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Trimethoprim-associated electrolyte and acid-base abnormalities: a review

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Abstract

Introduction: The antimicrobial trimethoprim is structurally related to potassium-sparing diuretics and may consequently lead to derangements in electrolyte and acid-base balance. Since no report so far analyzed the literature documenting individual cases with electrolyte and acid-base derangements induced by trimethoprim, a systematic review was carried out.

Evidence acquisition: We retained 53 reports documenting 68 cases (42 males and 26 females 23 to 96 years of age) of electrolyte or acid-base derangements occurring on trimethoprim for about 5 days.

Evidence synthesis: One hundred five electrolyte imbalances were detected in the 68 patients: hyperkalemia (>5.0 mmol/L) in 62 (91%), hyponatremia (<135 mmol/L) in 29 (43%) and metabolic acidosis (pH<7.38 and bicarbonate <19 mmol/L) in 14 (21%) cases. Following possible predisposing factors for electrolyte and acid-base abnormalities were found in 54 (79%) patients: high-dose trimethoprim, comedication with drugs that have been associated with electrolyte and acid-base derangements, preexisting kidney disease, age ≥80 years and diabetes mellitus.

Conclusions: High-dose trimethoprim, co-medicated with drugs that have been associated with electrolyte and acid-base derangements, poor kidney function, age ≥80 years and diabetes mellitus predispose to trimethoprim-associated electrolyte and acid-base abnormalities. Clinicians must recognize patients at risk, possibly avoid drug combinations that may worsen the problem and monitor the laboratory values.

Introduction

Trimethoprim, alone or in combination with sulfamethoxazole, is a generally well tolerated drug, which is widely prescribed for a number of infections [1-2]. Because it is structurally related to the potassium-sparing diuretics amiloride and triamterene, which inhibit the sodium channels of the principal cells in the collecting tubule [3], trimethoprim interferes with the reabsorption of sodium in the distal nephron and may subsequently lead to hyperkalemia, hyponatremia, and metabolic acidosis [4].

To our knowledge, no report so far analyzed the literature documenting individual patients with the aforementioned derangements in electrolyte and acid-base balance. The aims of this systematic review were to document the clinical and biochemical presentation of electrolyte and acid-base balance disturbances associated with trimethoprim, and to investigate their predisposing factors.

Evidence acquisition

Data search

We recently (March 1, 2020) carried out a literature search with no date limits of the Medical Subject Headings terms (trimethoprim OR co-trimoxazole OR sulfamethoxazole) AND (sodium OR potassium OR acid-base balance OR hyponatremia OR hyperkalemia OR acidosis OR hypobicarbonatemia) in the U.S. National Library of Medicine and Excerpta Medica databases. Reports published as letters or full-length articles were considered. The references of all included articles were also scanned. The principles underlying the U.K. Economic and Social Research Council guidance on the conduct of narrative synthesis and the "Preferred reporting items for systematic reviews and meta-analyses" statement were employed [5]. Reports published in Dutch, English, French, German, Italian, Portuguese or Spanish were eligible.

Data extraction

For the final analysis, we retained exclusively reports describing individual humans on trimethoprim presenting with hyperkalemia (>5.0 mmol/L), hyponatremia (<135 mmol/L) or metabolic acidosis (pH<7.38 and bicarbonate <19 mmol/L). Observational studies not individually describing the reported cases were not included.

For each included case, information on a) demographics, trimethoprim dosage (high: ≥15 mg/kg body weight per day; standard: 3-14 mg/kg body weight per day; low: ≤2.0 mg/kg body weight per day), and duration of therapy, b) co-medication, c) symptoms and clinical signs such as muscle weakness and pain, altered mental status, malaise, nausea or vomiting, and fainting, d) history of diabetes mellitus, pre-existing chronic kidney disease, e) laboratory values and f) possible fatal consequences was sought and extracted. The electrolyte and acid-base disturbances were classified as follows: hyperkalemia (mild: 5.1-5.9 mmol/L, moderate: 6.0-6.9 mmol/L, severe: ≥7.0 mmol/L), hyponatremia (mild: 130-134 mmol/L; moderate 121-129 mmol/L, severe ≤120 mmol/L), metabolic acidosis due to a fall in blood bicarbonate (mild: 14-18 mmol/L, moderate 10-13 mmol/L, severe ≤9 mmol/L). Cases with spuriously altered laboratory results (such as e.g. pseudohyponatremia) were excluded. Finally, the following five possible predisposing factors for electrolyte and metabolic acid-base disturbances were gauged [4,6]: 1. high-dose trimethoprim; 2. concomitant treatment with drugs that have been associated with electrolyte disturbances (such as a. blockers of the renin-angiotensin-aldosterone system, b. β-receptor antagonists, c. potassium sparing diuretics, d. calcineurin inhibitors, and e. supplementation with potassium salts); 3. preexisting chronic kidney disease; 4. age ≥80 years; and 5. diabetes mellitus. Data were sorted using a pilot-tested standardized form into a dedicated worksheet.

