Analysis of the Clinical Characteristics of Hyponatremia Induced by Trimethoprim/Sulfamethoxazole

Haibo Lei\textsuperscript{a} Xiang Liu\textsuperscript{a} Jiang Zeng\textsuperscript{b} Zhiqiang Fan\textsuperscript{c} Yang He\textsuperscript{c} Zuojun Li\textsuperscript{d} Chunjiang Wang\textsuperscript{d}

\textsuperscript{a}Department of Clinical Pharmacy, Xiangtan Central Hospital, Xiangtan, China; \textsuperscript{b}Department of Pharmacy, The Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, China; \textsuperscript{c}Department of Pharmacy, The First Hospital of Hunan University of Chinese Medicine, Changsha, China; \textsuperscript{d}Department of Pharmacy, The Third Xiangya Hospital, Central South University, Changsha, China

\textbf{Keywords}
Hyponatremia · Trimethoprim-sulfamethoxazole · Electrolyte disorders · Sodium

\textbf{Abstract}

\textbf{Background:} Trimethoprim-sulfamethoxazole (TMP/SMX) causes hyperkalemia, and hyponatremia caused by TMP/SMX is a challenge for clinicians. We described the clinical features of hyponatremia induced by TMP/SMX after collecting cases. \textbf{Summary:} The median age of the 24 patients (10 males and 14 females) was 67 years (range: 28–90 years). Hyponatremia induced by TMP/SMX manifested as nausea (41.7%) and vomiting (29.2%) or asymptomatic hyponatremia (20.8%). The median duration of hyponatremia was 5 days (range: 3–10 days). The median serum sodium concentration was 118 mmol/L (range: 101–128.1 mmol/L). The serum sodium levels gradually returned to the normal range at 4 days (median; range: 2–14 days) after withdrawing TMP/SMX. \textbf{Key Messages:} TMP/SMX-induced hyponatremia is a rare and serious adverse reaction. Clinicians should be aware of electrolyte disturbances caused by TMP/SMX and should always consider electrolyte monitoring.

\textbf{Introduction}

Hyponatremia, defined as serum sodium concentrations <135 mmol/L, is a common electrolyte disturbance encountered in clinical practice, occurring in up to 42.6% of hospitalized patients [1]. Hyponatremia can be caused by multiple etiologies with different pathophysiological mechanisms. Drugs are the most frequent causes of electrolyte abnormalities, including hyponatremia. Many medications are related to hyponatremia, such as diuretics, antidepressants, antiepileptics, antibiotics, newer antihypertensive agents, and proton pump inhibitors [2]. Hyponatremia is independently associated with an increased risk of in-hospital mortality [3, 4]. Severe hyponatremia can result in cerebral edema, seizures, coma, and eventually death [5]. However, many patients with hyponatremia are asymptomatic and the condition may be life-threatening if left untreated.

Trimethoprim-sulfamethoxazole (TMP/SMX) is a synthetic sulfonamide antibacterial combination product containing a ratio of 5:1 of SMX to trimethoprim. SMX is a structural analog of para-aminobenzoic acid that competitively binds to the enzyme dihydropteroate synthetase, inhibiting the conversion of para-aminobenzoic...
acid to dihydrofolic acid. TMP impedes the conversion of dihydrofolic acid to tetrahydrofolic acid by binding to the enzyme dihydrofolate reductase [6]. TMP/SMX blocks two steps in the bacterial biosynthesis of essential nucleic acids and proteins to kill bacteria. With increasing bacterial resistance, the role of TMP/SMX has changed. TMP/SMX continues to be the drug of choice for prophylaxis and the treatment of human immunodeficiency virus-related infections and various less common bacterial infections, including Pneumocystis carinii, Nocardia, toxoplasmosis, and Tropheryma whippelii infections [7]. TMP/SMX is available in oral and intravenous preparations and is generally well tolerated, with adverse reactions occurring in 6–8% of individuals [7]. Gastrointestinal and cutaneous symptoms are the most commonly encountered adverse effects. TMP/SMX causes hyperkalemia, particularly at a higher dosage [8]. The first case of hyponatremia caused by TMP/SMX was reported in 1984 [9]. Hyponatremia induced by TMP/SMX has been reported occasionally but is often less highlighted by clinicians; its prevalence is unknown. In this study, we analyzed and discussed the clinical characteristics of TMP/SMX-induced hyponatremia, providing a reference for the safe and reasonable clinical application of TMP/SMX.

