Trimethoprim/sulfamethoxazole induced multiorgan dysfunction

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SUMMARY

A 22-year-old African-American man with AIDS who had recently started on trimethoprim/sulfamethoxazole daily for pneumocystis jirovecii pneumonia prophylaxis presented with an altered mental state, malaise and nausea was found to have hepatitis, pancreatitis, rhabdomyolitis, acute kidney injury and haemolytic anaemia. Cessation of Bactrim and supportive care with volume expansion resolved his clinical symptoms and laboratory abnormalities.

BACKGROUND

Trimethoprim/sulfamethoxazole (TMP/SMX) is the preferred medication for pneumocystis jirovecii pneumonia (PJP) prophylaxis and treatment in immunocompromised patients. Multiorgan adverse events, in patients with HIV on TMP/SMX have been reported in as many as 50% of patients.¹ This is the first case reported in the literature of simultaneously diagnosed hepatitis, pancreatitis, rhabdomyolitis, acute kidney injury and haemolytic anaemia in a patient probably due to initiation of TMP/SMX.

CASE PRESENTATION

A 22-year-old African-American soldier with recent progression to AIDS (CD4 134 cells/mcl) presented with 1 week of altered mental state, weakness, nausea and vomiting. The patient was known to be HIV-positive and qualitatively confirmed G6PD deficiency for the past 2 years. He had no other medical or surgical history. He reported intermittent use of diazepam for sleep, but denied any recent increased activity, the use of supplements, herbal, over the counter medications or illegal drugs. TMP/SMX DS was started on a daily basis for PJP prophylaxis 2 weeks prior to emergency room presentation.

INVESTIGATIONS

On examination, the patient had oropharyngeal candidiasis and mild abdominal tenderness over bilateral lower quadrants.

Initial laboratory studies were significant for hyponatremia, hyperkalemia, anion gap metabolic acidosis and acute kidney injury. Platelet level was $135 \times 10^9/l$. Furthermore, the patient had biochemical evidence of pancreatitis, hepatitis, rhabdomyolysis and haemolytic anaemia (table 1). Urinalysis (UA) was significant for large blood with three red blood cells. There were no casts nor significant cells in the UA.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for any separate problem for this patient is broad, however a combination of all the findings narrows the differential considerably. His HIV positivity may cause unique presentation of common diseases, however, that could not by itself account for the number of findings. The use of illicit drugs, supplements, alcohol, acetaminophen or salicylate toxicity was made unlikely by reviewing the history, serum and urine toxicology. Gallstone pancreatitis was less probable given negative imaging studies and labs that were not suggestive of an obstructive pattern. Microangiopathic diseases were considered but dismissed due to the lack of schistocytes. TMP/SMX remained the only unifying diagnosis for all his separate problems.

TREATMENT

Cessation of TMP/SMX and intravenous normal saline for volume depletion improved the patient's clinical and laboratory abnormalities within 2 days.

OUTCOME AND FOLLOW-UP

Laboratory values normalised prior to discharge with the exception of asymptomatic haemolytic anaemia that continued to improve on follow-up, 1 month after discharge. The patient was told to avoid further TMP/SMX exposure. He was treated for oropharyngeal candidiasis with fluconazole and clotrimazole troches. He was started on antiretroviral therapy with truvada/atazanavir/ritonavir. PJP prophylaxis was continued using monthly inhaled pentamidine.

DISCUSSION

Gastrointestinal disturbances (ie, nausea, vomiting and diarrhoea) are the most common adverse reactions to TMP/SMX. A few reported cases of fulminant hepatitis, pancreatitis or rhabdomyolysis exist in the literature, most commonly in HIV patients.¹⁻⁴ Fewer than 15 cases of TMP/SMX induced rhabdomyolysis have been reported in immunocompromised patients with HIV/AIDS.² The published literature does not directly correlate dose and duration of TMP-SMX to frequency of adverse effects. Management with hydration and cessation of inciting drug improves symptoms rapidly.¹ After a literature review, this was the first case in which TMP/SMX was associated with hyponatremia, pancreatitis, hepatitis, rhabdomyolysis and acute kidney injury.

