

*J Antimicrob Chemother* 2012
doi:10.1093/jac/dks008
Advance Access publication 27 January 2012

The combination of chloroquine and minocycline, a therapeutic option in cerebrospinal infection of Whipple’s disease refractory to treatment with ceftriaxone, meropenem and co-trimoxazole

Gerhard E. Feurle1*, Verena Moos2, Thomas Schneider2, Florence Fenollar3 and Didier Raoult3

1 DRK Krankenhaus Neuwied, Neuwied, Germany; 2 Medizinische Klinik I, Charité-Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany; 3 Unité de Rickettsies, Faculté de Médecine, Université de la Méditerranée, Marseille, France

*Corresponding author. Tel: +49-2631-981401; Fax: +49-2631-981492; E-mail: g.e.feurle@t-online.de

**Keywords:** *Tropheryma whipplei*, *T. whipplei*, cerebral Whipple’s disease

Sir,

Whipple’s disease is a chronic infection caused by *Tropheryma whipplei*. In a prospective study, the CNS was found to be involved in 38.5% of the cases. Treatment is not always successful. Co-trimoxazole (trimethoprim/sulfamethoxazole) has been reported to be significantly more effective than tetracycline; however, resistance to co-trimoxazole has also been observed. More recently, there have been reports describing resistance of CNS infections to treatment with ceftriaxone, a bactericidal antibiotic penetrating the blood–brain barrier.

In 2002, a patient presented with diarrhoea, weight loss to 64 kg, anaemia (8.4 g/dL haemoglobin) and erythrocyte sedimentation rate of 33 mm/h. The medical history revealed relapsing arthritis since 1991 and pericarditis necessitating pericardial resection in 1993. Gastrointestinal biopsies disclosed periodic acid–Schiff (PAS)-positive macrophages typical of untreated Whipple’s disease in the mucosa of the duodenum and the ileum and in the submucosa of the colon. The patient had no cerebral symptoms. However, microscopic examination of centrifuged CSF obtained by spinal puncture showed a PAS-positive macrophage typical of Whipple’s disease (histopathology carried out by Dr Reinhard Golz, Wuppertal), and the PCR to *T. whipplei* in the CSF was positive. The patient was admitted to a prospective treatment trial, as reported in Feurle et al. He was randomized to 2 g of ceftriaxone infused intravenously once daily for 2 weeks, followed by oral co-trimoxazole at a dosage of 160/300 mg twice daily for 12 months. While the patient recovered from all signs and symptoms of Whipple’s disease, the PCR for *T. whipplei* remained positive in the CSF for 5.5 years despite additional treatment with 1 g of meropenem infused intravenously thrice daily for 2 weeks followed by co-trimoxazole for another year. After a further year of co-trimoxazole, the CSF was still positive in the *T. whipplei* PCR, while the patient was receiving this treatment. PAS-positive macrophages in duodenal mucosal biopsies and in the CSF had disappeared. CT and magnetic resonance imaging of the brain did not reveal any structural abnormality. At this time, the patient had no symptoms of systemic or cerebral Whipple’s disease.

The presence of *T. whipplei* in the CSF was confirmed by sequence analysis of the amplification product, and the viability was established by culture in MRC5 fibroblasts and in axenic medium. *In vitro* susceptibility of the cultured strain to ceftriaxone, meropenem, tetracyclines and co-trimoxazole is shown in Table 1. The risk of this patient developing symptomatic cerebral disease seemed unpredictable. After obtaining written informed consent for an individual treatment attempt, this patient was treated with chloroquine and tetracycline, a combination suggested previously. Chloroquine (or hydroxychloroquine) enhances antimicrobial activity of tetracyclines by raising the pH of the phagolysosomes within macrophages.

Minocycline was selected as the tetracycline in this case as this compound has been reported to cross the blood–brain barrier well. Taking advantage of this pharmacokinetic property, we were probably the first to treat a patient with cerebral Whipple’s disease with minocycline. They did not combine it with chloroquine. Others prefer the combination of doxycycline and chloroquine.