Methods

Search Strategy

We searched PubMed/Medline, Web of Knowledge, the Evidence-based Medicine database, Elsevier, Springer Link, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and China Science and the Technology Journal Database in Chinese and English from 1984 to 2020. We identified the literature regarding hyponatremia induced by TMP/SMX using the search terms “hyponatremia,” “trimethoprim-sulfamethoxazole,” “trimethoprim,” “TMP/SMX,” “TMP,” “sulfamethoxazole,” “syndrome of inappropriate antidiuretic hormone secretion,” “SIADH,” “electrolyte disturbance,” and “renal salt wasting.”

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: We collected case reports of TMP/SMX-induced hyponatremia for inclusion as preliminary studies. (1) The diagnosis of hyponatremia was clear and related to TMP/SMX. (2) These studies had complete clinical data, including basic patient information, usage and the dosage of TMP/SMX, clinical symptoms, laboratory examination, treatment and outcome. The exclusion criteria were as follows: duplicate literature, reviews, mechanism studies, animal studies, and studies with only an abstract no full text.

Survey Items

Two researchers independently conducted a preliminary screening of the literature according to the inclusion and exclusion criteria, and then the group discussed the literature to be included in the analysis. We used a self-designed data extraction table to extract the following patient information: nationality, sex, age, primary disease, combined disease, TMP/SMX application, combined medication, clinical symptoms, laboratory examination, and disposal and prognosis.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The results were expressed as medians with ranges and percentages (%).

Results

Patient Characteristics

We identified and screened 1,276 studies using the search strategy described in the Methods section. After careful review by 2 independent authors, only 21 studies were included according to the inclusion and exclusion criteria (Table 1) [9–29]. The basic information of 24 patients (10 male and 14 female) is summarized in Table 2. The patients were mainly Americans (37.5%) and Asians (41.7%). The mean age of these patients was 67 years (range: 28–90 years). TMP/SMX was mainly used to treat Pneumocystis and Nocardia pneumonia and urinary tract infections caused by Escherichia coli. The daily dose of TMP/SMX was mainly <10 mg/kg/day in 11 patients (52.4%) and 15–20 mg/kg/day in 8 patients (38.1%). The median time of hyponatremia was 5 days (range: 3–10 days). Fifteen patients (62.5%) used medications that caused electrolyte disturbances at the same time, such as steroid therapy in 7 patients (46.7%), antidepressant drugs, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and diuretics in 3 patients (20.0%). Twenty patients (83.3%) had underlying diseases, such as hematologic neoplasms, cancer, autoimmune disease, acquired immunodeficiency syndrome, endocrine system diseases, central nervous system diseases, cardiovascular diseases, and respiratory diseases. Two patients developed hyponatremia within 3 days after the re-administration of TMP/SMX [14, 16].

Clinical Manifestations

The clinical manifestations of hyponatremia induced by TMP/SMX are summarized in Table 3. Nausea in 10 patients (41.7%) and vomiting in 7 patients (29.2%) were the most common clinical symptoms of TMP/SMX-induced hyponatremia, followed by weakness and fatigue in 5 patients (20.8%), confusion in 3 patients (12.5%), and an altered conscious state in 3 patients (12.5%). Six patients (25.0%) presented with asymptomatic hyponatremia.
Table 1. Basic data of the 24 included patients

