Lack of Efficacy of AMP Against Recrudescent Genital Herpes Infections in Guinea Pigs

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AMP was evaluated for its efficacy against herpes simplex virus type 2 genital infections in guinea pigs. Vaginally infected animals were treated twice a day with AMP at 50 mg/kg per dose for 2 weeks. Subcutaneous doses were started 10 weeks postinfection. AMP treatment did not reduce the number of animals with recrudescence episodes when compared with saline-treated controls. In addition, AMP treatment did not reduce either the number of lesions or the duration of the recrudescent episodes which did develop. These results suggest that AMP has no effect on recrudescent herpes simplex virus type 2 genital infections.

AMP, a natural cellular nucleotide, has been reported to be effective against recurrent herpes simplex virus type 1 (HSV-1) in both humans (4) and mice (1) and also to be active against latent varicella-zoster virus in humans (5). In the clinical study, it was suggested that AMP may eradicate latent HSV-1 from the nervous system. In the mouse study, AMP was found to inhibit reactivation of lesions by HSV-1 but not to eradicate latent virus.

We now report the results of a study in which the effect of AMP against recrudescent episodes of an HSV-2 vaginal infection in guinea pigs was examined. This model was recently used to demonstrate the efficacy of the acyclic nucleoside 9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG) against both primary and recurrent genital herpes infections (E. B. Fraser-Smith, D. F. Smeet, and T. R. Matthews, submitted for publication).

In the present study, female Hartley strain guinea pigs of 200 ± 40 g average weight from Charles River Breeding Laboratories, Wilmington, Mass., were used. The animals were inoculated intravaginally with 3.3 × 10^5 PFU of HSV-2, MS strain, obtained from Earl Kern, University of Utah School of Medicine, Salt Lake City, Utah. For the next 9 weeks, guinea pigs that had recovered completely from the primary infection were observed daily for recrudescences.

AMP treatment was started at 10 weeks postinfection in 18 animals which were experiencing recrudescences. The animals were injected subcutaneously with AMP (Sigma Chemical Co., St. Louis, Mo.) twice a day, 8 h apart, at a concentration of 50 mg/kg per dose (100 mg/kg per day). Another 18 animals were treated with saline and served as controls. All guinea pigs were monitored daily for recrudescences during the 2-week treatment. The number of recrudescent lesions was recorded for each animal with the position of each lesion marked on a diagram.

The mean number of lesions observed during the 2-week period was calculated by using the number of guinea pigs in a group which developed recrudescence episodes rather than the total number of animals per group. Thus, the calculated scores are a measure of the severity of the lesions themselves rather than a measure of lesion severity in the entire group. To calculate the duration of recrudescences, a single episode was defined as the reappearance of lesion(s) after 2 or more lesion-free days.

Statistical evaluation of differences in the number of animals which developed recrudescences was done by a two-tailed Fisher exact probability test (3). Differences in lesion numbers and duration were evaluated by a two-tailed t test (2).

The present results show that AMP treatment administered during the recrudescent phase did not reduce the number of animals with genital herpes. Some 44% of the AMP-treated animals and 50% of the saline-treated control animals developed at least one recrudescence during the 2-week period of treatment (Table 1; $P > 0.9$). In addition, AMP treatment did not reduce the severity of the recrudescent episodes which did occur. Neither the number of lesions nor the duration of each episode of the AMP-treated group was statistically different from that of the saline-treated control group (Table 1; $P > 1.5$).

The fact that the natural nucleotide AMP was not able to prevent or reduce recrudescent episodes is in contrast to data obtained with the synthetic acyclic nucleoside DHPG. With DHPG, recrudescent episodes were prevented.
### TABLE 1. Effect of AMP on development of HSV-2 recrudescent lesions in vaginally infected guinea pigs

<table>
<thead>
<tr>
<th>Weeks postinfection</th>
<th>Compound</th>
<th>Animals with lesions/total animals</th>
<th>Mean no. of lesionsa</th>
<th>Mean days of duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>AMPb</td>
<td>7/18c</td>
<td>0.20c</td>
<td>NAd</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>8/18</td>
<td>0.32</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>AMPc</td>
<td>8/18c</td>
<td>0.38c</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>6/18</td>
<td>0.36</td>
<td>NA</td>
</tr>
<tr>
<td>10–11</td>
<td>AMPd</td>
<td>8/18c</td>
<td>0.29c</td>
<td>2.3f</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>9/18</td>
<td>0.34</td>
<td>2.8</td>
</tr>
</tbody>
</table>

a Determined by using the number of guinea pigs which developed recrudescent lesions rather than the total number of animals per group.
b AMP was administered twice a day each week at 50 mg/kg per dose.
c AMP values were not significantly different (P > 0.20) from saline control values (two-tailed Fisher exact test and two-tailed t-test).
d NA, Not analyzed.

in a significant number of animals when the compound was given prophylactically in a concentration of 25 mg/kg per dose (50 mg/kg per day) (Fraser-Smith et al., submitted for publication). In addition, Stanberry et al., have shown that acyclovir is also effective in treating recurrent HSV-2 disease in guinea pigs (L. R. Stanberry, E. R. Kern, J. T. Richards, and J. C. Overall, Jr., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemotherapy 22nd, Miami Beach, Fla., abstr. no. 419).

The fact that AMP lacks efficacy against HSV-2 recrudescent infections supports the observation of Blue et al. (1) that AMP does not eradicate latent virus. However, the present results with AMP do not support the observation of Sklar et al. (4, 5) on the efficacy of AMP treatment of human patients. Neither does it support the finding of Blue et al. (1) that AMP can inhibit reactivation of lesions in mice. Recurrent genital herpes, in contrast to recurrent HSV-1 or varicella-zoster virus infections, seems unaffected by AMP treatment.

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### LITERATURE CITED