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Trimethoprim-Induced Hyperkalaemia
Clinical Data, Mechanism, Prevention and Management

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Abstract

Cotrimoxazole (trimethoprim-sulfamethoxazole) is a combination antimicrobial that is frequently used to treat a wide variety of infections. Only recently has hyperkalaemia been recognised as a relatively common complication of therapy with trimethoprim. Hyperkalaemia has been demonstrated to occur with the administration of both high and standard dosages of trimethoprim.

The recognition of this disorder of potassium homeostasis prompted the investigation and ultimate description of the mechanism by which trimethoprim causes hyperkalaemia. Trimethoprim was found to reduce renal potassium excretion through the competitive inhibition of epithelial sodium channels in the distal nephron, in a manner identical to the potassium-sparing diuretic amiloride. Increased risk for hyperkalaemia with trimethoprim treatment appears to be related to both higher dosages and underlying renal impairment. It is probable that other disturbances in potassium homeostasis, such as hyopoaldosteronism and treatment with medications that impair renal potassium excretion, are also risk factors for hyperkalaemia with trimethoprim therapy.

Prevention of this adverse reaction depends upon recognition of patients at risk of developing hyperkalaemia as well as proper dosage selection of trimethoprim for the patient's prevailing glomerular filtration rate. Management of hyperkalaemia often mandates discontinuation of the drug, volume repletion with isotonic fluids, and other therapies specific to hyperkalaemia. In circumstances where continued treatment with trimethoprim is required, induction of high urinary flow rates with intravenous fluids and a loop diuretic, as well as alkalinisation of the urine, have been shown to block the antikaliuretic effect of trimethoprim on distal nephron cells.

Trimethoprim is an antimicrobial agent that is employed extensively in combination with sulfamethoxazole (as cotrimoxazole) to treat a number of infections.[1,2] Bacterial cell growth is prevented by this drug through the interruption of tetrahydrofolic acid production by the inhibition of the enzyme dihydrofolate reductase in infecting organisms.[1-3] Following oral administration, trimethoprim is completely absorbed from the gastrointestinal tract.[3] Once in the systemic circulation, approximately 65 to 70% of trimethoprim is protein bound.[3] Within 24 hours of ingestion, trimethoprim reaches high urinary concentrations, with 50 to 60% of the drug excreted by the kidney.[3]

In a number of published studies, adverse reactions to trimethoprim have been noted to occur when this drug is administered in combination with sulfamethoxazole.[1,2,4] The adverse effects most commonly reported include skin rash, gastrointestinal discomfort and haematological disturbances.[1,2] Surprisingly, nephrotoxicity is an exceedingly rare complication of trimethoprim therapy. In fact, there were no episodes of acute renal insufficiency and only 1 case of renal tubular acidosis in 649 recipients of cotrimoxazole surveyed in the 1978 report of Lawson and Jick.[1] Furthermore, disturbances in potassium homeostasis were not reported in any of these large surveillance studies.[1,2,4] In a few case reports, allergic interstitial nephritis and crystal-associated nephropathy were described.[4-7] Only recently has treatment with trimethoprim been noted to cause mild to moderate and, at times, potentially life-threatening hyperkalaemia.[8-11] It is important to note that it is trimethoprim, and not sulfamethoxazole, that is the culprit drug causing the observed elevation in serum potassium levels when this drug combination is employed. The following sections will provide the clinical data that led to the recognition of trimethoprim as the cause of hyperkalaemia, the laboratory investigations that elucidated the mechanism by which trimethoprim causes hyperkalaemia, the manoeuvres useful in the prevention of hyperkalaemia, and finally the appropriate management of hyperkalaemia when it develops in the setting of trimethoprim therapy.

1. Clinical Data

Upon review of the literature (table I), one finds that the initial report of hyperkalaemia complicating treatment with high dosage trimethoprim (20 mg/kg/day) was published in 1983.[12] A leukaemic patient with *Pneumocystis carinii* pneumonia was noted to develop severe hyperkalaemia, metabolic acidosis, hyponatraemia and renal salt wasting during therapy with a relatively high dosage of oral cotrimoxazole (trimethoprim 160mg and sulfamethoxazole 800mg every 6 hours). Renal function was normal, and adrenal function was also found to be intact. These metabolic perturbations were rapidly corrected upon discontinuation of the drug and infusion of saline. Subsequent rechallenge of the same patient with cotrimoxazole resulted in the recurrence of hyperkalaemia (serum potassium level 7.0 mEq/L). Although the mechanism of hyperkalaemia remained obscure, it was speculated that cotrimoxazole somehow inhibited renal potassium excretion either by a direct effect on distal nephron potassium secretion or by the induction of tubular resistance to aldosterone. At this time, however, trimethoprim was not suspected as the culprit drug.