| Reference | Country | Age/sex | Indication       | Dosage                  | Time, days | Clinical symptoms                      | Serum sodium (before/after) | Serum osmolality, mOsm/kg | Urine sodium | Urine osmolality, mOsm/kg | Treatment                               |
|-----------|---------|---------|------------------|-------------------------|------------|--------------------------------------|-----------------------------|------------------------------|---------------|----------------------------|------------------------------------------|
| [9]       | UK      | 75/f    | UTI              | 200 mg bid*             | 4          | Nausea, anorexia                      | 136/107                    | 225                          | 31            | 523                        | Discounted, fluid restriction             |
| [10]      | Sweden  | 83/f    | Pneumonia (A. xylosoxidans) | 160/800 mg iv q8 h     | 5          | Nausea                               | 134/110                    | 242                          | 117           | 478                        | Discounted, salt tabs, tolvaptan         |
| [11]      | Japan   | 57/f    | Prophylaxis      | 160/800 mg po qd       | 3          | NR                                   | 143/125                    | 264                          | 92            | 510                        | Discounted                               |
| [12]      | USA     | 54/f    | Sinus infection  | 160 mg po bid          | 3          | Nausea, vomiting, fatigue            | NR/101                     | 225                          | 128           | 128                        | Discounted, fluid restriction, NS         |
| [13]      | Iran    | 55/f    | PP               | 15 mg/kg iv            | 10         | Nausea, vomiting, confused, lethargic| 146/110                    | 240                          | 50            | NR                         | Discounted, HS, restore after 2 d         |
| [14]      | Germany | 66/m    | Prophylaxis      | 960 mg po bid          | NR/3       | Tremo                                 | NR/104                     | 226                          | NR            | 238                        | Discounted                               |
| [15]      | India   | 49/m    | UTI (E. coli)    | 20 mg/kg/day po*       | 7          | Fatigue, nausea, vomiting            | NR/115                     | 248                          | 142           | 161                        | Discounted, high salt diet, restore after 4 d |
| [16]      | USA     | 82/f    | UTI (GBS)        | 160/800 mg po bid      | 7/3        | Depression, insomnia, nausea         | 132/121                    | NR                           | NR            | NR                         | Discounted, NS, restore after 8 d         |
| [17]      | Australia | 69/f   | PJP              | 320/1600 mg iv q8 h    | 5          | Confused                              | NR/118                     | 248                          | 135           | 398                        | Discounted, HS, restore after 5 d         |
| [17]      | Australia | 90/f   | UTI (E. coli)    | 300 mg po qd*          | 4          | Nausea, vomiting, delirium           | NR/123                     | 255                          | 107           | 377                        | Discounted, restore after 4 d             |
| [17]      | Australia | 75/m   | UTI              | 300 mg po qd*          | 5          | ACS                                  | NR/123                     | 264                          | 118           | 411                        | Discounted, NS                           |
| [18]      | USA     | 28/m    | PJP              | 15 mg/kg/d iv*         | 5          | Tachycardia                          | 135/118                    | 245                          | 136           | 682                        | Discounted, salt tabs, tolvaptan, NS, restore after 2 d |
| [19]      | USA     | 86/m    | UTI              | 80/400 mg po bid       | 4          | AMS, weakness, fatigue               | NR/127                     | 275                          | 86            | 659                        | Discounted, fluid restriction, NS, restore after 8 d |
| [20]      | Israel  | 78/f    | UTI              | NR                     | 7          | Weakness, abdominal pain, nausea, vomiting | NR/115                    | 250                          | 114           | 457                        | Discounted                               |
| [21]      | UK      | 53/f    | PCP              | 20 mg/kg po*           | 12         | Weakness                             | 137/118                    | NR                           | 41            | 287                        | Discounted, restore after 7 d             |
| [22]      | Japan   | 64/m    | PCP              | 12 g/d po              | 4          | ACS                                  | 139/109                    | NR                           | NR            | NR                         | Continued, HS, fluid restriction          |
| [22]      | Japan   | 59/m    | PCP              | 12 g/d iv              | 6          | NR                                   | 141/126                    | NR                           | NR            | NR                         | Discounted, HS, fluid restriction         |
| Reference | Country | Age/sex | Indication | Dosage | Time, days | Clinical symptoms | Serum sodium (before/after) | Serum osmolality, mOsm/kg | Urine sodium | Urine osmolality, mOsm/kg | Treatment |
|-----------|---------|---------|------------|--------|------------|-------------------|--------------------------|-------------------------|--------------|--------------------------|-----------|
| [23]      | USA     | 42/m    | PCP        | 20 mg/kg/day iv* | 4         | NR       | 137/121          | NR                      | 142          | 706                     | Discounted |
| [24]      | USA     | 64/f    | Pneumonia  | 16 mg/kg/day iv* | 5         | NR       | NR/128            | NR                      | NR           | NR                      | Discounted, restore after 3 d |
| [25]      | USA     | 68/m    | Brain abscesses (Nocardia) | 15 mg/kg iv q6 h | 3       | Abdominal pain, nausea, vomiting | 136/124          | 261          | 53          | 235                  | Discounted, salt tablets, restore after 2 d |
| [26]      | USA     | 83/f    | Pneumonia (A. xylosoxidans) | 160/800 mg iv q6 h | 3       | NR       | NR/110            | 242         | 114          | 478                  | Continued, tolvaptan, fluid restriction, salt tablets |
| [27]      | Turkey  | 65/f    | PCP        | 15 mg/kg iv q6 h* | 10      | NR       | 136/120          | 254         | 170          | 529                  | Discounted, fluid restriction, HS, restore after 4 d |
| [28]      | USA     | 72/m    | Pneumonia (N. cyriacigeorgica) | 480/2400 mg po bid, 10 mg/kg/day* | 5       | Confused | 133/112          | 245         | 109          | 422                  | Discounted, fluid restriction, salt tablets, restore after 14 d |
| [29]      | China   | 75/f    | UTI (E. coli) | 80/400 mg po bid | 6       | Nausea, vomiting | 140.6/128.1 | NR          | NR          | NR                  | Continued, HS, sodium bicarbonate |

