Acute psychosis related to use of trimethoprim/sulfamethoxazole in the treatment of HIV-infected patients with *Pneumocystis jirovecii* pneumonia: a multicentre, retrospective study

Kuan-Yeh Lee¹, Chung-Hao Huang², Hung-Jen Tang³, Chia-Jui Yang⁴, Wen-Chien Ko⁵, Yen-Hsu Chen², Yi-Chien Lee⁶ and Chien-Ching Hung¹*

¹Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; ²Department of Internal Medicine, Kaohsiung Medical University Hospital and Kaohsiung Medical University, Kaohsiung, Taiwan; ³Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan; ⁴Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan; ⁵Department of Internal Medicine, National Cheng-Kung University Hospital and National Cheng-Kung University College of Medicine, Tainan, Taiwan; ⁶Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan

*Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.
Tel: +886–2-23123456, ext. 67552; Fax: +886-2-23707772; E-mail: hcc0401@ntu.edu.tw

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Objectives: A recent study reported that trimethoprim/sulfamethoxazole caused acute psychosis in four renal transplant patients with *Pneumocystis jirovecii* pneumonia. We aimed to investigate the incidence of and factors associated with trimethoprim/sulfamethoxazole-related acute psychosis in HIV-infected patients with *P. jirovecii* pneumonia.

Methods: We reviewed the medical records of HIV-infected patients who presented with *P. jirovecii* pneumonia and received trimethoprim/sulfamethoxazole at six major hospitals in Taiwan from July 2009 to May 2011. Acute psychosis was defined as the occurrence of hallucinations or delusions following the initiation of trimethoprim/sulfamethoxazole during hospitalization.

Results: During the study period, 135 patients receiving trimethoprim/sulfamethoxazole for *P. jirovecii* pneumonia were enrolled and 16 (11.9%; 95% CI, 6.3%–17.4%) developed acute psychosis after a median duration of 5 days of trimethoprim/sulfamethoxazole treatment (range, 3–11 days). The incidence increased from 0% (0/16) in patients who received a daily trimethoprim dose of $\leq$12 mg/kg to 23.5% (4/17) in those who received a daily trimethoprim dose of $>18$ mg/kg. In multivariate logistic regression analysis, a higher daily dose of trimethoprim/sulfamethoxazole (OR, per 1 mg increase of trimethoprim, 1.40; 95% CI, 1.12–1.76; $P=0.0035$) and use of adjunctive steroids (OR, 4.43; 95% CI, 1.14–17.15; $P=0.031$) were associated with acute psychosis.

Conclusions: In this case series, 11.9% of HIV-infected patients developed acute psychosis while receiving trimethoprim/sulfamethoxazole for *P. jirovecii* pneumonia. While the study was limited by its retrospective design, the risk appeared to increase with increasing daily dose of trimethoprim/sulfamethoxazole in those vulnerable patients with multiple risks for acute psychosis.

Keywords: hallucinations, steroids, hyponatraemia, HIV infection

Introduction

*Pneumocystis jirovecii* pneumonia is one of the most common and important causes of pulmonary complications and respiratory failure among HIV-infected patients, especially among those who are not on combination antiretroviral therapy (cART) and antimicrobial prophylaxis for *P. jirovecii* pneumonia.¹,² Trimethoprim/sulfamethoxazole, at a recommended daily dose of 15–20 mg/kg of the trimethoprim component, is the antimicrobial agent of choice for treatment and prophylaxis for *P. jirovecii* pneumonia.³ Adverse effects related to the CNS have rarely been reported with trimethoprim/sulfamethoxazole treatment. A recent study from the UK suggests that use of trimethoprim/sulfamethoxazole at a total daily dose of trimethoprim ranging from 600 to 1440 mg caused acute psychosis in four renal transplant recipients with *P. jirovecii* pneumonia.⁴ In this multicentre,
A retrospective study, we aimed to investigate the incidence of and factors associated with acute psychosis related to trimethoprim/sulfamethoxazole in HIV-infected patients with P. jirovecii pneumonia.