Four years later, mild-to-moderate hyperkalaemia and hyponatraemia were reported in 4 patients with AIDS.[13] These electrolyte disturbances were ascribed to an underlying state of hyporeninaemic hypoaldosteronism in these patients. However, it is notable that all 4 patients were also receiving treatment with cotrimoxazole. Although it is impossible to determine the cause of the hyperkalaemia, it is certainly possible that trimethoprim caused or at least contributed to the elevation in serum potassium levels in this group of patients.[13] None the less, trimethoprim was not recognised as a potential cause of hyperkalaemia in these patients.

In an important drug efficacy study, hyperkalaemia was reported as an adverse reaction in patients with AIDS treated orally with either high dosage cotrimoxazole (trimethoprim 20 mg/kg/day and

Table I. Selected reports of hyperkalaemia with trimethoprim therapy

Year	No. of patients	Peak serum potassium (mEq/L)	Dosage of trimethoprim	Risk factors	Reference
1983	1	7.0	640 mg/day	NR	12
1987	4	5.5-6.4	NR	NR	13
1990	10	5.1-6.1	20 mg/kg/day	NR	14
1993	1	7.9	20 mg/kg/day	Renal impairment	8
1993	30	>5.0 (50%) >6.0 (10%)	20 mg/kg/day	NR	9
1993	25	>5.5 (28%) >6.0 (12%)	20 mg/kg/day	Renal impairment	10
1994	1	5.3	320 mg/day	Renal impairment, older age	15
1994	1	6.0	320 mg/day	Older age	16
1994	1	6.2	320 mg/day	Older age	17
1994	1	7.0	400 mg/day	Renal impairment, NSAID	18
1995	1	6.3	600 mg/day	NR	19
1996	80	>5.0 (62.5%) >5.5 (21.2%)	320 mg/day	Renal impairment	20
1996	1	6.8	20 mg/kg/day	Renal impairment, ACE inhibitor	21
1997	1	7.8	320 mg/day	Hypoaldosteronism	22
1997	122	>5.6 (20.3%)	600 to 1200 mg/day	NR	23
1999	51	>5.0 (18%) >5.5 (6%)	320 mg/day	NR	24

NR = not reported; **NSAID** = nonsteroidal anti-inflammatory drug.

sulfamethoxazole 100 mg/kg/day) or high dosage trimethoprim-dapsone (20 mg/kg/day and 100 mg/kg/day, respectively) for *Pneumocystis carinii* pneumonia.[14] In this antimicrobial trial published in 1990, hyperkalaemia occurred in 53% of the patients treated with trimethoprim-dapsone and in 20% of those receiving cotrimoxazole. In those who developed hyperkalaemia, serum potassium levels ranged between 5.1 and 6.1 mEq/L. However, no explanation for this disturbance in potassium homeostasis was sought, and, as a result, hyperkalaemia as an adverse reaction of trimethoprim remained essentially unknown.

In 1993, life-threatening hyperkalaemia was observed in a patient with AIDS who was receiving a high dosage of intravenous cotrimoxazole.[8] The serum potassium level in this patient increased from 4.6 to 7.9 mEq/L after 9 days of therapy. At the time of hyperkalaemia, the urinary potassium level was found to be inappropriately low at 5 mEq/L, supporting impaired renal tubular potassium secretion as the cause of hyperkalaemia. Adrenal function was normal, and administration of fludrocortisone 0.3 mg/day failed to increase urinary potassium excretion.[8] On the other hand, discontinuation of cotrimoxazole was associated with normalisation of the serum potassium level.[8] This was more evidence incriminating trimethoprim as the causative agent in the development of hyperkalaemia.