ACS, altered conscious state; AMS, altered mental status; A. xylosoxidans, Achromobacter xylosoxidans; E. coli, Escherichia coli; GBS, Group B Streptococcus; HS, hypertonic saline; IV, intravenous; NS, normal saline; N. cyriacigeorgica, Nocardia cyriacigeorgica; NR, not reported; PCP, Pneumocystis carinii pneumonia; PJP, Pneumocystis jirovecii pneumonia; PP, Pneumocystis pneumonia; UTI, urinary tract infection. * Represents the trimethoprim dose.
Laboratory Tests

The laboratory test results are described in Table 2. The median serum sodium concentration of hyponatremia induced by TMP/SMX was 118 mmol/L (range: 101–128.1 mmol/L), and the median serum potassium concentration was 5.3 mmol/L (range: 3.1–6.6 mmol/L). Twenty patients (83.3%) developed severe hyponatremia (≤125 mmol/L). The median plasma osmolality was 248 mOsm/kg (range: 225–275 mOsm/kg). The median level of serum bicarbonate was 17.3 mmol/L (range: 8–24 mmol/L). Urine studies showed that the median urine osmolality was 439.5 mOsm/kg (range: 128–706 mOsm/kg), the median urine sodium was 114 mmol/L (range: 31–170 mmol/L), and the median urinary fractional excretion of sodium was 1.61%. Acute kidney injury occurred in 3 patients (12.5%) [24, 25, 28]. Renin and aldosterone were elevated in 4 patients [11, 13, 18, 27].

Treatment and Prognosis

Twenty patients (83.3%) immediately stopped TMP/SMX when hyponatremia occurred (Table 4). Normal saline was administered to 7 patients (29.2%), hypertonic saline to 8 patients (25.0%), fluid restriction to 8 patients (33.3%), salt tablets to 4 patients (16.7%), and a high-salt diet to 1 patient (4.2%). Three patients (12.5%) were given high-dose tolvaptan (≥30 mg/day) to treat hyponatremia [19, 23, 24]. The serum sodium levels of these patients gradually returned to the normal range at a median time of 4 days (range: 2–14 days).

Discussion

Hyponatremia occurs frequently in hospitals and usually brings challenges in diagnosis or treatment. TMP/SMX-induced hyponatremia is often misdiagnosed as a syndrome of inadequate antidiuretic hormone secretion (SIADH). The exact mechanism of TMP/SMX-induced hyponatremia is unclear. Current research suggests that renal salt wasting may be the main underlying mechanism of hyponatremia caused by TMP/SMX [18, 30]. TMP is similar in structure to amiloride and acts as a potassium-sparing diuretic by blocking the epithelial sodium channel in the collection tube, resulting in natriuresis, hyperkalemia, and metabolic acidosis [31]. A retrospective study found that 72.3% of hospitalized patients who had used high-dose TMP/SMX (8 mg/kg/day of TMP for ≥3 days) had hyponatremia, with the severity of hyponatremia depending on longer duration and higher cumulative doses of TMP/SMX [32]. Mori et al. [33] retrospec-