### Methods

#### Study population

From July 2009 to May 2011, medical records of HIV-infected patients aged \( \geq 18 \) years who were hospitalized for P. jirovecii pneumonia and received trimethoprim/sulfamethoxazole at six major designated hospitals for HIV care around Taiwan (National Taiwan University Hospital, Chiayi Christian Hospital, Far Eastern Memorial Hospital, Chi Mei Medical Center, Kaohsiung Medical University Hospital and National Cheng Kung University Hospital) were retrospectively reviewed using a standardized computerized case record form. The study was approved by the Research Ethics Committees of the participating hospitals and the need for informed consent was waived. Patients were excluded from analysis if they had pre-existing psychiatric diseases or were taking antipsychiatric therapy prior to this admission; had impaired consciousness due to any identified organic pathology of the CNS or used sedative agents prohibiting evaluation of mental status; received a parenteral or oral form of trimethoprim/sulfamethoxazole for \(< 3\) days; received a dose of \(< 5 \) mg/kg/day of the trimethoprim component; or started a course of anti-pneumocystosis therapy lasting \( > 3 \) days at other hospitals before seeking HIV care at the participating hospitals.

#### Definitions

Patients were diagnosed as having P. jirovecii pneumonia if P. jirovecii was identified by cytology, histopathology or PCR assay of the respiratory specimens, or if there was a typical clinical history and image finding of interstitial pneumonitis for which anti-pneumocystosis therapy was initiated.\(^3\)\(^4\)\(^5\) The diagnosis of acute psychosis was based on the diagnostic criteria for ‘substance-induced psychotic disorder’ defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR).\(^6\) The essential features include prominent hallucinations or delusions that are judged to be due to the direct physiological effects of a substance. The disturbance must not be better accounted for by a psychotic disorder that is not substance induced, and the diagnosis is not made if the psychotic symptoms occur only during the course of delirium. The diagnosis was mainly made by the primary physicians, and psychiatric specialist consultation was obtained if deemed necessary depending on the physician’s judgement.

#### Data collection

A standardized, computerized case record form was used to record the patient’s demographics, body weight, body mass index, plasma HIV RNA load, CD4 cell count, antiretroviral agent used, serum creatinine level, serum lactate dehydrogenase (LDH), oxygen saturation and maximal oxygen therapy required, dose of trimethoprim/sulfamethoxazole, use of adjunctive steroids and dose, concurrent or pre-existent illnesses and medications, intensive care unit (ICU) admission and in-hospital mortality. For patients with acute psychosis, we also recorded the onset of symptoms, clinical features, brain imaging or investigations performed on CSF specimens and the management of acute psychosis and clinical response.

#### Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were reported as medians and ranges, and were compared using the Mann–Whitney test. Categorical variables were expressed as numbers and percentages, and were compared using the Pearson \( \chi^2 \) test or Fisher’s exact test, as appropriate. Multivariate logistic regression analysis was used to evaluate the association between each independent variable and risk of acute psychosis. Variables with \( P \) values \(< 0.10 \) in the univariate analyses were entered in a multivariate logistic regression model with the backward elimination method. \( P \) values \(< 0.05 \) were considered statistically significant.

### Results

During the study period, a total of 150 patients were identified as having received trimethoprim/sulfamethoxazole for P. jirovecii pneumonia and 135 patients were included for analysis (Figure 1). Fifteen patients were excluded because of pre-existing psychiatric diseases \((n=1)\), impaired consciousness due to the use of sedative agents \((n=2)\), receipt of trimethoprim/sulfamethoxazole for \(< 3\) days \((n=4)\) or at a daily dose \(< 5 \) mg/kg/day \((n=3)\) and having received trimethoprim/sulfamethoxazole at other hospitals \((n=5)\). The clinical characteristics of these 135 patients are shown in Table 1.

Acute psychosis was diagnosed in 16 patients \((11.9\% ; 95\%\ CI, 6.3\% – 17.4\%\) following the administration of trimethoprim/sulfamethoxazole. The median time of onset was 5\( \) days \((\text{range, 3 – 11 days})\). All patients who developed acute psychosis were receiving a parenteral form of trimethoprim/sulfamethoxazole. Six patients \((37.5\%\) had visual hallucinations, six patients \((37.5\%)\) had visual and auditory hallucinations and two patients \((12.5\%)\) had hallucinations without a specific description in their medical records. The other two patients \((12.5\%)\) presented with agitation and bizarre behaviours such as irrational attempts to remove intravenous catheters.