Also in 1993, careful observations were made on 30 hospitalised HIV-infected patients treated with either high dosage cotrimoxazole or trimethoprim-dapsone.[9] A rise in serum potassium level occurred in 27 of the 30 patients. A peak serum potassium level >5.0 mEq/L developed in 50% of the patients, and 3 patients (10%) reached a potassium level >6.0 mEq/L. In 7 patients studied in more detail, urinary potassium levels averaged 11.3 ± 5.8 mEq/L (± SD) at a time when mean serum potassium levels were 5.9 ± 0.9 mEq/L (± SD). Discontinuation of trimethoprim-containing medications in 3 patients normalised both serum and urinary potassium levels.[9] None of the patients had renal impairment and adrenal function was intact. It appeared that a decrease in renal potassium excretion accounted

for the development of hyperkalaemia in patients treated with trimethoprim.[9]

More evidence linking hyperkalaemia to cotrimoxazole therapy was noted in a retrospective review of all patients with HIV infection who were treated for more than 6 days with cotrimoxazole (trimethoprim 20 mg/kg/day + sulfamethoxazole 100 mg/kg/day) between 1989 and 1991.[10] 19 of 25 patients (76%) who met the study criteria and received this medication developed an increase in serum potassium level of ≥1.0 mEq/L from their baseline. Seven patients (28%) exhibited a serum potassium level >5.5 mEq/L, and 3 (12%) exceeded 6.0 mEq/L. Hyperkalaemia did not develop in any of the 26 hospitalised control patients with HIV infection who were not treated with trimethoprim. This study confirmed the previous observations that high dosages of trimethoprim were associated with the development of hyperkalaemia when used to treat patients infected with the HIV virus.[10]

Following these descriptions of hyperkalaemia complicating treatment of patients with AIDS with high dosage trimethoprim-containing regimens, astute clinicians began to observe the association of hyperkalaemia with cotrimoxazole therapy in patients without HIV infection.[15-18,25] In addition, several reports of hyperkalaemia complicating standard dosage (≤320 mg/kg/day) cotrimoxazole treatment also emerged.[15-18,25] In 1993, 2 patients who developed hyperkalaemia initially with high dosage and subsequently with standard dosage cotrimoxazole were described.[25] Both patients were elderly and had underlying renal impairment. Three cases reported in 1994 also described the development of hyperkalaemia with standard dosage cotrimoxazole therapy.[15-17] Hyperkalaemia occurred within 3 to 7 days of drug therapy and the serum potassium level increased significantly to ≥6.0 mEq/L in 2 of the patients. These patients were also elderly (>70 years) and none had obvious renal insufficiency, although the calculated creatinine clearance was 32 ml/min in 1 patient. Discontinuation of trimethoprim resulted in resolution of hyperkalaemia.

In yet another case report, trimethoprim 200mg twice daily administered without sulfamethoxazole was associated with the development of severe hyperkalaemia (7.0 mEq/L) after 4 days of therapy for a urinary tract infection.[18] It is likely that concurrent treatment with the nonsteroidal anti-inflammatory drug (NSAID) diclofenac and underlying mild renal insufficiency exacerbated the potassium-altering effect of trimethoprim. Hyperkalaemia was also observed in a patient with a soft tissue infection who was treated with a higher than standard dosage of intravenous trimethoprim (600mg) in combination with sulfamethoxazole.[19] The rise in serum potassium level developed in spite of a normal urinalysis, stable serum creatinine level (0.9 mg/dl) and the absence of other risk factors for hyperkalaemia.[19] As noted in all of the previous reports, resolution of hyperkalaemia occurred upon discontinuation of this drug.

Severe hyperkalaemia (serum potassium level 6.8 mEq/L) was described after 9 days of high dosage trimethoprim therapy in a lung transplant patient with mild renal insufficiency who was receiving concurrent therapy with enalapril.[21] Discontinuation of trimethoprim and enalapril and infusion of isotonic saline with furosemide (frusemide) resulted in rapid correction of hyperkalaemia.[21] Finally, hyporeninaemic hypoaldosteronism was also found to be a risk for severe hyperkalaemia with standard dosage trimethoprim therapy.[22] Serum potassium level increased to 7.8 mEq/L in an elderly man with documented hyporeninaemic hypoaldosteronism treated with this medication.[22]