Table 2. Summary of the basic information of the 24 included patients

| Parameter                                | Value, n (%) |
|------------------------------------------|--------------|
| Sex (24)b                                |              |
| Female                                   | 14 (58.3)    |
| Male                                     | 10 (41.7)    |
| Age (24)b                                |              |
| Year                                     | 67 (28.90)a  |
| Region (24)b                             |              |
| USA                                      | 9 (37.5)     |
| Japan                                    | 3 (12.5)     |
| Australia                                | 3 (12.5)     |
| UK                                       | 2 (8.3)      |
| Iran                                     | 1 (4.2)      |
| India                                    | 1 (4.2)      |
| Sweden                                   | 1 (4.2)      |
| Israel                                   | 1 (4.2)      |
| Turkey                                   | 1 (4.2)      |
| Germany                                  | 1 (4.2)      |
| China                                    | 1 (4.2)      |
| Indication (24)b                         |              |
| Pneumonia                                | 12 (50.0)    |
| Urinary tract infection                  | 8 (33.3)     |
| Prophylaxis                              | 2 (8.3)      |
| Sinus infection                          | 1 (4.2)      |
| Brain abscesses                          | 1 (4.2)      |
| Bacterium (17)b                          |              |
| Pneumocystis                             | 8 (47.1)     |
| Pneumocystis carinii                    | 5 (62.5)     |
| Pneumocystis jiroveci                   | 2 (25.0)     |
| Nocardia                                 | 3 (17.7)     |
| Nocardia cyriacigorgia                  | 1 (33.3)     |
| Nocardia farcinica                      | 1 (33.3)     |
| Escherichia coli                        | 3 (17.7)     |
| Achromobacter xylooxidans               | 2 (11.8)     |
| Group B Streptococcus                   | 1 (5.9)      |
| Daily dose of TMP/SMX (21)b              |              |
| 15–20 mg/kg/day                         | 8 (38.10)    |
| 10–15 mg/kg/day                         | 2 (9.5)      |
| <10 mg/kg/day                           | 11 (52.4)    |
| Route of administration (24)b           |              |
| Oral                                     | 13 (54.2)    |
| Intravenous                              | 11 (45.8)    |
| Onset time of hyponatremia (24)b         |              |
| Days                                     | 5 (3.10)a    |
| Underlying illness (20)b                 |              |
| Solid cancer                             | 3 (15.0)     |
| Hematologic neoplasms                   | 2 (10.0)     |
| Kidney transplant                       | 2 (10.0)     |
| Autoimmune disease                      | 5 (10.0)     |
| AIDS                                     | 3 (15.0)     |
| Endocrine system diseases                | 4 (20.0)     |
| Central nervous system diseases          | 4 (20.0)     |
| Cardiovascular diseases                  | 9 (45.0)     |
| Respiratory diseases                     | 4 (20.0)     |
| Concomitant medication (15)b             |              |
| Steroid therapy                          | 7 (46.7)     |
| Antidepressant drugs                     | 3 (20.0)     |
| ACEI/ARB                                 | 3 (20.0)     |
| Diuretics                                | 3 (20.0)     |

TMP/SMX, trimethoprim-sulfamethoxazole; AIDS, acquired immunodeficiency syndrome; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. a Median (minimum-maximum). b Represents the number of patients among a total of 24 on whom information regarding this particular parameter was provided.
tively found that patients treated with TMP/SMX will also have electrolyte disturbances even with a low dose (TMP: <80 mg) or standard dose (TMP: 80–120 mg), indicating a dose-dependent effect. Generally, electrolyte disturbances were observed more frequently with high-dose TMP/SMX, and low doses can also cause both hyperkalemia and hyponatremia.

Nervous system symptoms are the main clinical manifestations of hyponatremia, ranging from nausea, vomiting, headache and general malaise to changes in mental status, seizures, and even coma [12]. Our study showed that TMP/SMX-induced hyponatremia mainly manifests as nausea, vomiting, weakness, and fatigue and can also manifest as asymptomatic hyponatremia. TMP/SMX mainly causes severe hyponatremia (serum sodium ≤125 mmol/L) with or without elevated potassium. TMP may cause a distal acidification defect, with hyperkalemia contributing to the development of acidosis through effects on the renal handling of ammonia and aldosterone secretion. This leads to a decreased serum bicarbonate level, which is consistent with our clinical findings [34]. Renin/aldosterone tends to be suppressed in SIADH and elevated in renal salt wasting [18]. Urinary sodium excretion of hyponatremia is related to the waste of kidney salt> 20 mmol/L [35].

