FAILURE OF RIFAMPIN TO INHIBIT ADENOVIRUS REPLICATION

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Failure of Rifampin to Inhibit Adenovirus Replication

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Rifampin failed to inhibit adenovirus replication in tissue culture. The data suggest that rifampin would be ineffective as a chemotherapeutic agent against adenovirus disease.

Rifampin is an antibiotic originally isolated from Streptomyces mediterraneus (8). The compound is well absorbed orally and reaches peak serum concentrations 2 to 3 hr after an oral dose (7). Rifampin has potent antibacterial and antitubercular effects, and because it enters the secretions, it has been particularly useful for the treatment of pulmonary tuberculosis and the meningococcal carrier state (1, 5).

Antiviral effects have also been demonstrated for rifampin, although the concentrations of the antibiotic required for antiviral activity are several hundred-fold greater than those producing antibacterial effects. The compound has a clear antiviral effect on a number of deoxyribonucleic acid viruses, including vaccinia, variola minor, cowpox (6, 9), African swine fever virus (3), and trachoma agent (2).

Although an inhibitory effect of rifampin on adenovirus proliferation has been suggested, the evidence to date has not been conclusive (9, 10). Rifampin would have obvious applications in controlling outbreaks of adenovirus disease among military trainees (11) if the drug inhibited adenovirus proliferation at concentrations attained in the respiratory secretions. With this in mind, we evaluated in vitro the effect of rifampin on the proliferation of adenovirus types commonly isolated from military recruits.

Adenovirus type 3 strain G.B., type 4 strain RI-67, type 7a strain S-1058, and Herpesvirus hominis strain Myxo 1814 were kindly provided by Sylvia Cunningham, Medical Resources Branch, National Institute of Allergy and Infectious Diseases, Bethesda, Md. All virus strains and cell culture lines were determined to be free from mycoplasma contamination. Adenovirus types and H. hominis virus were passed twice in primary human embryonic kidney (HEK) cells (HEM Laboratories) and at least twice in continuous human epithelium cells (HEp-2).

A 50\% tissue culture infective dose (TCID_{50}) was calculated for the growth of the virus strains cultured with and without rifampin. For this purpose, serial dilutions ranging from 10^{-7.5} to 10^{-10} of adenovirus or H. hominis were prepared. Amounts of 0.1 ml of each virus dilution alone and were incubated for up to 17 days. As an alternative, 100 TCID_{50} of virus was inoculated into HEK tubes containing rifampin at a concentration of 0.390 to 200 \mu g/ml of MEM, and incubated for 7 days.

HEK tubes were read daily, and virus cytopathogenic effect (CPE) was estimated visually at 25 to 100\%. For the calculation of each TCID_{50}, tissue culture tubes were considered to be infected if a virus-specific CPE affected 74\% or more of the cell sheet. In addition, toxic effects of rifampin were recorded semiquantitatively as a percentage depending on the degree of rounding, granulation, and vacuolization of the cell monolayers in the presence of rifampin and MEM, but not virus.

Rifampin was toxic to HEK cells at concentrations of 25 \mu g/ml or greater. A rifampin con-
This may explain why previous workers have noted the enhancement of viral CPE by the cytotoxicity of the antibiotic.

In summary, we did not demonstrate an antiviral effect of rifampin on the proliferation of adenovirus types 3, 4, and 7, or H. hominis. The toxicity of high concentrations of rifampin for primary HEK cells was especially prominent after the third day of incubation (Fig. 1), and this may explain why previous workers had shown an inhibitory effect of rifampin on adenovirus plaque formation in HeLa cells. Adenovirus plaques require at least 7 days to develop (10).

Our experiments did not demonstrate that rifampin inhibited adenovirus proliferation; however, more sensitive techniques that measure the rate of synthesis of specific adenovirus precursors might have shown an inhibitory effect, particularly for adenovirus type 3. Our in vitro studies demonstrate that rifampin at 0.5 μg/ml, the peak concentration achieved in saliva after the fourth oral dose of 600 mg (4), is not likely to affect in vivo the course of an adenovirus infection. Whether rifampin would suppress in vivo an adenovirus viremia remains to be determined, because peak concentrations of 27.7 μg/ml are achieved in serum after an oral dose of 900 mg of rifampin (7).

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