In the present study, the dosage of chloroquine, based on a body weight of 83 kg, was 1725 mg of chloroquine phosphate in divided doses orally on day 1, and 575 mg on the second to the fourth day, followed by one 250 mg chloroquine phosphate tablet once daily for 45 days. A serum concentration of 165 µg/L chloroquine (therapeutic range 20 to 200 µg/L) was obtained. Minocycline was given at a dosage of one 100 mg minocycline tablet twice daily for 45 days. This dosage had to be reduced to 100 mg daily from day 5 to day 8 because of vertigo. Vestibular toxicity manifesting as dizziness, ataxia and nausea is a

---

### Table 1. *In vitro* antimicrobial susceptibility of the cultured *T. whipplei* strain, assessed by methods reported previously

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>axenic medium</th>
<th>MRC5 fibroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Minocycline</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.06</td>
<td>5</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

---

1295
common side effect of this tetracycline.\textsuperscript{12} The plasma concentration of minocycline, determined by HPLC, was 2.1 mg/L.

The serum and respective plasma concentrations were determined 5 weeks after onset of treatment and 14 h after the last medication.

The PCR for \textit{T. whippelii} in the CSF was negative, both 12 and 24 months later. The patient has been asymptomatic now for more than 9 years after the initial examination and treatment.

Obviously, this new treatment option, found to be efficacious in a single patient, should be evaluated in a prospective trial. The regimen is attractive as the combination of minocycline and chloroquine can be given orally. However, vestibular side effects (occurring in \textgreater 70\% of women taking 100 mg of minocycline every 12 h)\textsuperscript{13} will render any study difficult. Our male patient had to reduce the dose of minocycline for several days.

The observation in this patient indicates that host factors and not necessarily \textit{in vitro} antimicrobial susceptibilities may determine success or failure of antimicrobial treatment in cerebrospinal infection of Whipple's disease. The host factors in this patient are unknown.

Our experience may be useful for other cases of refractory cerebrospinal infection with \textit{T. whippelii}.

**Acknowledgements**

The plasma concentration of minocycline was kindly determined by C. Dilger (AAI Pharma Deutschland GmbH, Ulm, Germany). The serum concentration of chloroquine was kindly determined by the MVZ für Laboratoriumsmedizin Koblenz-Mittelrhein.

**Funding**

Funded by the 5th Framework Program of the European Commission.

**Transparency declarations**

No financial conflicts to declare.

**References**

1. Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology 2010; 138: 478–86.
Advance Access publication 25 January 2012

**Acute necrotizing pancreatitis related to tigecycline**

Marta Mascarello\textsuperscript{1,*}, Giovanni Papa\textsuperscript{2}, Zoran Marij Arne\v{z}\textsuperscript{2} and Roberto Luzzati\textsuperscript{1}

\textsuperscript{1}Infectious Diseases Unit, University Hospital of Trieste, Trieste, Italy; \textsuperscript{2}Department of Plastic and Reconstructive Surgery, University Hospital of Trieste, Trieste, Italy

*Corresponding author. Tel: +39-040-399-2594; Fax: +39-040-399-2652; E-mail: martamasc@ yahoo.it

**Keywords:** adverse reactions, propofol, multidrug-resistant bacteria

Sir,

Because we are confronted with the increasing use of tigecycline for the treatment of infections due to multidrug-resistant bacteria, it is important to note that two recent meta-analyses raise concerns about the efficacy and safety of therapy with this antibiotic. A higher overall mortality and a higher incidence of adverse effects, especially nausea and vomiting, have been observed with tigecycline compared with other regimens.\textsuperscript{1,2}

Tigecycline-induced acute pancreatitis is considered an uncommon event, with an estimated incidence between 1\% and 1\%. The mechanism remains unknown.\textsuperscript{3} Five cases of interstitial or oedematous pancreatitis have been reported, all of which occurred during the second week of therapy in patients without other risk factors for pancreatitis. None of the patients required intensive care.\textsuperscript{3,6} To our knowledge, we report on the first case of acute necrotizing pancreatitis related to tigecycline. A young paraplegic patient was admitted to the infectious diseases unit for a chronic osteomyelitis of the right ischio-pubic bone associated with an infected right