Previous studies have found that African-American patients, elderly individuals, patients with renal disease, and patients with diuretics have an increased risk of de-

### Table 3. Clinical information of the 24 included patients

| Parameter                   | Clinical features | Value, n (%) | Normal range |
|-----------------------------|-------------------|--------------|--------------|
| Presenting symptoms (24)b   | Nausea            | 10 (41.7)    |              |
|                            | Vomiting          | 7 (29.2)     |              |
|                            | Fatigue and weakness | 5 (20.8) |              |
|                            | Anorexia          | 2 (8.3)      |              |
|                            | Tachycardia       | 2 (8.3)      |              |
|                            | Confused          | 3 (12.5)     |              |
|                            | Altered conscious state | 3 (12.5) |              |
|                            | Delirium          | 1 (4.2)      |              |
|                            | Lethargic         | 1 (4.2)      |              |
|                            | Abdominal pain    | 2 (8.3)      |              |
|                            | Tremor            | 1 (4.2)      |              |
|                            | Depression        | 1 (4.2)      |              |
|                            | Asymptomatic      | 6 (25.0)     |              |
| Sodium                      | Before medication (14)b | 136.5 (132, 146)a | 135–145 mmol/L |
|                            | After medication (24)b | 118 (101, 128.1)a |              |
|                            | 130–135 mmol/L    | 0 (0)        |              |
|                            | 125–130 mmol/L    | 4 (16.7)     |              |
|                            | ≤125 mmol/L       | 20 (83.3)    |              |
| Potassium                   | Before medication (8)b | 4.2 (2.7, 4.96)a | 3.5–5.5 mmol/L |
|                            | After medication (18)b | 5.3 (3.1, 6.6)a |              |
| Creatinine                  | Before medication (12)b | 0.85 (0.11, 1.6)a | 0.7–1.2 mg/dL |
|                            | After medication (17)b | 1.1 (0.47, 4)a |              |
| Serum osmolarity (18)b      | 248 (225, 275)a | 285–295 mOsm/kg |
| Bicarbonate (9)b            | 17.3 (8, 24)a | 22–29 mmol/L |
| Urine sodium (17)b          | 114 (51, 170)a | <20 mmol/L |
| Urine osmolality (18)b      | 439.5 (128, 706)a | 50–1,400 mOsm/kg |
| FENa (10)b                  | 1.61 (0.36, 6.5)a | <1% |

FENa, fractional excretion of sodium. a Serum sodium, potassium, and creatinine in parentheses represent the median value (range: minimum-maximum) before and after administration. b Represents the number of patients among a total of 24 on whom information regarding this particular parameter was provided.
developing hyponatremia [19, 36]. Stephens et al. [37] found that approximately one-third of children aged <18 years receiving intravenous SMP/TMX developed hyponatremia, and concomitant furosemide administration was one of the most common risk factors. SMP/TMX combined with systemic corticosteroids with mineralocorticoid effects may compensate for TMP-related hyponatremia [11]. A case-control study showed that the simultaneous use of TMP/SMX and inhibitors of the renin-angiotensin system increases the risk of hyperkalemia. These results suggest that ACEIs/angiotensin receptor blockers can amplify the adverse effects of TMP on the renal distal tubule [38]. Caution should be taken when TMP/SMX is combined with hyponatremic-inducing drugs, such as serotonin receptor uptake inhibitors [28]. Some patients with hyponatremia have a complex and multifactorial etiology. A thorough investigation should be conducted to ensure the correct diagnosis, particularly when diseases that may cause hyponatremia, such as malignancy, adrenal insufficiency, and hypothyroidism, are present [39, 40]. Human immunodeficiency virus infection may be associated with SIADH, with previous studies reporting SIADH in up to 53% of hospitalized patients with acquired immune deficiency syndrome [41].

TMP/SMX-induced hyponatremia can be resolved by discontinuing the drug, intravenous saline hydration, a high-salt diet or 3% saline. The effectiveness and safety of vasopressin receptor antagonists in treating symptomatic or acute hyponatremia are not yet well established. However, a few studies have proven that a massive dose of tolvaptan (30 mg) can effectively treat hyponatremia caused by TMP/SMX in patients who are refractory to salt tablets and fluid restriction [10]. Our study found that the serum sodium concentration returned to the normal range approximately 4 days after stopping TMP/SMX. Additionally, Huntsberry et al. [16] and Herzog et al. [14] found that hyponatremia recurred after re-exposure to TMP/SMX with a shorter onset time [14, 16].