Seven patients \((43.8\%)\) with acute psychosis underwent lumbar puncture and none had pleocytosis in the CSF specimens. Computed tomography or magnetic resonance imaging of the CNS was performed in six patients \((37.5\%)\), and no identifiable organic brain lesions were detected. Fifteen patients recovered fully from acute psychosis after adjustment of trimethoprim/sulfamethoxazole therapy: trimethoprim/sulfamethoxazole was replaced with primaquine and clindamycin in five patients \((31.3\%)\); four \((25.0\%)\) received reduced doses of trimethoprim/sulfamethoxazole; two \((12.5\%)\) changed from a parenteral to an oral form at the same dose; one \((6.3\%)\) changed from a parenteral to an oral form at a reduced dose; one \((6.3\%)\) switched to trimethoprim only at a reduced dose \((15 \text{ to } 12.5 \text{ mg/kg/day of trimethoprim component})\); and one \((6.3\%)\) received the same dose at a reduced infusion rate. The remaining one patient died on the day that acute psychosis occurred. Seven patients \((43.8\%)\) developed acute psychosis during their stay in ICUs, and in three of these patients the psychotic symptoms resolved with discontinuation of trimethoprim/sulfamethoxazole or change from a parenteral to an oral form.

Comparisons of clinical characteristics of patients with and without acute psychosis are shown in Table 1. There were no statistically significant differences in HIV-related variables \((\text{CD4 cell count, HIV viral load and receipt of cART})\) between the two groups. Variables associated with the development of acute psychosis included a higher daily dose of trimethoprim/sulfamethoxazole \((P=0.003)\), a higher level of serum LDH at
150 patients with P. jirovecii pneumonia screened

15 patients excluded:
1- with pre-existing psychiatric diseases
2- with impaired consciousness
4- receiving trimethoprim/sulfamethoxazole for <3 days
3- with trimethoprim dose <5 mg/kg/day
5- starting anti-pneumocystosis therapy at other hospitals

135 patients included for analysis

Patients with acute psychosis  
\( n = 16 \)

Patients without acute psychosis  
\( n = 119 \)

Figure 1. Study flow.

Table 1. Clinical characteristics of HIV-infected patients receiving trimethoprim/sulfamethoxazole for P. jirovecii pneumonia

