Hinton broth following the standard ISO method 20776-1:2006, and these results were considered the reference standard against which all other results were compared. Temocillin Etests were used according to the manufacturer’s instructions. Susceptibility to temocillin using the Phoenix system was determined according to BSAC breakpoints for Enterobacteriaceae for systemic infections (susceptible if MIC ≤8 mg/L). ³ 

If the Etest or Phoenix results were within a 2-fold dilution of the BMD MIC for an isolate, the methods were deemed as being in agreement. Unless the Phoenix result advised a retest, e.g. due to insufficient growth, the first test results were used for the evaluation and comparison of the different antimicrobial susceptibility testing (AST) methods. Disagreements between BMD and the Etest or Phoenix methods were then subjected to further investigation by repeating the Phoenix test in duplicate.

Etest MICs showed good correlation with those obtained by BMD—they were within one doubling dilution in 93.6% of isolates.

Overall, there appeared to be discrepant results between the Phoenix system and one of the alternative susceptibility methods for 102 isolates (97 deemed intermediate by Phoenix and 5 deemed resistant) and a discrepancy between Phoenix and both other methods in 93. Therefore, Phoenix AST was repeated, in duplicate, for the 102 isolates to confirm or refute the original Phoenix result.

Of these 102 isolates, the second and third Phoenix AST results were consistent with the original result for 88 (86.3%). However, for 17 (16.7%) samples, the initial Phoenix AST result was not consistent between runs—these results were therefore excluded from our analysis.

Of the 264 remaining isolates, 246 were proven to be susceptible using BMD (MIC ≤8 mg/L) and concordant results were found by Etest in 236 (95.9%). However, the Phoenix system declared only 162 (65.9%) susceptible. Seventeen isolates were ‘susceptible only for UTI’ (MIC >8 to ≤32 mg/L) by BMD and 26 by Etest. In comparison, far more were categorized as ‘susceptible only for UTI’ by Phoenix—96. Only one isolate was found to be resistant (MIC >32 mg/L) by the reference method, and two by Etest, whereas six were declared resistant by the Phoenix method. Table 1 summarizes the results for temocillin susceptibility for all three methods.

In conclusion, this study indicates that ‘susceptible’ results produced by the Phoenix system, using the NMIC-84 card according to the manufacturer’s recommendations, are reliable. However, the majority of isolates found to be ‘susceptible only for UTI’ and ‘resistant’ by Phoenix were actually fully susceptible (MIC ≤8 mg/L) as determined by the reference method. We therefore recommend that isolates categorized as such be retested using another method.

Table 1. Summary of temocillin AST results of 264 isolates comparing the BMD, Etest and Phoenix methods (percentages of total shown in brackets for each method)

<table>
<thead>
<tr>
<th></th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>246 (93.2%)</td>
<td>17 (6.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Etest</td>
<td>236 (89.4%)</td>
<td>26 (9.8%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Phoenix</td>
<td>162 (61.4%)</td>
<td>96 (36.4%)</td>
<td>6 (2.3%)</td>
</tr>
</tbody>
</table>

A similar observation has been made with the Vitek 2 system (bioMérieux, Marcy l’Etoile, France), albeit with a lower frequency of error.⁴ The reason for the high level of discrepancy between Phoenix and BMD or Etest remains speculative, but could be due to instability of the temocillin within the Phoenix panels.

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We would like to thank Dr Guzin Surat for her help in the initial work towards this study and Michelle James for her assistance in using the Phoenix system.

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Transparency declarations

None to declare.

References


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Pharmacokinetics of maraviroc administered at 150 mg once daily in association with lopinavir/ritonavir in HIV-positive treatment-naive patients

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Sir,

In recent years there has been increasing interest in nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens as a new potential strategy of anti-HIV therapy. In this context, dual regimens including a boosted protease inhibitor associated with raltegravir or maraviroc have been suggested. VEMAN is an Italian, multicentre, randomized, controlled trial comparing lopinavir/ritonavir (400/100 mg twice daily) plus either tenofovir/emtricitabine or maraviroc (150 mg once daily) in treatment-naive subjects. In this study, the maraviroc-containing arm showed excellent virological (100% of subjects with HIV-RNA \( \leq 50 \) copies/mL) and immunological (T CD4 \( + \) gain of 286 cells/\( \text{mL} \)) efficacy at 48 weeks. Once-daily 150 mg dosing of maraviroc when administered with boosted protease inhibitors was suggested at first by a post hoc analysis of the MOTIVATE study, potentially overcoming the current recommendation (150 mg twice-daily dosing). This reduced dose has been evaluated in pharmacokinetic (PK) studies with boosted atazanavir\(^{4,5}\) and boosted darunavir\(^6\), while data on the combination with lopinavir/ritonavir have not been reported. Therefore our aim was to describe the PK profile of such an association in a substudy of the VEMAN trial.