Analysis

Results are presented as frequency or as median and interquartile range, as appropriate. The Fisher exact test was used to compare dichotomous variables and the Kruskal Wallis H test to compare ordered categorical data [7]. Statistical significance was set at $P<0.05$.

Evidence synthesis

Search results

For the final analysis, we retained 53 original papers published between 1978 and 2019 in English (N=47), French (N=4), German (N=1) or Spanish (N=1), which reported individual cases of electrolyte or acid-base imbalance observed on medication with trimethoprim [8-60]. Twenty-eight reports were from North America, 14 from Europe, 6 from Asia, 2 from Oceania, 2 from South America and 1 from Africa.

Findings

The aforementioned reports documented 68 cases (42 males and 26 females 23 to 96 years of age) of electrolyte or acid-base derangements occurring during treatment with trimethoprim for about 5 days, as shown in table 1. None of the 68 patients was on low-dose trimethoprim. Trimethoprim was combined with sulfamethoxazole in 66 (97%) cases. The vast majority of cases (57%, N=39) were asymptomatic. Following symptoms or signs were observed, in order of decreasing frequency, in the remaining 29 patients (43%): muscle weakness and pain, altered mental status, malaise, nausea or vomiting, and fainting (table 1).

One hundred five electrolyte imbalances were detected in the 68 patients: hyperkalemia in 62 (91%), hyponatremia in 29 (43%) and metabolic acidosis in 14 (21%) cases. The electrolyte imbalance was isolated in 41 and combined in the remaining cases: two imbalances in 20 and three imbalances in the remaining 8 cases. Hyperkalemia and hyponatremia were moderate to severe in the majority of cases. By contrast, metabolic acidosis was rarely severe (table 1).
Treatment with high-dose trimethoprim, concomitant treatment with drugs that have been associated with hyperkalemia, hyponatremia or metabolic acidosis, preexisting chronic kidney disease, age ≥80 years and diabetes mellitus were often (N=54; 79%) observed in the patients (table 1). None of the aforementioned factors possibly predisposing to an electrolyte imbalance on medication with trimethoprim was detected in the remaining 14 (21%) patients.

A 72-year old Spanish man on high-dose trimethoprim (in association with sulfamethoxazole) because of Pneumocystis jirovecii pneumonia died in the context of serious cardiac arrhythmias caused by a severe hyperkalemia of 8.2 mmol/L [47].

Discussion

Nausea, vomiting, itching skin lesions and hematologic abnormalities [1,61] are the most frequent adverse reactions to trimethoprim (mostly in combination with sulfamethoxazole). Textbooks and reviews do not or only marginally mention the possible occurrence of electrolyte or acid-base abnormalities. The present review of the literature documents about 70 patients, who were found to have very often hyperkalemia, often hyponatremia and sometimes metabolic acidosis while on treatment with standard-dose or high-dose trimethoprim. Hyperkalemia and hyponatremia

were on the average moderate to severe and metabolic acidosis mild to moderate. In the mentioned cases, the clinical presentation included symptoms and signs such as muscle weakness and pain, altered mental status, malaise, nausea or vomiting and fainting, that likely reflect hyperkalemia, hyponatremia or both. Unsurprisingly, approximately 60% of the patients were asymptomatic, confirming the old saying "the first sign of hyperkalemia may be death" [6,62].

In this analysis, disruptions in electrolyte and acid-base balance were mainly observed ≤14 days after onset of trimethoprim and occurred in patients with risk factors such as high-dose trimethoprim, concurrent medication with drugs that have been associated with electrolyte disturbances, preexisting chronic kidney disease, age ≥80 years and diabetes mellitus.

