Antimicrobial activity data in support of nitrofurantoin three times per day

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Sir,

The treatment of urinary tract infections (UTIs) is increasingly difficult due to the rising resistance of uropathogens towards commonly used antimicrobials, such as sulphonamides, quinolones and even third-generation cephalosporins. Nitrofurantoin, a useful agent against non-complicated cystitis, faces very low resistance prevalence, even in countries where resistance to other drugs is rather high. This seems to be the consequence of the fitness cost associated with nitrofurantoin resistance. However, the use of nitrofurantoin is often hindered by the need for four doses per day, according to most guidelines (a modified-release formulation is available in some countries, allowing just two doses per day, but it can only be used by adults). Should this treatment regimen be reduced to three doses per day, adherence to treatment should improve, making nitrofurantoin an acceptable option for more patients and physicians, and reducing the usage of wider-spectrum drugs, which is fostering resistance. We reviewed the available pharmacokinetic information on nitrofurantoin and re-assessed some antimicrobial activity parameters, leading us to conclude that nitrofurantoin three times per day could be as effective as four times per day in the treatment of UTIs.

Urinary concentrations of nitrofurantoin when it is given three times per day, assessed for the lowest recommended dose (100 mg every 8 h, for women averaging 63 kg in weight, i.e. 5 mg/kg/day), have been published before. When administered every 8 h, nitrofurantoin concentration in urine was below the reported MIC for 90% of isolates (MIC90) for uropathogenic Escherichia coli (UPEC) of 16 mg/L for ~3 h before the second dose, while urine concentration was always above the assumed MIC90 when nitrofurantoin was administered every 6 h. We determined the MICs for 100 nitrofurantoin-susceptible UPEC isolates by serial microdilution in liquid medium (Mueller–Hinton broth (Fluka), using nitrofurantoin from Sigma), which were all in the range of 4–16 mg/L. However, the routine serial dilution procedure for MIC determination can hide subtle differences; when assessing the MIC in one-by-one mg/L concentration series for the 8–16 mg/L range, the maximum MIC value observed was 13 mg/L. By using this new MIC value, the time period for which urinary concentrations are below the MIC would shorten, and it would shorten further if using the highest recommended dose of 7 mg/kg/day for children (~140 mg three times per day for adults).

To further explore the potential clinical relevance of the under-the-MIC window of urinary concentration, we measured the post-antibiotic effect of nitrofurantoin upon Es. coli ATCC 25922. Exponential-phase cultures in Mueller–Hinton broth were diluted to \( \approx 1 \times 10^6 \) cfu/mL and exposed to 50, 100 or 200 mg/L nitrofurantoin for 30 min at 35°C; cells were pelleted, washed twice and resuspended in fresh Mueller–Hinton broth and further incubated at 35°C. We counted cfu initially, and turbidity was measured every 30 min at 600 nm. Bacterial count was not affected by this brief exposure (which was expected for an agent usually considered to be bacteriostatic), but growth was arrested for at least 2 h after a 100 or 200 mg/L exposure and 1.5 h after a 50 mg/L exposure.

Taken together, these data indicate that nitrofurantoin three times per day, either in adults where the twice daily formulation is not available, or in children, could be effective in the management of UTIs, increasing adherence to nitrofurantoin treatment and sparing the use of other antibiotics. A clinical trial to test the efficacy of nitrofurantoin three times per day against uncomplicated cystitis is warranted.

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Transparency declarations

None to declare.
Levofloxacin weight-adjusted dosing and pharmacokinetic disposition in a morbidly obese patient

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Sir,

Obese patients may show differences in several pharmacokinetic parameters of many commonly used antimicrobials,1 and they often require a correction of the recommended dosages for non-obese subjects. Unfortunately, studies evaluating antimicrobial dosages in obese patients are limited and only a few are focused on patients with morbid obesity. Among fluoroquinolones, dosage recommendations are available only for ciprofloxacin, but data from these studies are contradictory.2,3 Levofloxacin is increasingly recommended in clinical guidelines for the treatment of respiratory infections, including pneumonia,4 and the lack of studies evaluating its plasma concentrations in obese patients can potentially result in treatment failures in this population. We have had the opportunity to study the basic pharmacokinetic/pharmacodynamic parameters of levofloxacin in a patient with severe morbid obesity.

A patient in their mid-50s with severe morbid obesity (weight, 179 kg; height, 1.74 m; and body mass index, 56.2 kg/m²), chronic obstructive pulmonary disease and sleep apnoea–hypopnoea syndrome treated with nasal continuous positive airway pressure (CPAP) was admitted to an emergency department. The patient presented with an acute hypercapnic respiratory failure secondary to a lower respiratory tract infection and cocaine abuse. On admission, the chest X-ray did not show opacities. Blood test results were: serum creatinine, 73.37 μmol/L; creatinine clearance, 78 mL/min; leucocyte count, 6990/mm³ (75.4% neutrophils); and C-reactive protein, 3.2 mg/L. The values of arterial blood gases drawn on room air were: pH, 7.21; PaCO₂, 80 mmHg; and PaO₂, 28 mmHg. Non-invasive mechanical ventilation was immediately initiated and administered for 20 h, followed by nocturnal CPAP in addition to oxygen and standard medical treatment. Sputum cultures yielded Streptococcus pneumoniae susceptible to levofloxacin (MIC = 1 μg/L).

An actual body weight-adjusted levofloxacin dose of 4 mg/kg/12 h (750 mg/12 h) infused intravenously over 1 h was started (this dose was calculated according to a ciprofloxacin dosing recommendation in obese individuals5). On day 3 of levofloxacin treatment, when presumably steady state had been achieved (levofloxacin elimination half-life = 6–8 h), serum concentrations were obtained. Serial blood samples were drawn 0, 1.5, 3, 4, 5, 8 and 12 h after the start of the infusion. The calculated pharmacokinetic parameters are detailed in Table 1.

Table 1. Pharmacokinetic parameters of levofloxacin in the patient

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>8.68</td>
</tr>
<tr>
<td>Ctrough (mg/L)</td>
<td>4.64</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.5</td>
</tr>
<tr>
<td>AUC0–12 h (mg.h/L)</td>
<td>71.6</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>10.47</td>
</tr>
<tr>
<td>t1/2β (h)</td>
<td>16.15</td>
</tr>
<tr>
<td>Vss (L)</td>
<td>243.9</td>
</tr>
<tr>
<td>Vss (L/kg TBW)</td>
<td>1.34</td>
</tr>
</tbody>
</table>

Cmax, peak plasma concentration; Ctrough, plasma concentration at 12 h; Tmax, time to reach Cmax; AUC0–12 h, area under plasma concentration-time curve from zero to 12 h; CL, total body clearance; t1/2β, half-life; Vss, steady-state volume of distribution; TBW, total body weight.