In the midst of this flurry of reports, the effect of standard dosage cotrimoxazole on serum potassium levels was studied over a 14-month period in 80 hospitalised patients without HIV infection.[20] 25 well-matched patients treated with other antibacterials served as a control group. Trimethoprim-treated patients developed a 1.21 mEq/L increase in serum potassium level and reached a peak serum potassium level of 5.1 ± 0.5 mEq/L (± SD). A statistically significant difference in the mean potassium levels in the treatment group and the control group was noted after 4 to 5 days of therapy.[20] In

an analysis of subgroups, patients with a serum creatinine level≥1.2 mg/dl developed a higher peak potassium level (potassium 5.37 ± 0.59 mEq/L) than did patients with serum creatinine level <1.2 mg/dl (potassium 4.95 ± 0.48 mEq/L). Serum potassium level increased to >5.0 mEq/L in 62.5% of patients and >5.5 mEq/L in 21.2% of the patients.[20] These data confirmed the previous case reports suggesting that standard dosage trimethoprim causes hyperkalaemia in a significant percentage of hospitalised patients. It also appeared that renal insufficiency, even if only of moderate severity, is an important risk factor for this occurrence.

In 1996, a comparison of the efficacy of oral cotrimoxazole, dapsone-trimethoprim and clindamycin-primaquine in the treatment of *Pneumocystis carinii* pneumonia in patients with AIDS was published.[26] Although the initial article reported a low incidence of hyperkalaemia, it was subsequently noted that hyperkalaemia developed more frequently in patients treated with the trimethoprim-containing medications compared with those treated with clindamycin-primaquine.[23,27] Specifically, 13 of 64 patients treated with cotrimoxazole (20.3%) and 6 of 58 patients treated with dapsone-trimethoprim (10.3%) developed a serum potassium level >5.6 mEq/L.[23] Only 2 of 57 patients treated with clindamycin-primaquine (3.5%) developed a serum potassium level >5.6 mEq/L.[23] Thus, the association of hyperkalaemia with trimethoprim therapy was again confirmed in a large group of patients.

More recently, a prospective study examined the effect of standard dosage cotrimoxazole, as compared with other antibacterials, on serum potassium levels in otherwise healthy outpatients treated at an ambulatory clinic.[24] Serum potassium levels were measured at baseline and after 5 days of therapy. Although 81.5% (41 of 51) of trimethoprim-treated patients developed a rise in serum potassium level, only 18% (9 of 51) had a serum potassium level ≥5.0 mEq/L and only 6% (3 of 51) had a serum potassium level ≥5.5 mEq/L.[24] In contrast, the 46 matched control patients had a decline in serum potassium level and none developed hyperkalaemia. A closer look at the 3 patients who developed serum potassium levels >5.5 mEq/L reveals that these patients were significantly older (60 *vs* 45 years) and had higher baseline serum creatinine levels as compared with the rest of the treatment group.[24] It is safe to conclude that although trimethoprim is associated with an increase in serum potassium level in most patients, it rarely leads to clinically significant hyperkalaemia in healthy outpatients without other disturbances in potassium homeostasis.

Synthesis of the available clinical data on trimethoprim-induced hyperkalaemia reveals a number of pertinent findings.[8-12,14-27] An increase in serum potassium level, which ranges from 0.36 to 1.21 mEq/L or greater, occurs in most (76 to 100%) of patients who receive this drug. Hyperkalaemia develops after approximately 3 to 10 days of therapy with trimethoprim, with average onset after 4 to 5 days of treatment. Larger studies demonstrate that 18 to 62.5% of patients treated with trimethoprim develop a serum potassium level ≥5.0 mEq/L, and that 10 to 21% develop a serum potassium level >5.5 mEq/L.[9,10,14,22,23,27] Furthermore, it appears that more severe hyperkalaemia, with levels between 6 and 7 mEq/L, occurs more commonly in patients treated with high dosages of trimethoprim.[8-10,12,14,21] Although many of these studies have conclusively shown that clinically important hyperkalaemia can develop in the absence of other risk factors for this cation disorder, renal insufficiency (serum creatinine ≥1.2 mg/dl) is associated with the greatest risk in patients treated with both high dosage and standard dosage trimethoprim.[20] Available case reports and a few patient series have also suggested that older age, hypoaldosteronism and treatment with certain potassium-altering medications (ACE inhibitors, NSAIDs) may exacerbate the hyperkalaemic effect of trimethoprim.[15-18,21,25]