A subset of patients in the lopinavir/ritonavir plus maraviroc arm of the VEMAN study was included in a pharmacological analysis. After written informed consent was obtained, blood plasma samples were collected (at week 4) at selected timepoints (pre-dose and 1.5, 3, 4.5, 6, 8, 12 and 24 h after last maraviroc dose intake). This protocol was approved by the local Ethics Committee. Maraviroc concentrations were measured through a validated HPLC-UV method (limit of detection and limit of quantification of 5 and 19.5 ng/mL, respectively), while lopinavir and ritonavir concentrations were measured through an HPLC method coupled with mass spectrometry (HPLC/MS-MS; limits of detection/quantification for lopinavir and ritonavir of 29.3/58.6 ng/mL and 4.9/9.8 ng/mL, respectively). Based on individual concentration–time data, PK parameters were calculated by non-compartmental analyses: average concentration (\( C_{\text{ave}} \)) is the AUC over time ratio. Results are expressed as medians (IQRs).

Ten male Caucasian patients were enrolled; age, weight and body mass index were 37 years (35–44 years), 70 kg (67–97 kg) and 24 kg/m\(^2\) (22.2–28.5 kg/m\(^2\)), respectively. At baseline HIV-RNA and CD4 cell count were 4.38 log 10 copies/mL (4.1–4.8 log 10 copies/mL) and 273 cells/\( \text{mL} \) (250–359 cells/\( \text{mL} \)), respectively. Maraviroc PK parameters are shown in Figure 1 and displayed in the included table. All patients showed a maraviroc average concentration \( > 75 \) ng/mL, while 9 of 10 patients presented a minimal concentration \( \geq 25 \) ng/mL. Lopinavir AUC, \( C_{\text{max}} \), \( C_{\text{ave}} \), half-life, clearance and volume of distribution were 90621 ng/mL h (62629–109064 ng/mL h), 11054 ng/mL (7438–13386 ng/mL), 2544 ng/mL (1812–4872 ng/mL), 6.8 h (5.5–10.7 h), 4.41 L/h (3.66–6.44 L/h) and 50.4 L (40.4–84.9 L), respectively. Ritonavir AUC, \( C_{\text{max}} \), \( C_{\text{ave}} \), half-life and volume of distribution were 5426 ng/mL h (3333–6885 ng/mL h), 849 ng/mL (444–1265 ng/mL), 115 ng/mL (84–146 ng/mL), 4.5 h (3.4–4.6 h), 18.7 L/h (14.5–30 L/h) and 14.3 L (10.9–25.4 L), respectively.

<table>
<thead>
<tr>
<th></th>
<th>( \text{AUC}_{0-24} ) (ng/mL h)</th>
<th>( C_{\text{max}} ) (ng/mL)</th>
<th>( C_{\text{ave}} ) (ng/mL)</th>
<th>( T_{\text{max}} ) (h)</th>
<th>Half-life (h)</th>
<th>Clearance (L/h)</th>
<th>( V ) (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>(3923–5516)</td>
<td>(491–689)</td>
<td>(39–64)</td>
<td>(159–221)</td>
<td>(1.3–3)</td>
<td>(27.3–38.2)</td>
<td>(284–632)</td>
</tr>
</tbody>
</table>

Figure 1. Maraviroc (MVC) plasma PK profile over time. The table underneath details the drug parameters over 24 h. Values are expressed as medians (IQRs).
This is the first report of maraviroc plasma concentrations when the drug is given as 150 mg once daily with lopinavir/ritonavir. It is noteworthy that the current recommended minimum effective values of the trough concentration (50 ng/mL) and average concentration (100 ng/mL) were derived from a sub-study of the MOTIVATE trial, where patients were administered 150 mg of maraviroc once daily or twice daily; these cut-off values are most likely applicable to multi-experienced subjects. A subsequent analysis of the MERIT trial, in fact, showed lower pharmacological requirements in treatment-naive patients. All patients in our study were treatment naive and showed average concentrations >75 ng/mL for near maximal virological efficacy according to exposure–response analysis of the MERIT study. Furthermore, the post hoc analysis of the MOTIVATE trial did not confirm the relationship between the efficacy and plasma concentration of maraviroc administered with protease inhibitors, further supporting the evaluation of maraviroc at reduced dosing when associated with the latter. Interestingly, maraviroc exposure in our patients is comparable to the PK of the same dose in association with atazanavir/ritonavir (AUC 4330 ng·h/mL and C_{ave} 180 ng/mL) and darunavir/ritonavir (C_{ave} 43 ng/mL). Moreover, lopinavir and ritonavir exposure did not seem to be affected by the coadministration of maraviroc, as all PK parameters were comparable to what was previously reported.

In conclusion, our study suggests that once-daily 150 mg dosing of maraviroc appears to be pharmacologically adequate in association with lopinavir/ritonavir in treatment-naive subjects. The potential impact in terms of regimen simplification and cost savings, coupled with the promising immunovirological results of the VEMAN study, deserves further clinical evaluation.

Acknowledgements
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Successful use of fidaxomicin in recurrent Clostridium difficile infection in a child

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Sir, Clostridium difficile infection (CDI) is a disease with an increasing incidence in the paediatric population, increasing from 7.24 to 12.80/10000 hospitalizations from 1997 to 2006 in the USA.1 The explanation for this increase has not yet been determined,