Antiviral and Cytotoxic Effects of Mycophenolic Acid

(Accepted 24 January 1969)

Mycophenolic acid, produced by various species of the genus *Penicillium*, has been shown to have both antibacterial and antifungal properties (see Korzybski, Kowszyk-Gindifer & Kurylowicz 1967). Mycophenolic acid was found to be antiviral in tissue culture. The Agar Diffusion Test (Herrmann et al. 1960) was employed, using 100 µg per well. It gave zones of plaque inhibition of 40 to 60 mm. against vaccinia, herpes simplex, Semliki Forest, encephalomyocarditis, Coxsackie (B1, CONN. 5) and influenza (A-NWS) viruses. The degree of inhibition against vaccinia virus compared favourably with that obtained with the known antivaccinial compounds iododeoxyuridine (80 mm.) and methisazone (75 mm.). When incorporated into the agar overlay in a normal plaque technique, it was found that the median plaque inhibitory concentration was 0.3 to 1 µg/ml. for vaccinia virus, the same as that obtained with iododeoxyuridine and methisazone. Experiments in which mycophenolic acid was added at different times in the growth cycle of vaccinia and Semliki Forest viruses failed to detect any action on a specific part of the growth cycle.

Mycophenolic acid inhibited the multiplication in tissue culture of chick embryo fibroblasts and baby hamster kidney cells (BHK 21) at 0.3 to 1 µg/ml. Chick embryo fibroblasts were, however, able to recover from the concentration ≥ 100 µg/ml. Microscopic observations failed to detect any abnormalities in the morphology of chick embryo fibroblasts treated with mycophenolic acid. On the other hand, in baby hamster kidney cells 1 and 3 µg/ml., besides causing a decrease in cell numbers, caused an enlargement of the cells and of the nuclei. In a few cells the nucleus was distorted, with vacuoles of nuclear material appearing to balloon out into the cytoplasm. Multinucleated cells, sometimes with the nuclei joined by a thread of nuclear material, were also observed. Cells grown first in the presence of compound and then in its absence appeared normal. Mycophenolic acid might prove a useful inhibitor in the study of nuclear and mitotic control mechanisms.

In vivo antiviral tests were done using a number of different viruses. The compound was suspended in 1% methyl cellulose and injected subcutaneously into mice of about 20 g. At 500 mg./kg. adequate inhibitory concentrations were found to persist in serum for at least 16 hr. No in vivo antiviral action at 250 mg./kg. was observed against neurovaccinia, Semliki Forest and encephalomyocarditis viruses.

Mycophenolic acid, because of its differential cytotoxicity, was tried against mouse sarcoma virus (Harvey, 1964). Two-week-old TO mice were used, and mycophenolic acid was given 2 days before infection and for 2 weeks after infection. The spleens were weighed at 3 weeks. There was no splenomegaly in mice of 10 to 12 g. unless they were treated with an immunosuppressant drug (Table 1). Animals treated with mycophenolic acid also developed splenomegaly, perhaps because mycophenolic acid acted in a similar way to an immunosuppressant.

In summary, mycophenolic acid inhibited a number of unrelated viruses in tissue culture probably because of its cytotoxicity. The morphology of baby hamster kidney cells grown in the presence of mycophenolic acid was abnormal. It was not possible
Short communications

to demonstrate any in vivo antiviral action against neurovaccinia, Semliki Forest, encephalomyocarditis and mouse sarcoma viruses. With the last virus, mycophenolic acid appeared to act as an immunosuppressant.

Table I. Effect of mycophenolic acid and immunosuppressants on spleen weights of mice infected with mouse sarcoma virus

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Mean spleen weight (mg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>—</td>
<td>119</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>3 mg./day</td>
<td>215</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>300 μg./day</td>
<td>200</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10 μg./day</td>
<td>330</td>
</tr>
</tbody>
</table>

Two week old (10–12 g.) TO mice were used. Drug was given for 2 days before infection, and continued for 2 weeks. Spleens were weighed at 3 weeks. Drug alone in no case induced splenomegaly.

Since this paper was prepared, Williams et al. (1968) have described similar results, namely that mycophenolic acid showed antiviral activity in vitro but not in vivo. On the other hand, Williams et al. (1968) reported an antitumour action against a number of tumours including the splenomegaly induced by Friend virus. We found that mycophenolic acid potentiated the splenomegaly induced by mouse sarcoma virus (HAgVEY strain).

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REFERENCES


(Received 30 December 1968)