2. Mechanism of Hyperkalaemia

In 1993, the mechanism by which trimethoprim causes hyperkalaemia was elucidated.[8,9] The A6 cell line, a model of distal nephron tubular cells,

was employed to search for any direct effect of trimethoprim on sodium or potassium transport.[8] In these studies, trimethoprim was shown to rapidly and reversibly inhibit amiloride-sensitive sodium transport. These results are not a complete surprise, since trimethoprim shares structural similarity with amiloride. A trimethoprim concentration of 1 mmol/L inhibited the amiloride-sensitive short-circuit current by a mean of 83%, and 50% inhibition was achieved with a concentration of 0.12 mmol/L. Sulfamethoxazole or its principal metabolite, *N*-acetylsulfamethoxazole, did not inhibit short-circuit current in these cells.[8]

The combination of these observations suggests a specific inhibitory effect of trimethoprim on sodium channel transport in A6 cells. Inhibition of distal nephron epithelial sodium channels by trimethoprim is similar to the action of amiloride to inhibit sodium channels and function as a potassium-sparing diuretic, causing hyperkalaemia through this mechanism.[8] Using intact rats and microperfusion techniques, distal nephron sodium and potassium transport was studied.[9] In the intact rat studies, intravenous trimethoprim decreased urinary potassium excretion by 40% and increased urinary sodium excretion by 46%. Microperfusion of rat distal tubules with trimethoprim decreased the transepithelial voltage in a dose-dependent fashion.[9] Distal tubule transepithelial voltage was maximally reduced at a luminal trimethoprim concentration of 1 mmol/L. A 10-fold lower concentration (0.1 mmol/L) inhibited the transepithelial voltage by approximately 25%. Taken together, the presence of both decreased renal potassium secretion and depolarisation of the transepithelial voltage over a period of luminal perfusion of trimethoprim indicates that trimethoprim inhibits sodium channels in the luminal membrane of the mammalian distal tubule. The effect of trimethoprim in the distal tubule is similar to the effect that has been previously observed with amiloride.

It is therefore reasonable to conclude that hyperkalaemia develops as a result of the amiloride-like action of trimethoprim to reduce renal potassium excretion. Furthermore, the drug concentrations employed in these studies can be achieved in the urine of humans treated with a standard dosage of trimethoprim and are therefore relevant to clinical practice.[8,9] As an example, a 200mg oral dose of trimethoprim will achieve a urinary concentration of approximately 1.1 mmol/L, a concentration within the range that inhibits sodium channel transport and blunts renal potassium excretion.[9] Hence, the hyperkalaemia associated with both high dosage and standard dosage trimethoprim therapy in humans is readily explained by this mechanism.[8,9]

Additional data to support the potassium-sparing mechanism of trimethoprim were published in 1996.[28] The effect of intrarenal trimethoprim infusion (0.2 mg/kg/min) on renal blood flow, glomerular filtration rate (GFR), urine volume and renal sodium and potassium excretion was studied in a group of anaesthetised dogs.[28] Trimethoprim infusion into one kidney was associated with an ipsilateral diuresis, natriuresis and antikaliuresis without affecting the contralateral kidney. Amiloride infusion in these dogs competed with these physiological effects of trimethoprim. In addition, both saline loading and intravenous furosemide reversed the antikaliuretic effect of trimethoprim in the ipsilateral kidney, despite continued intrarenal trimethoprim infusion.[28] These results confirmed that trimethoprim reduces renal potassium excretion through its action to block sodium channels in the distal nephron in a manner identical to amiloride. Furthermore, an increased delivery of sodium and volume to the distal nephron, as induced by saline and furosemide, was shown to abrogate the antikaliuretic effect of trimethoprim. A therapeutic intervention to overcome the problem of hyperkalaemia in patients who require continued therapy with this antibacterial was provided by these results.

The effect of varying pH on trimethoprim action on distal nephron potassium secretion in both A6 cells and in intact rats has also been examined.[29] It was hypothesised that trimethoprim, like amiloride, is a weak base (pKa 7.24) which blocks epithelial sodium channels more fully when protonated

(cationic form). It follows that an increase in urine pH above 7.0 would substantially decrease the protonated (cationic) form of trimethoprim and blunt its ability to block sodium channel activity. In A6 cells, at a pH of 8.2, more trimethoprim (340 mmol/L) was required to inhibit the amiloride short circuit current by 50% than the amount (50 mmol/L) required at a pH of 6.3. Alkalinisation of the urine with acetazolamide in intact rats infused with trimethoprim reversed the potassium-sparing effect of trimethoprim compared with rats infused with trimethoprim alone.[29] These results indicate that trimethoprim induces antikaliuresis through the blockade of sodium channel activity in the distal nephron, and that the protonated (cationic) form of this drug more effectively interferes with sodium channels. These data also suggest that alkalinisation of the urine blocks the effect of trimethoprim on distal nephron potassium secretion, and provides another useful intervention in patients who develop hyperkalaemia.

