Amiodarone increases positive-strand RNA virus replication in vitro: implications for its use in patients with viral infections

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Sir,

Amiodarone, a cationic amphiphilic drug, is a widely used antiarrhythmic agent endowed with anti-infective properties.¹ Recently, at concentrations close to serum levels reached in patients, it has been shown to inhibit Ebola virus infection in vitro by interfering with the viral entry step.²,³ Amiodarone accumulates in cell membranes and acidic organelles, inducing changes that recapitulate the phenotype observed in Niemann–Pick type C disease.¹ Interestingly, the inhibitory effect of amiodarone on Ebola virus infection appears to correlate with its ability to induce a Niemann–Pick C-like phenotype.³ To counteract the 2014 outbreak of Ebola virus disease (EVD) in West Africa, the WHO Ebola Response Roadmap focused on ‘accelerated development and clinical evaluation of promising experimental interventions’.¹ In this context, several clinical trials were announced by the end of 2014, among which one aimed to investigate the effect of amiodarone in patients with EVD.⁴ To clarify amiodarone antiviral properties, we studied its effect on infections due to Crimean–Congo haemorrhagic fever virus, an enveloped negative-stranded RNA virus, dengue virus serotype 4 (DENV4), an enveloped positive-stranded RNA virus and enterovirus 8362 (EV8362), a naked positive-stranded RNA virus. The effect on viral release was investigated using the same experimental setting previously employed for Ebola virus.³ Vero cells, pretreated for 16 h with 5 and 10 µM amiodarone, were infected with the different viruses at the appropriate moi, cultured in the presence of amiodarone for 24–48 h and viral progeny was estimated by viral titration.³ –⁵ As reported in Table 1, in the case of Crimean–Congo haemorrhagic fever virus we observed a mild effect on viral titre, thus supporting the specificity of amiodarone activity towards Ebola virus. On the other hand, DENV4 viral progeny was slightly increased by amiodarone treatment, independent of the concentration employed. However, the value was not statistically significant. By contrast, more than a 1 log increase in infectious particle production was detected in present in the absence of amiodarone pretreatment (data not shown). It has been demonstrated that autophagy modulates the replication of RNA viruses⁶ and enterovirus 71-induced autophagy increases viral replication and pathogenesis.⁷ Thus, the increased replication of EV8362 could be explained by the amiodarone-induced autophagy.¹,⁸ Although additional studies in vitro and in vivo on the effects of amiodarone on enterovirus and other positive-stranded RNA viruses are required, the possibility of enterovirus coinfection in patients with EVD should be taken into account in clinical trials involving amiodarone. Furthermore, infection with enterovirus should also be considered in the vast cohort of patients treated with amiodarone for cardiac arrhythmias. Finally, it appears that cationic amphiphilic drugs, in general, should be studied for possible interference with the life cycle of clinically important positive-stranded RNA viruses.

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Transparency declarations
None to declare.

References

Table 1. Amiodarone differentially affects viral progeny release of negative-strand and positive-strand RNA viruses

<table>
<thead>
<tr>
<th>Amiodarone (µM)</th>
<th>CCHFV (focus-forming units/mL)</th>
<th>DENV4 (pfu/mL)</th>
<th>EV8362 (pfu/mL)</th>
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<tbody>
<tr>
<td>0</td>
<td>6.0×10⁸</td>
<td>3.8×10⁶</td>
<td>1.3×10⁶</td>
</tr>
<tr>
<td>5</td>
<td>7.4×10⁸</td>
<td>6.0×10⁵</td>
<td>2.3×10⁶</td>
</tr>
<tr>
<td>10</td>
<td>3.5×10⁸</td>
<td>6.6×10⁵</td>
<td>2.7×10⁶</td>
</tr>
</tbody>
</table>

CCHFV, Crimean–Congo haemorrhagic fever virus; pfu, plaque-forming unit. Values represent the mean of two replicates of a representative experiment performed for each virus. The experiments were performed at least three times for each virus.
Dolutegravir-induced colitis in an HIV-infected patient

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Sir,

Many of the gastrointestinal (GI) conditions associated with HIV disease have become more frequent over the past two decades. Diarrhoea from opportunistic infections has become less common, and HIV-associated diarrhoea is now more often due to non-infectious causes such as ART-related adverse events and HIV enteropathy.1 Diarrhoea associated with ART is most commonly caused by PIs, which may damage the intestinal epithelial barrier and/or alter chloride ion secretion. Less is known about the diarrhoea associated with the other classes of ART.

Newer antiretroviral agents offer improvements in potency and activity as well as tolerability. Dolutegravir was approved by the US FDA in August 2013 and is currently recommended as initial treatment in HIV-infected patients, both as part of the fixed-dose combination tablet including abacavir/lamivudine/dolutegravir and separately with tenofovir/emtricitabine.2 The efficacy of dolutegravir has been demonstrated in several randomized clinical trials (SPRING-1, SPRING-2, SINGLE, FLAMINGO and SAILING).3–7 In a recent safety review of dolutegravir, nausea, diarrhoea and headache were the most commonly reported treatment-related adverse effects. Diarrhoea occurred more often in patients on PI-based therapy (darunavir/ritonavir) than in those on dolutegravir, and the diarrhoea observed with dolutegravir was generally mild in intensity and typically did not prompt discontinuations or changes in treatment.8 Notably, treatment-emergent diarrhoea of at least moderate intensity occurred in <1% of patients receiving dolutegravir.5,7

We report the case of a woman with chronic HIV infection who, after 18 months of treatment with abacavir/lamivudine and efavirenz, switched to abacavir/lamivudine and dolutegravir to accommodate a new job with a varied schedule including night shifts. The patient's CD4 cell count was 780 cells/mm3 and HIV RNA concentration was <20 copies/mL prior to making the ART change. Her medical history included chronic kidney disease stage 3, hyperlipidaemia, hypothyroidism, osteopenia and allergic rhinitis. Medications aside from ART included alendronate, cholecalciferol, levothyroxine, loratadine, montelukast and pravastatin, all of which she had been taking for at least 2 years.

Approximately 3 weeks after the change from efavirenz to dolutegravir, she developed moderate diarrhoea characterized by 6–10 loose watery stools per day associated with urgency and occasional incontinence. She had no fevers or chills and denied any anorexia, nausea, vomiting or abdominal pain. She denied any sick contacts and had not received any recent antimicrobials or other new medications. The results of initial evaluations, including a stool assay for Clostridium difficile and a multiplex PCR test using the FilmArray GI Panel, which detects 22 common viruses, bacteria and parasites that cause infectious diarrhoea, were negative. Pathogens included in the FilmArray GI Panel are as follows: Campylobacter (jejuni, coli and upsaliensis), Clostridium difficile (toxin A/B), Plesiomonas shigelloides, Salmonella, Yersinia enterocolitica, Vibrio species (including a specific target for Vibrio cholerae), enteroaggregative Escherichia coli, enteropathogenic E. coli, enterotoxigenic E. coli It/st, Shiga-like toxin-producing E. coli stx1/stx2 (including a specific target for E. coli O157), Shigella/enteroinvasive E. coli, adenovirus F 40/41, astrovirus, norovirus GI/GII, rotavirus A, sapovirus (I, II, IV and V), Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica and Giardia lamblia.

The patient’s symptoms persisted for an additional 2 weeks, so she underwent colonoscopy with biopsy. The colon and terminal