 3 in urinary (including renal failure acute)
- 1 as a result of anaphylaxis/cardiac arrest

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

Trimethoprim is a medicine widely used to treat and prevent UTIs and is commonly used in the elderly, particularly women who are more susceptible to UTIs. Although resistance to trimethoprim is common, it is an effective empirical treatment as it has efficacy against most common uropathogenic bacteria, such as *E. coli, Klebsiella* spp. and *Proteus mirabilis*. However, there has been evidence to suggest there are significant risks involved with trimethoprim treatment, particularly in the elderly population and with concomitant use of ACE inhibitors and ARBs. The evidence is limited as the combination product co-trimoxazole (trimethoprim + sulfamethoxazole) was investigated rather than trimethoprim alone. Additionally, the designs were nested case-control studies or retrospective database analyses which had additional limitations on their results.

New evidence provided in the Crellin et al study has shown that trimethoprim is associated with an increased risk of acute kidney injury and hyperkalaemia compared with other antibiotics used for treating UTIs in the elderly population. This study accounted for the limitations in previous studies, and also adds to previous knowledge by showing these adverse reactions affect all elderly groups, not just elderly patients taking concomitant ACE inhibitors or ARBs. Conversely, the new evidence did not support the previously proposed association with sudden death.

[redacted]

The current statements made in the data sheets convey that the elderly may be more susceptible to adverse effects, however they do not make any specific warnings reflecting the evidence presented by Crellin et al. To support appropriate antibiotic prescribing, the data sheets should provide prescribers with information on risks in the elderly if supported by robust evidence. This could be in the form of a warning (expanding on what is already stated) or raised to a contraindication if the evidence suggests that the risk of trimethoprim

outweighs the benefits. Specific risks can be identified, or the wording could reflect an increased susceptibility to all adverse reactions/classes of adverse reactions (eg. Electrolyte issues).

5 ADVICE SOUGHT

The Committee is asked to advise:

- If there is evidence of a changed/increased risk of adverse outcomes from trimethoprim in the elderly (≥65 years) population
- What specific adverse reactions (if any) have a changed/increased risk in the elderly population
- If any changes to the data sheet are required
- If further communication outside of MARC's Remarks in *Prescriber Update* are required.

6 ANNEXES

1. Crellin et al, 2018
2. CARM data

7 REFERENCES

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