Finally, an additional mechanism to explain the effect of trimethoprim on renal potassium excretion has been proposed.[30] Both *in vivo* experiments in rats and *in vitro* investigations using micropuncture technique to test the effect of short term (90 minutes) and long term (14 days) trimethoprim infusion on potassium homeostasis and on renal ATPase activity were undertaken. Short term trimethoprim infusion blunted urinary potassium excretion and decreased Na^+-K^+-ATPase activity in the proximal tubule and collecting duct.[30] In contrast, long term trimethoprim infusion caused hyperkalaemia, a reduction in urinary potassium excretion, and a more pronounced decline in Na^+-K^+-ATPase activity in the cortical collecting tubule as compared with the proximal tubule. However, trimethoprim had no measurable effect on either H^+-K^+-ATPase or H^+-ATPase activity.[30] It was concluded that trimethoprim is identical in action to amiloride and, like this drug, inhibits both epithelial sodium channel activity and basolateral Na^+-K^+-ATPase function. These effects ultimately result in reduced renal potassium excretion and hyperkalaemia.

3. Prevention and Management of Hyperkalaemia

3.1 Prevention

Knowledge of the potassium-altering potential of trimethoprim as well as recognition of the factors that impart an increased risk for hyperkalaemia are the most important elements required to prevent occurrence of this electrolyte disorder. It has been clearly demonstrated that a dose-dependent impairment of renal potassium excretion occurs with trimethoprim and is a major risk factor for the development of hyperkalaemia (table II). It thus follows that high dosage trimethoprim can and will cause hyperkalaemia in patients both with and without HIV infection, even in the absence of other concurrent risks for hyperkalaemia. Recognising the potential for hyperkalaemia in patients treated with a high dosage of this drug will allow physicians to carefully monitor patients for clinically significant changes in serum potassium levels. It is intuitive that the superimposition of other risk factors in patients treated with high dosage trimethoprim will further increase the likelihood and the severity of hyperkalaemia. Renal insufficiency is the other important factor that imparts risk for this electrolyte disorder. Therefore, in the presence of either or both of these 2 risk factors, trimethoprim should be administered with caution and close monitoring. In such patients, serum potassium level and renal function (blood urea nitrogen or serum creatinine) should be monitored on a daily

Table II. Risk factors for trimethoprim-induced hyperkalaemia

Definite risk factors
High dosage trimethoprim (20 mg/kg/day)
Renal insufficiency (serum creatinine level ≥1.2 mg/dl)
Probable risk factors
Hypoaldosteronism
Potassium-altering medications
nonsteroidal anti-inflammatory drugs
ACE inhibitors
potassium-sparing diuretics
other drugs
Older age (hypoaldosteronism, unrecognized renal impairment)

basis to identify the development of either hyperkalaemia or renal insufficiency. In addition, the dosage of trimethoprim should be adjusted for the prevailing level of GFR, since overdosage will further reduce renal potassium excretion.

Patients treated with standard dosage trimethoprim may also develop hyperkalaemia in the absence of other causes of impaired potassium homeostasis. However, the rise in serum potassium level will be less severe compared with patients treated with high dosage trimethoprim. In patients who possess one or more risk factors, such as renal impairment, hypoaldosteronism, older age or treatment with medications that can impair potassium balance, hyperkalaemia can also be severe with standard dosage therapy (table II). It is therefore prudent to recognise and address these risk factors prior to therapy with trimethoprim. This will allow clinicians to stratify patient risk and measure serum potassium levels at regular intervals, facilitating early identification of hyperkalaemia. Since the elevation in serum potassium level begins at approximately 4 to 5 days of standard dosage therapy, it is reasonable to initially check serum potassium levels after approximately 3 days of treatment with trimethoprim. Patients at higher risk may require earlier and more frequent measurement of electrolytes and renal function parameters. As with high dosage therapy, adjusting the trimethoprim dosage for the underlying GFR (<30 ml/min) will also help reduce the incidence of hyperkalaemia (table III).