<table>
<thead>
<tr>
<th></th>
<th>Acute psychosis, ( n = 16 )</th>
<th>No psychosis, ( n = 119 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, ( n ) (%)</td>
<td>15 (93.8)</td>
<td>117 (98.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age (years), median (range)</td>
<td>35 (25–65)</td>
<td>36 (20–76)</td>
<td>0.73</td>
</tr>
<tr>
<td>Body mass index (kg/m²), median (range) ( \text{patients with available data} )</td>
<td>20.2 (16.0–35.9) (15)</td>
<td>19.8 (14.5–30.8) (116)</td>
<td>0.51</td>
</tr>
<tr>
<td>Impaired renal function at baseline, ( n ) (%)( ^a )</td>
<td>0 (0)</td>
<td>7 (5.9)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>CD4 (cells/µL), median (range)</td>
<td>40.5 (2–173)</td>
<td>38 (1–440)</td>
<td>0.72</td>
</tr>
<tr>
<td>HIV viral load ( \log_{10} ) copies/mL, median (range) ( \text{patients with available data} )</td>
<td>5.6 (4.6–6.2) (15)</td>
<td>5.1 (1.6–7.0) (113)</td>
<td>0.094</td>
</tr>
<tr>
<td>On cART, ( n ) (%)</td>
<td>0 (0)</td>
<td>18 (15.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Trimethoprim dose (mg/kg/day), median (range)</td>
<td>16.6 (13.7–22.2) (15)</td>
<td>14.8 (7.5–21.3) (113)</td>
<td>0.003</td>
</tr>
<tr>
<td>dose &lt;15 mg/kg/day, ( n ) (%)</td>
<td>2 (12.5)</td>
<td>65 (54.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>dose ≥15 mg/kg/day, ( n ) (%)</td>
<td>14 (87.5)</td>
<td>54 (45.4)</td>
<td></td>
</tr>
<tr>
<td>LDH (IU/L), median (range) ( \text{patients with available data} )</td>
<td>989 (337–2851) (12)</td>
<td>681 (190–2409) (68)</td>
<td>0.019</td>
</tr>
<tr>
<td>Adjunctive steroids, ( n ) (%)</td>
<td>13 (81.3)</td>
<td>64 (53.8)</td>
<td>0.037</td>
</tr>
<tr>
<td>Steroid dose (equivalent to prednisone) (mg/day), mean (range)</td>
<td>75 (25–100)</td>
<td>77.5 (15–200)</td>
<td>0.49</td>
</tr>
<tr>
<td>Steroid dose (equivalent to prednisone) &gt;40 mg/day, ( n ) (%)</td>
<td>9 (56.3)</td>
<td>50 (42.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hyponatraemia (serum sodium level &lt;135 mmol/L), ( n ) (%) ( \text{patients with available data} )</td>
<td>12 (75.0) (16)</td>
<td>74 (68.5) (108)</td>
<td>0.77</td>
</tr>
<tr>
<td>Serum sodium level (mmol/L), mean (range) ( \text{patients with available data} )</td>
<td>133 (126–140) (15)</td>
<td>130 (109–142) (68)</td>
<td>0.28</td>
</tr>
<tr>
<td>Decrease in serum sodium of ≥5 mmol/L, ( n ) (%) ( \text{patients with available data} )</td>
<td>4 (30.8) (13)</td>
<td>25 (43.9) (57)</td>
<td>0.58</td>
</tr>
<tr>
<td>( O_2 ) therapy &gt;FiO2 60%, ( n ) (%) ( \text{patients with available data} )</td>
<td>9 (56.3) (16)</td>
<td>22 (30.6) (72)</td>
<td>0.052</td>
</tr>
<tr>
<td>ICU admission, ( n ) (%)</td>
<td>7 (43.8)</td>
<td>20 (16.8)</td>
<td>0.019</td>
</tr>
<tr>
<td>In-hospital mortality, ( n ) (%)</td>
<td>3 (18.8)</td>
<td>16 (13.4)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

\( \text{FiO}_2 \), fractional inspiratory oxygen pressure.

\( ^a \)Defined as an estimated glomerular filtration rate by the Cockcroft–Gault equation <60 mL/min/1.73 m² at baseline.

Baseline \( (P=0.019) \), use of adjunctive steroids \( (P=0.037) \) and ICU admission \( (P=0.019) \). Most patients developing acute psychosis had hyponatraemia (i.e. serum sodium levels <135 mmol/L), though the majority of them had serum sodium levels between 125 and 134 mmol/L and only one had a sodium level of 123 mmol/L (data not shown). In addition, there was no difference in the proportion of patients with a decline of serum sodium levels of ≥5 mmol/L during the treatment between patients with and without acute psychosis. The incidence of acute psychosis increased with the daily dose of trimethoprim/sulfamethoxazole, from 0% (0/16) in patients receiving a daily trimethoprim dose of ≤12 mg/kg to 23.5% (4/17) in those receiving a daily dose of >18 mg/kg (Figure 2). In multivariate logistic regression analysis (Table 2), a higher daily dose of trimethoprim/sulfamethoxazole...
sulfamethoxazole (OR, per 1 mg increase, 1.40; 95% CI, 1.12–1.76; P=0.0035) and use of adjunctive steroids (OR, 4.43; 95% CI, 1.14–17.15; P=0.031) were found to be independent factors associated with acute psychosis.

**Discussion**

There are only nine cases of acute psychosis in the English literature reportedly related to the use of trimethoprim/sulfamethoxazole; however, in this case series of HIV-infected patients receiving trimethoprim/sulfamethoxazole for *P. jiroveci* pneumonia, we found that 11.9% of patients developed acute psychosis and the incidence significantly increased with increasing daily dose of trimethoprim/sulfamethoxazole and the use of adjunctive steroids.