**Conclusion**

Hyponatremia is a serious and rare adverse reaction to TMP/SMX. Various doses of TMP/SMX may lead to hyponatremia. Close monitoring of serum sodium should be performed in patients who are receiving TMP/SMX therapy, particularly in patients with high-risk factors. Hyponatremia should be considered in patients on TMP/SMX who present with digestive or neurological symptoms.

**Conflict of Interest Statement**

The authors declare no conflicts of interest.

**Funding Sources**

This study was funded by the Natural Science Foundation of Hunan Province (No. 2021JJ80083).

**Author Contributions**

Chunjiang Wang and Haibo Lei designed the study, Xiang Liu provided clinical support, Jiang Zeng and Zhiqiang Fan collected the data, Zuojun Li and Yang He analyzed the data, Haibo Lei and Chunjiang Wang wrote the manuscript (original draft preparation), Xiang Liu and Jiang Zeng wrote the manuscript (review and editing), and Zhiqiang Fan and Zuojun Li provided conceptual advice. All the coauthors have agreed to the submission of the final manuscript.

**Table 4. Treatment of the 24 included patients**

| Parameter | Value, n (%) |
|-----------|-------------|
| Therapy (24) | 20 (83.3) |
| Discontinued | 4 (16.7) |
| Continued | 7 (29.2) |
| Normal saline | 6 (25.0) |
| Hypertonic saline | 8 (33.3) |
| Fluid restriction | 4 (16.7) |
| Salt tablets | 3 (12.5) |
| Tolvaptan | 1 (4.2) |
| High salt diet | 4 (2.14) |

TMP/SMX, trimethoprim-sulfamethoxazole. a Median (minimum–maximum). b Represents the number of patients among a total of 24 on whom information regarding this particular parameter was provided.

