Ciclopiroxolamine: A Vaginal Product with Microbiocidal Potential

L. J. D. Zaneveld (Consultant to PATH), D. P. Waller (Program for the Topical Prevention of Conception and Disease, TOPCAD), J. Sellers (PATH), F. Camus-Bablon (PATH)

**Introduction**

To accelerate the development of microbicides in India, where HIV and other sexually transmitted infections (STIs) are a serious problem, more than 2,200 topical products marketed in that country were screened for potential anti-HIV and cytostatic activity, and 60 pharmaceutical ingredients or formulations were tested more extensively. Those with significant HIV inhibitory activity were evaluated for activity against cercospora, cladosporium, lacotrichium, and spores. The products with the best results were evaluated for safety in the rabbit vaginal irritation assay and conduct compatibility test. Based on these tests, one of the most promising compounds is ciclopiroxolamine (CO). In addition to an extensive literature review, PATH performed a number of tests through its collaborators to extend the information regarding the activity and safety of CO.

Ciclopiroxolamine (6-cyclohexyl-1-hydroxy-4-methyl-2-[1H]-pyridone) (Mr: 268.35 Da; CAS no. 41621-49-2) is marketed worldwide, including in the countries marketed in India, Italy, Spain, Switzerland, Turkey, and others. This active ingredient is found in at least 14 vaginally administered products marketed in India, Italy, Spain, Switzerland, Turkey, and other countries. The dosage forms include creams, ointments, powders, solutions, and vaginal suppositories which usually contain 1% CO.

**Efficacy**

**Table 1. Inhibition of Non-STI-Causing Bacteria and Fungi**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>MIC, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides</td>
<td>1-24</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1-24</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>1-24</td>
</tr>
<tr>
<td>Micrococcus</td>
<td>1-24</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>1-24</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1-24</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>1-24</td>
</tr>
</tbody>
</table>

**General comments on HIV inhibition:**

- Several possible mechanisms of action:
  - Inhibits host cell to prevent viral fusion and/or entry
  - Post-entry effect: anti-retroviral activity
  - Post-entry inhibition of deoxyhypusyl dehydroxylase (inhibition of production of HIV-1 Rev protein, essential for HIV replication and HIV-1 directed pro-synthetic) 1

- Inhibits host cell enzymes and not a viral enzyme or nucleic acid so that HIV escape mutations should not occur.

**Table 2. Table of Inhibition of HIV**

<table>
<thead>
<tr>
<th>Assay</th>
<th>MIC, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding inhibition assay</td>
<td>1–3 hours</td>
</tr>
<tr>
<td>Cell death assay (cells + cyc topically treated + cells)</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Inhibitory effect (in vitro)</td>
<td>≤2 hours</td>
</tr>
</tbody>
</table>

**Safety**

- Approved for vaginal use: 2–3 times daily for up to 3 weeks. Also approved for use on skin (up to 4 weeks).
- Extensive animal safety testing performed, including long-term vaginal irritation, dermal safety, reproductive toxicity, mutagenicity, carcinogenicity, and others.
- More than 10 clinical studies with vaginal dosage and others.
- In addition, CO:
  - Is absorbed into the skin and vaginal wall, but only ~2%–6% reaches systemic circulation.
  - Is potent inhibitor of deoxyhypusyl dehydroxylase; cellular activity and safety of CO.
  - Shows selectivity index: >100
- Potent inhibitor of deoxyhypusyl dehydroxylase; cellular activity and safety of CO.

**Conclusion**

Ciclopiroxolamine is an exciting microbical candidate with a long history of proven safety in clinical use as a vaginal and skin product with anti-infective properties. It is already formulated, manufactured, and marketed worldwide in vaginal products. The next step is to obtain additional data on anti-HIV activity.

**References**