CASE REPORT IN
INTERNAL MEDICINE

Trimethoprim/sulfamethoxazole-induced acute renal failure: A case report

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Abstract

The patient was an 80-year-old man who arrived at the emergency room with breathing problems. He presented a history of chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus and early (stage 1) chronic renal failure with normal levels of creatinine and no sign and symptoms of renal disease. A chest X-ray showed pneumonia. Therefore, he was first treated with 1 g daily of ceftriaxone IV. We did not observe any clinical improvement, and for this reason, a sputum culture was performed to guide the right antibiotic treatment. Subsequently, we started a new antibiotic therapy with trimethoprim/sulfamethoxazole (TMP/SMX) adjusted to renal functioning. Appropriate medical treatment was administered, as well as urine alkalinisation. After the first day of treatment, the patient's clinical and laboratory status worsened very quickly, with an increased level of serum creatinine from 1.5 to 3.5 mg/dL. We stopped administering the antibiotic therapy immediately. However, we observed acute renal failure with a serum creatinine level of 9.0 mg/dL and four days after his admission, the patient died. Literature showed that patients can develop acute kidney injury (AKI) during or immediately following TMP/SMX therapy. Intrinsic renal impairment –rather, interstitial nephritis– appeared responsible for the great majority of cases, and impairment was transient if therapy was discontinued. In our study, despite the therapy with TMP/SMX was immediately discontinued, and our patient underwent appropriate medical treatment, urine alkalinisation and, then, haemodialysis, the AKI was rapidly fatal. In conclusion, particular attention should be paid to prescribing TMP/SMX to patients affected by chronic renal failure.

KEY WORDS: Acute kidney injury; anti-Bacterial agents; renal insufficiency, acute; trimethoprim/sulfamethoxazole.

Riassunto

Il nostro paziente era un uomo di 80 anni giunto in pronto soccorso per difficoltà respiratorie. Era affetto da malattia polmonare cronica ostruttiva (BPCO), ipertensione, diabete mellito e lieve insufficienza renale cronica (stadio 1) con normali livelli di creatinina ed assenza di segni e sintomi di malattia renale. Un esame radiografico del torace ha evidenziato una polmonite. Pertanto, egli venne trattato inizialmente con 1 gr/die di ceftriaxone ev. Non avendo osservato alcun miglioramento clinico, abbiamo eseguito un esame colturale sull'escreato per scegliere l'antibiotico specifico. Pertanto, abbiamo iniziato un antibioticoterapia con trimetoprim/sulfametossazolo (TMP/SMX) con un dosaggio modificato per la funzionalità renale. Abbiamo somministrato appropriata terapia medica ed alcalinizzato le urine. Dopo il primo giorno di trattamento, le condizioni cliniche e di laboratorio del paziente peggiorarono molto rapidamente, con un aumento dei livelli di creatininemia da 1,5 a 3,5 mg/dL. Abbiamo sospeso immediatamente l'antibioticoterapia. Tuttavia, abbiamo osservato la comparsa di insufficienza renale acuta con un livello di creatininemia pari a 9 mg/dL e, dopo 4 giorni dal ricovero, il paziente è morto. La letteratura scientifica ha mostrato che i pazienti durante o immediatamente dopo il trattamento con TMP/SMX possono sviluppare insufficienza renale acuta. Il danno renale idiopatico, piuttosto che la nefrite interstiziale sembrano essere i responsabili per la maggior parte dei casi evidenziati in letteratura ed il danno renale è transitorio se la terapia viene sospesa. Nel nostro caso, nonostante l'immediata sospensione della terapia con TMX/SMX, l'appropriato trattamento medico, l'alcalinizzazione delle urine e poi l'emodialisi, l'insufficienza renale acuta è stata rapidamente mortale. In conclusione, particolare attenzione dovrebbe essere prestata alla prescrizione di TMX/SMX in pazienti affetti da insufficienza renale cronica.

TAKE-HOME MESSAGE

Particular attention should be paid when prescribing trimethoprim/sulfamethoxazole to patients affected by chronic renal failure.

Competing interests - none declared.

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INTRODUCTION

Over the past 40 years, scholars have identified many adverse events associated with trimethoprim/sulfamethoxazole (TMP/SMX) [1]. According to a recent review, patients with chronic renal insufficiency are at increased risk of adverse effects associated with the use of TMP/SMX [2, 3]. Although uncommon, this drug can also cause renal injury in otherwise healthy patients. This adverse effect generally manifests as a form of drug hypersensitivity syndrome, most commonly acute interstitial nephritis [4]. A much less common mechanism by which TMP/SMX may cause acute kidney injury is obstructive tubulopathy resulting from the intraluminal precipitation of sulfamethoxazole [5]. In this study, we show a case of probably TMP/SMX-induced acute renal failure in a patient with early chronic kidney disease (CKD).

