An Evaluation of Hyperkalaemia and Acute Kidney Injury associated with In-hospital Co-trimoxazole Dosing

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Background

Moves to avoid broad-spectrum beta-lactam prescribing has seen an upsurge in co-trimoxazole usage. Ongoing concerns with co-trimoxazole associated hyperkalaemia and kidney injury exist. The impact of dosing on this remains unclear and high-risk groups are not well defined in the literature. To describe the dosing and patient-risk factors associated with co-trimoxazole treatment complications a retrospective observational study was undertaken in a single London Teaching hospital.

Method

All adult-patients receiving co-trimoxazole for 4 or more days therapy at a dose 960mg/day or more between February 2016 and April 2018 were identified from electronic prescribing records. Patients receiving treatment as an out-patient or on the intensive care unit were excluded from analysis. Electronic health records were used to extract relevant pathology results and concurrent medications. Changes in serum potassium from baseline to peak during treatment was calculated, as was estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation, enabling identification of Acute kidney injury (AKI) using RIFLE classification following change in eGFR from baseline. Linear regression was undertaken to identify variables associated with elevated serum potassium and AKI using GraphPad PRISM. Local ethical approval was obtained for this service evaluation [2018].

Results

Two hundred and eight patients were identified with a mean age of 62 years (range 20-98 years) and 59% were male. 159 patients had follow-up serum potassium levels available, of which 40(25%) had a potassium rise of 1mmol/L or greater whilst on treatment (max rise of 2.5mmol/l to peak of 6.4mmol/L).

Acute Kidney Injury

Co-trimoxazole treatment resulted in an increase of serum creatinine (SCr) of >50% (RIFLE criteria for AKI) in 14% of study patient (n = 146). RIFLE Injury (>100% increase in SCr) was evident in 4.8% of treated patients. No AKI RIFLE Failures identified in this study

Variables associated AKI include:
- Age >60 years (odds ratio [OR] = 5.13; 95% CI = 1.77-14.92; P=.003)
- Concurrent ACEi/ARB prescribed (OR 10.37; 95% CI 3.24-33.25; P= .0001)
- Doses ≥1.92g/day co-trimoxazole prescribed

Variables not associated with AKI include:
- Concurrent aldosterone antagonists (ns)
- Presence of chronic kidney disease (CKD CrCl<60ml/min) (ns)
- Prolonged treatment duration (ns)

Impact of Dose on AKI (RIFLE Risk [>50% Scr] or Injury [>100% SCr])

960mg/day	Control
1.96g/day	OR = 6.2; 95% CI 1.58-23.96; P= .009
2.88g/day	OR = 6.1; 95% CI 1.08-34.56; P= .04
>60mg/kg/day	OR = 4.8; 95% CI 1.06-22.02; P= .04

Hyperkalaemia

Co-trimoxazole treatment resulted in a transient increase of serum potassium (K+) of ≥ 1mmol/ml in 25% of study patient (n = 159). 6% of patients developed severe hyperK+ defined locally as >5.7mmol/l and 2.5% of patients required medical management of hyperK+ (defined as K+ >6.0mmol/l)

Variables associated with hyperK+ include:
- Age >60 years (odds ratio [OR] = 4.83; 95% CI = 2.2-10.64; P=.0001)
- Concurrent acute kidney injury (AKI) (OR 3.79; 95% CI 1.42-10.56; P= .008)
- Doses ≥1.92g/day co-trimoxazole prescribed (OR 5.13; 95% CI 2.1-12.5; P= .0003)

Variables not associated with hyperK+ include:
- Concurrent ACEi/ARB (OR 1.07; not-significant (ns))
- Concurrent aldosterone antagonists (OR 0.52; ns)
- Presence of chronic kidney disease (CKD CrCl<60ml/min) (OR 1.0, ns)
- Prolonged treatment duration (ns); peak hyperK+ effect seen in first 3 – 5 days of therapy

Impact of Dose on hyperK+ (defined as ≥ 1mmol/ml increase from baseline)

960mg/day	Control
1.96g/day	OR = 5.31; 95% CI 2.0-14.1; P= .0008
2.88g/day	OR = 4.9; 95% CI 1.28 – 18.86; P= .02
>60mg/kg/day	OR = 4.9; 95% CI 1.64-14.77; P= .045

Conclusions

Kidney function and serum potassium should be monitored following initiation of co-trimoxazole treatment. An association between co-trimoxazole and AKI appears more common among older patients, those concurrently prescribed ACEi/ARB therapy, and co-trimoxazole doses of ≥1.92g/day. A rise in serum potassium can be predicted at higher doses of co-trimoxazole and among elderly patients, but not in those who are concomitantly on ACEi/ARB agents, or those with CKD. Before initiating patients on co-trimoxazole therapy, the above risk factors should be assessed. Twice weekly U&Es are advised in patients with any risk factor for AKI or hyperkalaemia, with peak effects of treatment (increased serum creatinine or increased potassium) most commonly presenting after 3-5 days therapy. Baseline serum potassium may be useful in identifying high-risk patients, with high baseline serum potassium (e.g. 5.0mmol/L or greater) expected to encounter the greatest complications with hyperkalaemia.

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