The incidence of acute psychosis observed in this study is surprisingly high compared with the incidences reported in previous clinical trials of trimethoprim/sulfamethoxazole treatment for *P. jiroveci* pneumonia. In previous clinical trials, the incidence of any kind of neurological or psychological adverse effects, including hallucinations, altered mental status, delirium or confusion, ranged from 0% to 7.1%. The incidence of acute psychosis related to trimethoprim/sulfamethoxazole in HIV-infected patients is often difficult to estimate because of several other competing causes of psychosis, such as underlying...
Acute psychosis and trimethoprim/sulfamethoxazole

psychiatric illness, concurrent medications, hyponatraemia, use of steroids, critical illness and ICU admission. In this study we excluded patients with underlying psychiatric illness and impaired consciousness due to the use of sedative agents that are not uncommonly used in critically ill patients.

Hyponatraemia, which may contribute to disturbances in consciousness, is commonly seen in patients with AIDS. In our study, the frequency of hyponatraemia was similar between the patients with and without acute psychosis, and most patients developing acute psychosis had a serum sodium level between 125 and 134 mmol/L. Psychiatric adverse effects during treatment with systemic corticosteroids are common, and include anxiety symptoms, behavioural disturbances and psychotic features. The dose of corticosteroids is the most important risk factor, as shown in the study by the Boston Collaborative Drug Surveillance Program, in which the incidence of psychiatric disturbances increased in patients receiving higher doses of prednisone (1.3% in patients receiving ≤40 mg/day compared with 18.4% in those receiving >80 mg/day).  In this study we found that the use of adjunctive steroids was statistically significant associated with the development of acute psychosis. However, limited by the sample size, we were not able to demonstrate the dose–response association between the incidence of acute psychosis and the doses of corticosteroids (Table 1).

Delirium, defined as an acute and fluctuating disturbance of consciousness and cognition, is a common manifestation of acute brain dysfunction in critically ill patients, occurring in up to 80% of the most ill ICU populations. Hyperactive delirium, in the past referred to as ‘ICU psychosis’, is one of the subtypes and is characterized by agitation, restlessness, attempts to remove catheters and emotional lability. In this study, ICU admission was not an independent factor associated with the development of acute psychosis in the multivariate logistic regression model. In seven patients (43.8%) who developed acute psychosis during their stay in ICUs, three patients had resolution of psychotic symptoms after discontinuation or after changing to an oral form of trimethoprim/sulfamethoxazole.

In the multivariate logistic regression analysis, the risk of development of acute psychosis increased by 40% for every 1 mg/kg increase in daily dose of trimethoprim. About one-fifth of the patients developed psychosis when receiving a daily dose of >15 mg/kg of the trimethoprim component, the recommended dose for P. jirovecii pneumonia (15–20 mg/kg/day of trimethoprim component) by current guidelines. However, this recommendation has been extrapolated from data obtained from paediatric patients. Several studies have suggested that excessive, toxic concentrations of trimethoprim and sulfamethoxazole and intolerable adverse effects occurred when the recommended doses were prescribed in healthy subjects or HIV-infected patients. Given these findings, more studies are warranted to assess whether a reduced dose of trimethoprim/sulfamethoxazole is both safe and effective for treating P. jirovecii pneumonia in HIV-infected patients.

There are several limitations in our study. First, the medical records were reviewed retrospectively, and therefore detailed clinical data and the description of psychotic symptoms may not have been complete in some patients. Furthermore, the diagnoses of trimethoprim/sulfamethoxazole-related psychosis were determined by healthcare providers rather than confirmed by psychiatric specialists in most of these patients, and the patients were managed differently by their primary physicians. As a result, further prospective studies are warranted to ascertain a more accurate incidence of this adverse effect. Second, measurements of serum concentrations of trimethoprim/sulfamethoxazole were lacking in these patients, and wide inter-patient variability in trimethoprim/sulfamethoxazole pharmacokinetics has been observed in HIV-infected patients by Chin et al.

In conclusion, 11.9% of HIV-infected patients developed acute psychosis while receiving trimethoprim/sulfamethoxazole for P. jirovecii pneumonia in this case series. While the study was limited by its retrospective design, the risk appeared to increase with increasing daily dose of trimethoprim/sulfamethoxazole in those vulnerable patients with multiple risks of acute psychosis.

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Transparency declarations
None to declare.

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