无环鸟苷和环胞苷联合应用的抗单纯疱疹病毒作用

材料和方法

Vero 细胞 (非洲绿猴肾传代细胞) 和 1 型单纯疱疹病毒 (HSV-1) KOS 株，均由中国预防医学科学院病毒研究所供给。HSV 在 Vero 细胞中传代，病毒滴度维持在 10^6 PFU/ml 左右。ACV [盐酸阿昔洛韦 (3-乙酰氧基-9-甲氧基-1，9-双环 [3，3，1] 戊烷-2-酮，甲基乙酸) ]，作为一种新型抗病毒药物，具有良好的抗病毒活性和安全性，被广泛应用于临床。在此本文设计研究了 ACV 和 Cyd 联合用药在组织培养和实验动物模型上的抗 HSV 作用。

结果

ACV 和 Cyd 单独用药的感染率和死亡率

ACV 和 Cyd 分别连续给药 0.5，0.25，0.125，0.0625 和 0.03125 mg/ml 5 个浓度，观察它们在组织培养中抑制 HSV 空斑形成的作用。结果显示，ACV 和 Cyd 在不同浓度下均显示出良好的抗病毒作用，尤其是 Cyd 对 HSV-1 的抑制作用更为显著。

ACV 和 Cyd 联合用药的研究

1. ACV 和 Cyd 对 HSV-1 繁殖过程的影响

ACV 和 Cyd 在不同浓度下联合给药，结果显示，ACV 和 Cyd 在不同浓度下联合给药时的 ID₅₀ 和 FCIC₅₀ 均低于单药给药时的 ID₅₀ 和 FCIC₅₀。
Fig 1. Graphic evaluations and fractional inhibitory concentration (FIC) indices of acyclovir and cidofovir in various ratios of the combinations, (c) ID₅₀ of Cye with various concentrations of ACV, (d) ID₅₀ of ACV with various concentrations of Cye, FIC indices in parentheses.

The results indicate that ACV and Cye have the highest synergistic effects at a ratio of 3:1 (Cye 0.1 μg/ml to ACV). The FIC index is less than 0.5, indicating a synergistic relationship. The results also show that the combination of ACV and Cye has a significant synergistic effect on the inhibition of virus replication.

2. ACV ± Cye impact on plaque formation in two different ratios of 0.025, 0.125, and 0.625 μg/ml. The combination of ACV and Cye at a ratio of 3:1 (Cye 0.1 μg/ml to ACV) results in a significant reduction in plaque formation compared to ACV alone.

Tab 1. Inhibition of combinations of acyclovir and cidofovir (ACV) with cidofovir (Cye) on plaque formation by herpes simplex virus type 1 (HSV-1), n = 6, mean ± SD, *p < 0.05, **p < 0.01 vs control, ***p < 0.001 vs ACV or Cye alone.

<table>
<thead>
<tr>
<th>ACV (μg/ml)</th>
<th>Cye (μg/ml)</th>
<th>Plaque Formation (mean ± SD)</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>30 ± 5</td>
<td>0</td>
</tr>
<tr>
<td>200</td>
<td>0</td>
<td>22 ± 4</td>
<td>45</td>
</tr>
<tr>
<td>125</td>
<td>0</td>
<td>24 ± 5</td>
<td>39</td>
</tr>
<tr>
<td>125</td>
<td>34 ± 7</td>
<td>34 ± 7</td>
<td>0</td>
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<tr>
<td>127</td>
<td>32 ± 7</td>
<td>32 ± 7</td>
<td>18</td>
</tr>
<tr>
<td>125</td>
<td>62 ± 6</td>
<td>62 ± 6</td>
<td>83</td>
</tr>
</tbody>
</table>

Fig 2. Effects of ACV 0.15% and Cye 0.05% alone or in combination on herpes epidermal keratitis in rabbits. n = 6 eyes of 6 rabbits, mean ± SD, *p < 0.05, **p < 0.01 vs control, ***p < 0.001 vs ACV or Cye alone.

Discussion

In the present study, ACV and Cye were combined for treatment of HSV-1 keratitis. The results showed that the combination of ACV and Cye had a synergistic effect on the inhibition of plaque formation. The combination of ACV and Cye at a ratio of 3:1 (Cye 0.1 μg/ml to ACV) resulted in a significant reduction in plaque formation compared to ACV alone.

Some studies have suggested that the combination of ACV and Cye has a synergistic effect on the inhibition of plaque formation. The combination of ACV and Cye at a ratio of 3:1 (Cye 0.1 μg/ml to ACV) resulted in a significant reduction in plaque formation compared to ACV alone.

ACV is a selective inhibitor of HSV-1 and HSV-2, and its use is limited due to its narrow spectrum of activity and side effects. Cye, on the other hand, has a broader spectrum of activity and is less toxic. The combination of ACV and Cye may provide a more effective and safer treatment for HSV keratitis.
ABSTRACT Combined effect of acyclovir (ACV) and cycloheximide (Cyc) against herpes simplex virus type 1 (HSV-1) was investigated in cell culture and in experimental dendritic keratitis in rabbits. The 50% inhibition doses of HSV-1 plaque formation (ID50) by ACV and Cyc were 2.7 and 1.9 μg/ml, respectively. The combination of ACV with Cyc produced significantly synergistic activity against HSV-1 in cell culture. The optimal ratio was about 3:1 for ACV:Cyc. The combined therapy of 0.15% ACV with 0.05% Cyc produced an enhanced effect in the experimental dendritic keratitis in rabbits.

KEY WORDS combination drug therapy: acyclovir, cycloheximide; cultured cells, rabbit dendritic keratitis, herpesvirus hominis