On the basis of data from laboratory studies, manipulation of factors such as urinary flow rate and urinary pH may prevent or decrease the hyperkalaemic effect of trimethoprim if initiated prior to drug administration (table III). One such preventive intervention is the induction of high urinary flow rates (and increased sodium delivery to the distal nephron) using intravenous saline alone or in combination with furosemide. In general, intravenous saline should be given at a rate that will replete intravascular volume and increase urine output to 100 to 150 ml/hour. Furosemide, either in oral or intravenous form, will help induce and maintain high urine flows in some patients. This intervention will abrogate some of the antikaliuretic effects of trimethoprim and improve renal excretion of potassium.

Table III. Interventions available for prevention and management of trimethoprim-induced hyperkalaemia

Induction of high urine flow rates and enhanced sodium delivery to the distal nephron
volume repletion with intravenous saline
loop diuretics in volume-replete patients
Alkalinisation of the urine to achieve pH >7.5
sodium bicarbonate (oral or intravenous)
acetazolamide (avoid if acidosis is present)
Adjust the dosage of trimethoprim in the setting of renal impairment
decrease dosage to one-half for GFR <30 ml/min
avoid drug if GFR <15 ml/min
Discontinue trimethoprim if hyperkalaemia or renal failure is severe
Appropriate treatment of severe hyperkalaemia
calcium gluconate
insulin/glucose
nebulised β_2-agonist
sodium polystyrene sulfonate resin
haemodialysis (if required)

GFR = glomerular filtration rate.

In addition to increased urinary flow, alkalinisation of the urine is another potential manoeuvre to prevent or decrease the development of hyperkalaemia. Oral or intravenous sodium bicarbonate are both useful therapies to increase urinary pH. Addition of sodium bicarbonate to intravenous fluids in a concentration to achieve an isotonic solution (e.g. 1L of 0.45% saline + 75 mmol of $NaHCO_3$) is an option. Acetazolamide (125 to 250 mg) can be added to sodium bicarbonate therapy to facilitate bicarbonaturia and enhance urinary alkalinisation if a metabolic alkalosis develops. However, this drug should not be prescribed in the presence of a systemic acidosis. An increase in the urinary pH from 6.0 to above 7.5 will facilitate the production of the nonprotonated form of trimethoprim. As a result of this manipulation, trimethoprim inhibition of sodium channel activity will decline and its antikaliuretic effect will be less potent. Renal potassium excretion will improve and this will either prevent or reduce the ultimate rise in serum potassium level.

Combining these 2 interventions will certainly reduce the incidence of hyperkalaemia further. It is probably wise to use these manoeuvres prior to trimethoprim administration in patients who are considered to be at high risk of developing hyperkalaemia.

3.2 Management

If hyperkalaemia develops in a patient receiving trimethoprim, a number of interventions should take place. Acute management of hyperkalaemia takes precedence over all other therapies. Treatment should include intravenous calcium therapy to stabilise excitable membranes, insulin/glucose and nebulised β_2-agonists to move potassium into cells, and oral sodium polystyrene sulfonate resin to enhance gastrointestinal excretion of potassium (table III).[31] In patients with severe hyperkalaemia and whose renal function is impaired, haemodialysis is the most efficient modality to lower the serum potassium level.[31] It is probably prudent to also withdraw trimethoprim until the hyperkalaemia is adequately treated. Administration of intravenous saline to expand the intravascular space and to increase urine output should also be undertaken.

When the potassium level is normalised and if renal insufficiency is only mild, it is reasonable to reinstitute trimethoprim therapy if this medication is considered important to adequately treat the underlying infection. If this path is chosen, the preventive measures described in section 3.1 (dosage adjustment for underlying GFR, induction of high urinary flow rates, alkalinisation of the urine to pH >7.5) should be undertaken. These interventions will help maintain renal potassium excretion and allow continued treatment with trimethoprim.

4. Conclusion

It is now well established that hyperkalaemia is a relatively frequent complication of both high and standard dosage trimethoprim therapy. The case reports, small series of patients and large studies suggest that an increase in serum potassium level develops commonly, and serious and life-threatening hyperkalaemia can occur in a significant number of patients. It appears that trimethoprim therapy causes hyperkalaemia on the basis of the 'amiloride-like' effect of this drug on the distal nephron to reduce renal potassium excretion. Patients treated with high dosage trimethoprim as well as those patients with renal insufficiency and other disturbances in potassium homeostasis should be monitored closely when treated with this medication. Dosage adjustment, induction of high urinary flow rates and alkalinisation of the urine will often help in both the prevention and management of hyperkalaemia in patients treated with trimethoprim.

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