Iododeoxyuridine and Herpesviral Encephalitis: Lack of Inhibitory Action Against Low-Grade Viral Replication

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Equine herpesvirus 1 replicated in the brains of 2-week-old mice but did not produce fatal encephalitis; it thus simulated the majority of cases of herpes simplex encephalitis in man. This replication was not inhibited by iododeoxyuridine, although in tissue cultures the equine and human viruses were equally susceptible. The continued use of iododeoxyuridine for human encephalitis should be seriously questioned.

Encephalitis due to herpes simplex virus has frequently been treated with 5-iodo-2'-deoxyuridine (IUdR), although its value for this clinical condition has not been unequivocally demonstrated. In their study of 27 cases of herpes encephalitis over a 5-year period, Nolan et al. (2) observed a 66% survival rate both in their group of 18 patients treated with IUdR and in their untreated group of nine patients; but nine of the 13 survivors treated with IUdR recovered without serious impairments, whereas only one of the six untreated survivors was free of major residual damage. By the use of experimental models which consisted of herpes simplex viruses types 1 or 2 in mice, no inhibition of viral replication in the brain by IUdR could be demonstrated (1, 5), although viral replication in other tissues was considerably reduced (1).

The herpes simplex viruses replicate very well in the mouse brain and cause a rapidly fatal encephalitis, a situation that does not accurately reflect many of the cases of herpes encephalitis in the adult human. Viral destruction in the human brain is generally not as rapid or extensive as in the experimental mouse brain. Thus, the beneficial effects of low levels of IUdR on limited viral multiplication in the mature human brain cannot be accurately judged by studies of herpes simplex virus in the mouse.

We therefore used an animal model that consisted of equine herpesvirus 1 in mice. This herpesvirus grows as rapidly in tissue cultures as the herpes simplex viruses, but in the mouse brain causes various degrees of encephalitis, the extent of viral damage being dependent on the age of the mice. In mice less than 1 week old, the virus causes a rapidly fatal encephalitis; in animals of about 2 weeks of age or greater, there is viral replication in the brain for several days but the mice do not usually die (3).

The data presented in Table 1 demonstrate the similar susceptibilities to IUdR of equine herpesvirus 1 and herpes simplex virus 1, as indicated by both reduction in plaque numbers and reduction in plaque sizes. In these tests the IUdR (Calbiochem, La Jolla, Calif.) was included in the overlay medium at the indicated concentrations, as also was 3% rabbit antiserum that had been prepared against either the equine herpesvirus or herpes simplex virus 1; the antiserum prevented spread of virus by way of the medium. Between 0.5 and 1.0 μg of IUdR per ml was required for a 50% decrease in plaque numbers or in plaque diameters for either virus (Table 1).

In each of the mouse experiments the IUdR was inoculated intraperitoneally at 200 mg/kg of body weight per day. When concentrations higher than this were inoculated, even in the absence of virus, a number of the mice died. The IUdR was dissolved each day in Eagle medium with the aid of sodium hydroxide; it was inoculated in 0.05-ml amounts. The first IUdR inoculation was done on day zero, 3 h after the intracerebral or intranasal inoculation of the virus. Subsequent IUdR inoculations were given at 24-h intervals, namely, on days 1 to 4 or 5 postinoculation of virus.

The IUdR had no inhibitory action on the replication of equine herpesvirus that had been inoculated directly into the brains of 8- to 10- or 14- to 16-day-old mice, even though in the 2-week-old mice the degree of viral replication was modest (Fig. 1A and 1B).

IUdR treatment considerably reduced the amount of virus detectable in the lungs and blood of intranasally inoculated animals (Fig.

¹Deceased.
TABLE 1. Inhibitory effect of IUdR on equine herpesvirus 1 and on herpes simplex virus 1, as indicated by reduction in plaque counts and plaque sizes in cultures of rabbit kidney

<table>
<thead>
<tr>
<th>IUdR Conc (µg/ml)</th>
<th>Equine herpesvirus type 1</th>
<th>Herpes simplex virus type 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plaque numbers (%)</td>
<td>Plaque sizes (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plaque numbers (%)</td>
</tr>
<tr>
<td>0.4</td>
<td>70</td>
<td>81</td>
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<tr>
<td>0.8</td>
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<td>59</td>
</tr>
<tr>
<td>1.6</td>
<td>7</td>
<td>28</td>
</tr>
</tbody>
</table>

* The plaque numbers are expressed as a percentage of the number of plaques in the control petri dish cultures; the controls contained no IUdR in the overlay fluid.

The mean of the maximum diameters of at least 30 isolated plaques, expressed as a percentage of the mean diameter of the control plaques that were under medium that contained no IUdR. Plaques were counted or measured at 4 days postinoculation.

1C and 1D). But invasion of the brain in these mice did not appear to be inhibited; similar amounts of virus were detected in the brains of IUdR-treated and untreated mice at 3 and 4 days postinoculation (at 3 days postinoculation the mean virus titer in the brains of the IUdR-treated mice was 10^4.3 plaque-forming units as opposed to 10^4.6 plaque-forming units in the untreated controls). This latter observation is in harmony with that of Kern et al. (1) for intranasally inoculated herpes simplex type 2 in mice.

The replication of this virus in the brains of the mice was far less extensive and far less damaging than the replication of the herpes simplex viruses in the mouse brain, but even so it seemed to be in no way inhibited by the IUdR treatment. This study and other studies (1, 4, 5) indicate that IUdR has no inhibitory action whatsoever on deoxyribonucleic acid viruses in the mouse brain, and, in view of the lack of convincing evidence about its value against herpesviral replication in the human brain, its continued use for herpes encephalitis of man should be seriously questioned.

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LITERATURE CITED