The electrolyte and acid-base derangements induced by trimethoprim resemble those induced by amiloride and triamterene [3]. Similar abnormalities occur on treatment with inhibitors of the mineralocorticoid receptor [3] and in patients affected by hypoaldosteronism and primary [63] or secondary pseudohypoaldosteronism [64].

The present analysis did not address the medical management of electrolyte and acid-base abnormalities caused by trimethoprim. In addition to discontinuing trimethoprim and avoiding further drugs that may induce similar biochemical features, the management relies, in our opinion, on fluid replenishment in cases presenting with mild to moderate derangements. Furthermore, insulin (with glucose) or a $ß_2$-agonist is advised in cases with severe hyperkalemia to drive potassium into cells. Since insulin and $ß_2$-agonists do not remove potassium, additional therapy is usually required including cation exchange resins, loop diuretics or dialysis. Finally, intravenous calcium is given in the setting of impending cardiac arrest [6,62].

Trimethoprim is habitually given in combination with sulfamethoxazole (as cotrimoxazole) but in vitro studies point out that sulfamethoxazole does not block the sodium channels in the luminal membrane of the collecting tubule [65].

There are at least a major strength and a major weakness in this systematic review. It is our belief that it helps to delineate the clinical and biochemical features of electrolyte and acid-base abnormalities induced by trimethoprim. However, this analysis does not

identify the prevalence of electrolyte and acid-base derangements and the relative weight of the predisposing factors retained. Furthermore, for obvious reasons, patients with co-medications or chronic kidney disease might have had pre-existing electrolyte and acide-base abnormalities. Even if these abnormalities were previously unknown, their first detection under trimethoprim therapy suggests but does not definitely prove the cause-effect relationship. Future work is required to address these issues.

Conclusions

In conclusion, this study indicates that the vast majority of electrolyte and acid-base abnormalities induced by trimethoprim occur within 14 days or less in patients with poor kidney function, with disorders impairing renal potassium excretion such as diabetes mellitus or on concomitant treatment with drugs that disrupt the electrolyte and acid-base balance. Increased awareness of the potential for the mentioned, life threatening derangements is necessary. Clinicians must recognize patients at risk, possibly avoid drug combinations that may worsen the problem and monitor the electrolyte and acid-base balance.

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Notes

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Table 1

Table 1. Characteristics of 68 patients 23 to 96 years of age with hyperkalemia, hyponatremia or metabolic acidosis on medication with trimethoprim (high-dose, N=23; standard-dose, N=45; low-dose, N=0). Data are presented either as median and interquartile range or as frequency. Trimethoprim was combined with sulfamethoxazole as cotrimoxazole in 66 (97%) out of the 68 cases.

Gender, male : female	42 : 26
Age, years	68 [53-79]
Treatment duration	
days	5 [4-10]
≥14 days, N (%)	8 (12)
Symptoms - signs	
None, N (%)	39 (44)
Muscle weakness or pain, N (%)	13 (19)
Altered mental status, N (%)	8 (12)
Malaise, N (%)	7 (10)
Nausea or vomiting, N (%)	6 (8.9)
Fainting, N (%)	4 (5.9)
Electrolyte and acid-base derangements	
Hyperkalemia	
N (%)	62⁺ (91)
Concentration, mmol/L	6.9 [6.3-7.9]
Mild (5.1-5.9 mmol/L), N	7
Moderate (6.0-6.9 mmol/L), N	24
Severe (≥7.0 mmol/L), N	31·
Hyponatremia	
N (%)	29⁺ (43)
Concentration, mmol/L	124 [118-128]
Mild (130-134 mmol/L), N	6
Moderate (121-129 mmol/L), N	14
Severe (≤120 mmol/L), N	9·
Metabolic acidosis	
N (%)	14 (21)
Bicarbonate concentration, mmol/L	15 [13-17]
Mild (14-18 mmol/), N	9
Moderate (10-13 mmol/L), N	2
Severe (≤9 mmol/L), N	3
Predisposing factors	
None, N (%)	14 (21)
High-dose trimethoprim, N (%)	23 (34)
"Co-medication"*, N (%)	23 (34)
Chronic kidney disease, N (%)	21 (31)
Age ≥80 years, N (%)	15 (22)
Diabetes mellitus, N (%)	10 (25)
Death, N (%)	1 (1.5)

⁺P<0.001 versus hyponatremia and metabolic acidosis; ⁺P<0.05 versus metabolic acidosis; ·P<0.05 versus severe metabolic acidosis; *drugs that

have been linked with hyponatremia, hyperkalemia or metabolic acidosis: blockers of the renin-angiotensin-aldosterone system (N=14), β-receptor antagonists (N=7), calcineurin inhibitors (N=5), potassium-sparing diuretics (N=4), potassium supplementation (N=1).