Multiple studies indicate that sulfamethoxazole, a component of TMP/SMX, may be the main contributing factor resulting in adverse events. Toxic metabolites of sulfamethoxazole and the inability to clear these metabolites is postulated to be the

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Table 1 Laboratory findings at admission, date of discharge and follow-up

Lab	Normal range	Admission	Discharge (3 days after admission)	7 day/ 30 day** follow up
Na (mmol/l)	(135–145)	127	140	142
K (mmol/l)	(3.5–4.5)	5.2	4.5	4.4
Cl (mmol/l)	(98–107)	92	111	104
HCO ₃ (mmol/l)	(22–30)	14	24	29
BUN (mg/dl)	(9–20)	84	35	8
Cr (mg/dl)	(0.66–1.25)	6.85	1.99	0.8
AST (U/l)	(17–59)	626	167	85
ALT (U/l)	(20–125)	371	174	121
Total bilirubin (mg/dl)	(0.2–1.3)	1.6	1.1	0.4
Conjugated bilirubin (mg/dl)	(0–0.3)	0.2	n/a	n/a
Platelet (×10 ⁹ /l)	(140–420)	135	165	n/a
Hg (g/dl)	(14.0–17.0)	10.6*	8.8	10.5**
Hct (%)	(41–49)	31*	23.8	32.2**
LDH (U/l)	(313–618)	3382	n/a	n/a
Haptoglobin (mg/dl)	(30–200)	<20	n/a	n/a
CPK (U/l)	(55–170)	20 057	8350	n/a
Lipase (U/l)	(23–300)	1326	n/a	n/a

*With volume resuscitation, H/H drop to 7.2/21.4.

**Laboratory value at 30 day follow up.

BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CPK, Corey–Pauling–Koltun; AST, aspartate; ALT, alanine transaminase; Hct, haematocrit.

reason for an increased risk of adverse effects of TMP-SMX in HIV populations.

Sulfamethoxazole is metabolised by two different pathways: *N*-acetylation and an alternative pathway via cytochrome P450 oxidation.⁵ *N*-acetylation by *N*-acetyltransferase appears to be the primary mechanism by which sulfamethoxazole is metabolised. However, when *N*-acetyltransferase is deficient or has decreased function by a genetic cause, an alternative mechanism for the metabolism of sulfamethoxazole occurs. This alternative mechanism produces more oxidative toxic metabolite and hydroxylamine derivatives. Normally, this oxidative metabolite is detoxified by glutathione.^{5 6}

Although there are conflicting studies regarding whether HIV patients have decreased amount of glutathione, there is a consensus that HIV patients are under a higher oxidative state, evidenced by increased protein bound form of glutathione,

particularly in CD4 cells.³ This increased oxidative state in HIV patients may cause higher adverse incidences in comparison with patients without HIV. In the case of our patient, his G6PD deficiency and the haemolytic anaemia on presentation possibly show evidence that he had oxidative stress at the time of presentation.

Research is needed in order to determine if there is a need to risk stratify HIV patients who may have a higher risk of developing adverse effects from sulfamethoxazole use. AIDS patients with recent initiation of TMP/SMX, who present with multiorgan dysfunction without another cause should have TMP/SMX withheld and manage with supportive care.

Learning points

- ▶ Trimethoprim/sulfamethoxazole (TMP/SMX) can cause potentially life threatening adverse reactions including pancreatitis, hepatitis, rhabdomyolysis and acute kidney injury.
- ▶ Adverse reactions have a significantly higher incidence in HIV/AIDS patients.
- ▶ Sulfamethoxazole is probably the inciting component of TMP/SMX.
- ▶ Clinical improvement can be achieved with discontinuation of TMP-SMX and supportive care.

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Competing interests None.

Patient consent Obtained.

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