MIC and MBC of 0.03%. *S. equi, S. equisimilis* and the Lancefield’s group G streptococcus had an MIC and MBC of 0.12%. The MIC for *S. zooepidemicus* was 0.06% while the MBC was 0.12%.

Several reports on the in-vitro susceptibility of bacteria and fungi to tea tree oil have been published in recent years (Altman, 1988; Carson et al., 1995a,b). However, none has given data on the susceptibility of *S. pyogenes* to tea tree oil except for Altman’s reported MICCs of about 1% (v/v). The MICo of 0.12% demonstrated in our study suggests that tea tree oil may be effective against streptococci when used topically as a wound disinfectant.

Although systemic treatment is usually indicated for impetigo, topical treatment may also be of value (Barnett & Frieden, 1992; Shriner et al., 1995). Mupirocin has been used successfully for this problem and offers the advantage that it is effective against both *S. aureus* and *S. pyogenes* (Barnett & Frieden, 1992). However, the development of mupirocin-resistant *S. aureus* poses a problem (Riley et al., 1994). Tea tree oil has already demonstrated antibacterial activity against *S. aureus*, MRSA and mupirocin-resistant *S. aureus* (Carson et al., 1995a,b) and development of resistance to the oil has not been observed. Given that tea tree oil exhibits antibacterial activity against both of the organisms in impetigo, it may prove useful in topical treatment. Careful product formulation and clinical trials are now required to evaluate the potential of this natural product.

**References**


**Anaerobic activity of levofloxacin and metronidazole separately and in combination**


Sir,

The fluoroquinolone, levofloxacin, has a broad spectrum of antibacterial activity against aerobic and facultatively anaerobic microorganisms (Une et al., 1988; Fu et al., 1992; Pfaller, Barry & Fuchs, 1993) and it has moderate activity against some anaerobic bacteria (Marshall & Jones, 1993). The variety of microorganisms that are associated with intra-abdominal infections or pelvic inflammatory disease should be susceptible to levofloxacin and a second agent that is more active against the anaerobes, e.g. metronidazole. Clinical studies to evaluate such combined therapy are being considered. We first carried out in-vitro studies to determine whether there may be some unexpected antagonism or synergism against commonly encountered anaerobic bacteria.

Microdilution susceptibility tests were performed with a broth version of Wilkins-Chalgren medium without added blood or blood products. The inocula were $8 \times 10^5$ to $8 \times 10^6$ cfu/mL and MICs were recorded after 48 h at 35°C in anaerobic jars. The test panels contained serial dilutions of levofloxacin (0.06–64 mg/L) and metronidazole (0.12–8.0 mg/L) separately and combined in a checkerboard fashion. Fractional Inhibitory Concentrations (FICs) were calculated for different drug combinations. Synergy was defined as an FIC $\leq 0.5$ and combinations with FIC > 4.0 were deemed antagonistic (Eliopoulos & Moellering, 1991). Bactericidal endpoints were also determined with 50 selected isolates. After MICs were recorded, the trays were shaken and two 10 μL samples were removed from each well with no visible turbidity. The samples were transferred to blood agar plates and the number of viable cells was determined. The MBCs were defined...
Table. In-vitro activity of anaerobic bacteria to levofloxacin and metronidazole

<table>
<thead>
<tr>
<th>Species (no. tested)</th>
<th>MIC (mg/L) geometric mean (range)</th>
<th>Levofloxacin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteroides fragilis</em> (50)</td>
<td>1.92 (1.0–32)</td>
<td>0.90 (0.25–2.0)</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides thetaiotaomicron</em> (52)</td>
<td>6.46 (4.0–64)</td>
<td>0.91 (0.25–2.0)</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides distasonis</em> (20)</td>
<td>1.57 (0.5–8.0)</td>
<td>0.89 (0.25–2.0)</td>
<td></td>
</tr>
<tr>
<td><em>B. ovatus</em> (20)</td>
<td>10.9 (4.0–&gt;64)*</td>
<td>0.93 (0.5–1.0)</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides vulgatus</em> (20)</td>
<td>1.37 (0.5–8.0)</td>
<td>0.61 (0.12–2.0)</td>
<td></td>
</tr>
<tr>
<td><em>P. bivia</em> (14)</td>
<td>2.10 (1.0–4.0)</td>
<td>1.48 (0.12–4.0)</td>
<td></td>
</tr>
<tr>
<td><em>Closstridium</em> spp. (21)*</td>
<td>0.93 (0.12–8.0)</td>
<td>0.84 (0.12–4.0)</td>
<td></td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> spp. (21)</td>
<td>0.88 (0.25–8.0)</td>
<td>0.50 (0.12–2.0)</td>
<td></td>
</tr>
</tbody>
</table>

*For calculating geometric means, two (2) MICs that were ≥ 64 mg/L were assumed to be 128 mg/L.
*Includes 9 *Closstridium perfringens*, 5 *Closstridium difficile*, 3 *Closstridium bifermentans*, 2 *Closstridium ramosus* and 2 *Closstridium sporogenes*.

as the lowest concentration killing at least 99.9% of the cells in the initial inoculum. Accepting a 5% sampling error, rejection values of Pearson et al. (1980) were used to calculate MBCs, and Fractional Bactericidal Concentrations (FBCs) were calculated and interpreted as for FICs.

The species of anaerobic bacteria that were studied are listed in the Table. As expected, all 218 strains were susceptible to metronidazole (MIC 0.12-4.0 mg/L) and 56% were susceptible to levofloxacin (MIC ≤ 2.0 mg/L). Only two strains (*Bacteroides ovatus*) required levofloxacin MICs > 64 mg/L. The *Bacteroides* species included approximately equal numbers of cefoxitin-susceptible and -resistant strains. Cefoxitin-resistance did not affect the activity of either study drug. With one exception, the two drugs were only additive or indifferent. The one exception involved a *Peptostreptococcus* sp. with a synergistic FIC of 0.49 which was confirmed when retested. For one strain of *Prevotella bivia*, the metronidazole MIC was 1.0 mg/L and the MBC was 8.0 mg/L (eight-fold difference). The 49 other strains were bactericidal at a concentration no more than two times the MIC. Analysis of FBCs revealed no evidence of antagonism or synergy.

In summary, a broad spectrum of antibacterial activity should be expected when levofloxacin and metronidazole are used at the same time. The absence of antagonistic interactions is encouraging and cautious entry into clinical studies seems appropriate. Other fluoroquinolones might also be considered for this type of combination therapy.

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**References**


Nephrogenic diabetes insipidus associated with foscarnet— a case report

**J Antimicrob Chemother** 1996; 37: 1180–1181

**Sir,**

Nephrogenic diabetes insipidus (NDI) is caused by the partial or complete resistance of...