**References**

1. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*. 2003;337(1–2):169–72.
2. Ramos-Levi AM, Duran Rodriguez-Hervada A, Mendez-Bailon M, Marco-Martinez J. Drug-induced hyponatremia: an updated review. *Minerva Endocrinol*. 2014;39(1):1–12.
3. Wald R, Jaber BL, Price LL, Upadhyay A, Madia NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010;170(3):294–302.
8 Smilack JD. Trimethoprim-sulfamethoxazole. Mayo Clin Proc. 1999;74(7):730–4.
9 Eastell R, Edmonds CJ. Hyponatraemia associated with trimethoprim and a diuretic. Br Med J;289(6459):1658–9.
10 Ghali MGZ, Kim MJ. Trimethoprim-sulfamethoxazole-induced hyponatremia in an elderly lady with Achromobacter xylosidans pneumonia: Case report and insights into mechanism. Medicine. 2020;99(33):e20746.
11 Takubo M, Tanaka S, Kushimoto M, Ikeda J, Westfall TA, Benito P, et al. Trimethoprim-sulfamethoxazole-induced hyponatremia and hyperkalemia in patients with Pneumocystis carinii pneumonia. Intern Med. 1995;34(2):96–9.
12 Ahn YH, Goldman JM. Trimethoprim-sulfamethoxazole and hyponatremia. Ann Intern Med. 1985;103(1):161–2.
13 Kang J, Baumstein D. High dose trimethoprim-sulfamethoxazole exposure and hypernatremia. Am J Kidney Dis. 2019;73(5):686.
14 Kovuru K, Karthik K, Rivera S, Franco H, Cabeza Z, et al. Dose dependent hyponatremia associated with high-dose trimethoprim-sulfamethoxazole for treatment of disseminated nocardia infection after kidney transplantation. Am J Kidney Dis. 2018;71(4):559.
15 Kim M, Ghali M, Sandeep A. Tolvaptan resistance in the setting of siald in an 83 year old lady with pneumonia treated with iv trimethoprim-sulfamethoxazole. Am J Kidney Dis. 2018.
16 Mizrak D, Kalkan EA, Alkan A, Yerlikaya H, Koksoy EB, Karci E, et al. An unexpected cause of hyponatremia in a cancer patient: trimethoprim-sulfamethoxazole. J Oncol Sci. 2016;2(1):27–8.
17 Saha BK, Chong WHF. Trimethoprim-induced hyponatremia mimicking SIADH in a patient with pulmonary nocardiosis: use of point-of-care ultrasound in apparent euvolemic hypotonic hyponatremia. BMJ Case Rep. 2020;13(8):e235558.
18 Peng XY. One case of hyponatremia complicated with hyperkalemia induced by compassionate use of trimethoprim-sulfamethoxazole in an older adult. Clin Interv Aging. 2015;10:1091–6.
19 Khow KS, Yong TY. Hyponatremia associated with trimethoprim use. Curr Drug Saf. 2014 Mar;9(1):79–82.
20 Babayev R, Terner S, Chandra S, Radhakrishnan J, Mohan S. Trimethoprim-associated hyponatremia. Am J Kidney Dis. 2013;62(6):1188–92.
21 Dunn RL, Smith WJ, Stratton MA. Trimethoprim-sulfamethoxazole-induced hyponatremia. Consult Pharm. 2011;26(5):342–9.
22 Dreither J, Porath A. Severe hyponatremia induced by theophylline and trimethoprim. Arch Intern Med. 2001;161(2):291–2.
23 David LM, Ross J. Severe hyponatraemia and hyperkalemia in patients who received high dose co-trimoxazole. Sex Transm Infect. 1998;74(1):75–6.
24 Noto H, Kaneko Y, Takano T, Kurokawa K. Severe hyponatremia and hyperkalemia induced by trimethoprim-sulfamethoxazole in patients with Pneumocystis carinii pneumonia. Intern Med. 1995;34(2):96–9.
25 Akinbode-James O, Otunma J, Salerno D, et al. Incidence of hyponatremia with high-dose trimethoprim-sulfamethoxazole exposure. Am J Med. 2016;129(12):1322–8.
26 Kim M, Ghali M, Sandeep A. Tolvaptan resistance in the setting of siald in an 83 year old lady with pneumonia treated with iv trimethoprim-sulfamethoxazole. Am J Kidney Dis. 2018.
27 Mizrak D, Kalkan EA, Alkan A, Yerlikaya H, Koksoy EB, Karci E, et al. An unexpected cause of hyponatremia in a cancer patient: trimethoprim-sulfamethoxazole. J Oncol Sci. 2016;2(1):27–8.
28 Saha BK, Chong WHF. Trimethoprim-induced hyponatremia mimicking SIADH in a patient with pulmonary nocardiosis: use of point-of-care ultrasound in apparent euvolemic hypotonic hyponatremia. BMJ Case Rep. 2020;13(8):e235558.
29 Peng XY. One case of hyponatremia complicated with hyperkalemia induced by compassionate use of trimethoprim-sulfamethoxazole in an older adult. Clin Interv Aging. 2015;10:1091–6.
30 Kaufman AM, Hellman G, Abramson RG. Renal salt wasting and metabolic acidosis with trimethoprim-sulfamethoxazole therapy. Mt Sinai J Med. 1983;50(3):238–9.
31 Perazella MA. Hyperkalemia and trimethoprim-sulfamethoxazole: a new problem emerges 25 years later. Conn Med. 1997;61(8):451–8.
32 Tsapepas D, Chiles M, Babayev R, Rao MK, Jatily M, Salerno D, et al. Incidence of hyponatremia with high-dose trimethoprim-sulfamethoxazole exposure. Am J Med. 2016;129(12):1322–8.
33 Mori H, Kuroda Y, Imamura S, Toyoda A, Yoshida I, Wakami K, et al. Hyponatremia and/or hyperkalemia in patients treated with the standard dose of trimethoprim-sulfamethoxazole. Intern Med. 2003;42(8):665–9.
34 Hemstreet BA. Antimicrobial-associated renal tubular acidosis. Ann Pharmacother. 2004;38(6):1031–8.
35 Maesaka JK, Miyawaki N, Paliai T, Fishbane S, Durham JH. Renal salt wasting without cerebral disease: diagnostic value of urate determinations in hyponatremia. Kidney Int. 2007;71(8):822–6.
36 Gankam-Kengne F, Ayers C, Khera A, de Lemos J, Maalouf NM. Mild hyponatremia is associated with an increased risk of death in an ambulatory setting. Kidney Int. 2013;83(4):700–6.
37 Stephens K, Miller JL, Lewis TV, Neely S, Johnson PN. Hyponatremia with intravenous sulfamethoxazole/trimethoprim in children. Ann Pharmacother. 2020;54(4):351–8.
38 Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. Arch Intern Med. 2010;170(12):1045–9.
39 Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. N Engl J Med. 1989;321(8):492–6.
40 Hanna FW, Scanlon MF. Hyponatremia, hyponatremia, and role of arginine-vasopressin in hypopituitarism. N Engl J Med. 1989;321(8):492–6.