CASE REPORT

The patient was an 80-year-old man who arrived at the emergency room with breathing problems. He presented a history of chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus and early (stage 1) chronic renal failure with normal levels of creatinine and no sign and symptoms of renal disease. The physical examination showed dyspnoea (respiratory rate = 35) and regular heart sounds with a regular heart rate (HR = 77 bpm). Electrocardiographic (ECG) monitoring was normal, and the blood pressure was 150/70 mm Hg. A thoracic auscultation showed basal crackles. The neurological and abdominal examination was negative. A chest X-ray showed pneumonia; the most common phlogosis indices were elevated (C- reactive protein = 99 mg/L, white cells = 11,800, serum creatinine = 11,500). Therefore, he was admitted to the Emergency Department and was first treated with 1 g daily of ceftriaxone IV. We did not observe any clinical improvement, and for this reason, a sputum culture was performed to guide the right antibiotic treatment. It was positive for *Acinetobacter baumannii*. Subsequently, we started a new antibiotic therapy with TMP/SMX adjusted to renal functioning, which was based on the judgment of a specialist in infectious disease and susceptibility testing. Our patient had no prescription for any nephrotoxic medicinal products, and appropriate medical treatment was administered, as well as urine alkalinisation. After the first day of treatment, the patient's clinical and laboratory status worsened very quickly, with an increased level of serum creatinine from 1.5 to 3.5 mg/dL. We stopped administering the antibiotic therapy immediately. Laboratory tests excluded acute liver disorders. We started haemodialysis according to the nephrologist's prescription, but the patient's status required intensive care support. We observed acute renal failure with a serum creatinine level of 9.0 mg/dL. Finally, four days after his admission, the patient died.

DISCUSSION

Sulfa-containing medications can cause crystal-induced acute renal failure from intratubular deposition or renal impairment from allergic interstitial nephritis [6–12]. Intratubular crystal deposition can also occur with sulfamethoxazole. Because it is a weak acid, it is relatively insoluble in acid urine and tends to precipitate in the tubular lumen when the urine pH decreases to ≤ 5.5 [11, 12]. Indeed, both sulfadiazine and, less commonly reported, sulfamethoxazole can readily precipitate in the kidneys in certain clinical settings and cause an obstruction of the tubular lumen in the distal nephron from crystals admixed with cellular debris and proteinaceous material [6–12]. In the literature, the administration of sulfadiazine is associated with acute renal failure when used in greater than usual doses to treat toxoplasmosis and *Pneumocystis carinii* infections in AIDS patients, especially in the case of associated hypoalbuminemia and the impairment of venous blood flow from interstitial congestion and haemorrhage [6–10]. Oliguric acute renal failure, which develops on average within 7 days of starting therapy, often showed the development of sulpha-crystal tubular or calyceal deposition [6–10]. An examination of the urine sediment revealed red blood cells mixed with sulphonamide

crystals, which could resemble needle-shaped crystals, rosettes and 'shocks of wheat' [6–10]. Sulfamethoxazole is another drug from the sulphonamide class that, since the 1970s, has seldom been reported to cause pleomorphic crystalluria [13, 14]. Recently, two reports showed yellow to brown fan-shaped crystals (2009) [15] and different size and shape (2011) sulfamethoxazole-induced crystals [16]. However, sulfamethoxazole is widely used in clinical practice in association with trimethoprim; therefore, little is known about their role in causing acute renal failure. Verdesca et al. discussed the case of two patients treated with sulfamethoxazole who developed a crystalluria that was very similar to the sulfadiazine one [17]. Fraser et al. published the only systematic evaluation of alterations in renal function during therapy with TMP/SMX in largely middle-aged male hospitalized patients. It was discovered that 11.2% of patients developed acute kidney injury (AKI) during or immediately following TMP/SMX therapy [18]. In slightly more than half of the cases, no other factors contributing to AKI were identified, and the TMP/SMX was felt to be responsible. This study did not show a relationship between the dose of TMP/SMX and the likelihood of developing AKI. Intrinsic renal impairment –rather, interstitial nephritis or competition for creatinine clearance – appeared responsible for the great majority of cases, and impairment was transient if therapy was discontinued. Indeed, in nearly all cases likely due to TMP/SMX, AKI was resolved promptly after the discontinuation of therapy, and only one patient required dialysis [18]. According to Perazella, TMP/SMX may also form crystals in the urine of volume-depleted patients, resulting in AKI, and crystalluria may be seen in 0.4%–49% of these patients [19]. However, such crystals were not detected in Fraser's review [18]. In our study, despite the therapy with TMP/SMX was immediately discontinued, and our patient underwent appropriate medical treatment, urine alkalinisation and, then, haemodialysis, the acute renal failure was rapidly fatal. According to Fraser's review, a multivariate model showed that patients with hypertension and diabetes mellitus had an increased risk for renal insufficiency, especially if these conditions were poorly controlled. Our patient was affected by COPD, hypertension, diabetes mellitus and early (stage 1) chronic renal failure. According to the literature, nephrotoxicity from sulphonamides is preventable, because the correction of hypovolemia with isotonic intravenous solutions (NaCl, NaHCO3) can prevent crystal precipitation in tubules [6–12, 19]. The addition of a loop diuretic promotes high urine flow rates, and maintaining an alkaline urine pH increased sulphonamide solubility. Daily monitoring of the urine for crystalluria allows the prompt adjustment of sulphonamide dosing, and the discontinuation of sulphonamide therapy might be necessary. Dialysis and other supportive care measures can reduce associated morbidity. However, in our case, all these measures were ineffective. Therefore, particular attention should be paid to prescribing TMP/SMX to patients affected by chronic renal failure.

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