Figure 1- Legend

Trimethoprim-associated electrolyte and acid-base abnormalities.

Flowchart of the literature search process.

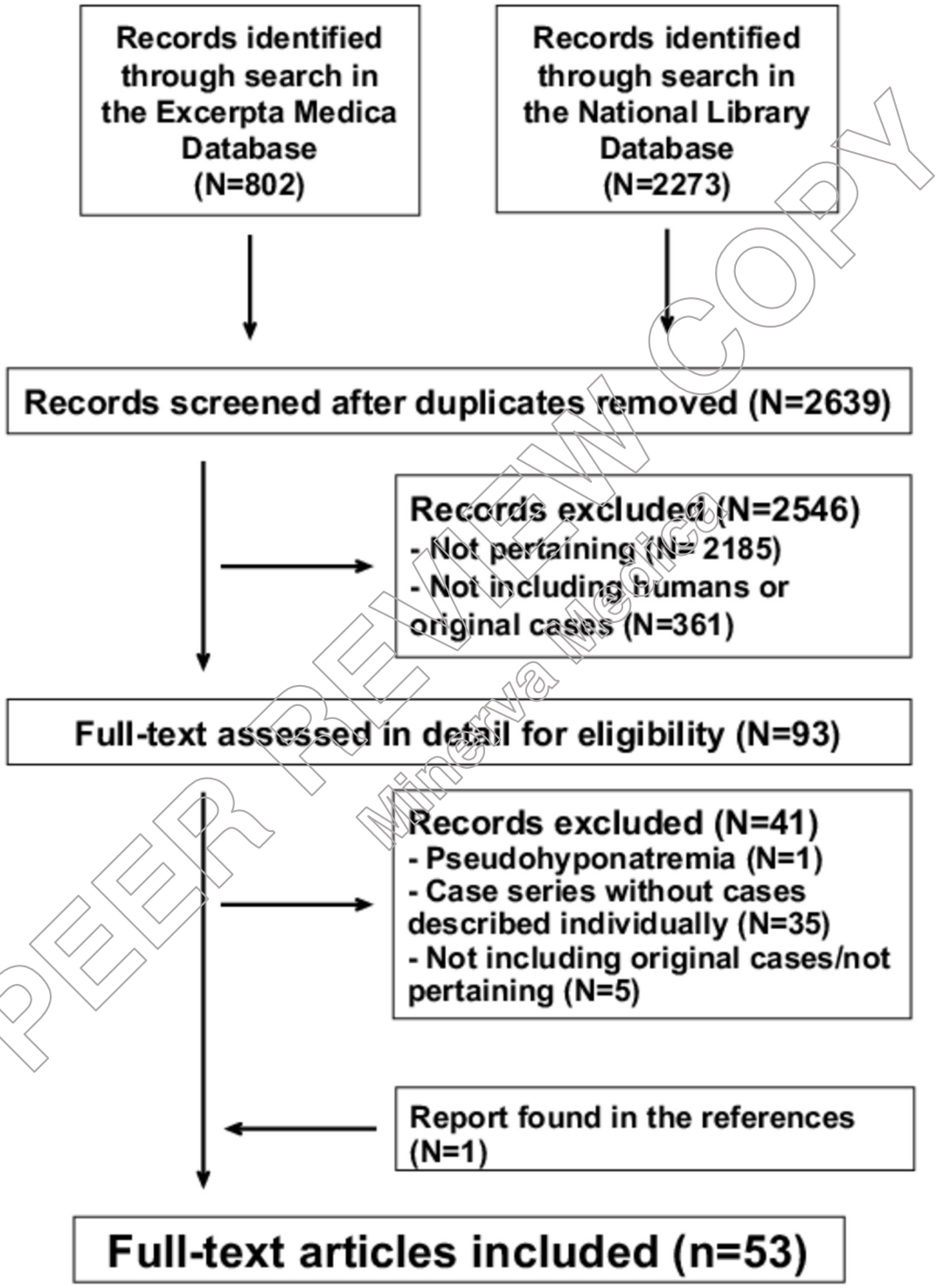

Figure 1