but rimantadine is concentrated in respiratory secretions to a greater extent than amantadine. For prophylaxis, the compounds must be administered daily for the period at risk (i.e., duration of the exposure). For therapy, amantadine or rimantadine is generally administered for 5–7 days.

Although these compounds are generally well tolerated, 5–10% of amantadine recipients experience mild central nervous system side effects consisting primarily of dizziness, anxiety, insomnia, and difficulty in concentrating. These effects are rapidly reversible upon cessation of the drug's administration. At a dose of 200 mg/d, rimantadine is better tolerated than amantadine; in a large-scale study of young adults, adverse effects were no more frequent among rimantadine recipients than among placebo recipients. Seizures and worsening of congestive heart failure have also been reported in patients treated with amantadine, although a causal relationship has not been established. The dosage of amantadine should be reduced to 100 mg/d in patients with renal insufficiency—i.e., a creatinine clearance rate (Cr_{Cl}) of <50 mL/min—and in the elderly. A rimantadine dose of 100 mg/d should be used for patients with a Cr_{Cl} of <10 mL/min and for the elderly.

RIBAVIRIN

Ribavirin is a synthetic nucleoside analogue that inhibits a wide range of RNA and DNA viruses. The mechanism of action of ribavirin is not completely defined and may be different for different groups of viruses. Ribavirin-5′-monophosphate blocks the conversion of inosine-5′-monophosphate to xanthosine-5′-monophosphate and interferes with the synthesis of guanine nucleotides as well as with that of both RNA and DNA. Ribavirin-5′-monophosphate also inhibits capping of virus-specific messenger RNA in certain viral systems.

Ribavirin administered as a small-particle aerosol to young children hospitalized with respiratory syncytial virus (RSV) infection has been clinically beneficial and has improved oxygenation in some studies (7 of 11). Although ribavirin has been approved for treatment of infants hospitalized with RSV infection, the American Academy of Pediatrics has recommended that it be considered on an individual basis rather than used routinely in that setting. Aerosolized ribavirin has also been administered to older children and adults (including immunosuppressed patients) with severe RSV and parainfluenza virus infections and to older children and adults with influenza A or B infection, but the benefit of this treatment, if any, is unclear. In RSV infections in immunosuppressed patients, ribavirin has been given in combination with anti-RSV immunoglobulins.

Orally administered ribavirin has not been effective in the treatment of influenza A virus infections. IV or oral ribavirin has reduced mortality rates among patients with Lassa fever; it has been particularly effective in this regard when given within the first 6 days of illness. IV ribavirin has been reported to be of clinical benefit in the treatment of hemorrhagic fever with renal syndrome caused by Hantaan virus and as therapy for Argentinean hemorrhagic fever. Oral ribavirin has also been recommended for the treatment and prophylaxis of Congo-Crimean hemorrhagic fever. Use of IV ribavirin in patients with hantavirus pulmonary syndrome in the United States has not been associated with clear-cut benefits.

Oral administration of ribavirin reduces serum aminotransferase levels in patients with chronic hepatitis C virus (HCV) infection; because it appears not to reduce serum HCV RNA levels, the mechanism of this effect is unclear. The drug provides added benefit when given by mouth in doses of 800–1200 mg/d in combination with interferon (IFN) α2b or α2a (see below), and the triple combination of ribavirin, IFN, and sofosbuvir or simeprevir has been approved for the treatment of patients with chronic HCV infection (see below). Recent data suggest that oral ribavirin may be beneficial in resolution of chronic hepatitis E infection associated with organ transplantation. Large oral doses of ribavirin (800–1000 mg/d) have been associated with reversible hematopoietic toxicity. This effect has not been observed with aerosolized ribavirin, apparently because little drug is absorbed systemically. Aerosolized administration of ribavirin is generally well tolerated but occasionally is associated with bronchospasm, rash, or conjunctival irritation. It should be administered under close supervision—particularly in the setting of mechanical ventilation, where precipitation of the drug is possible. Health care workers exposed to the drug have experienced minor toxicity, including eye and respiratory tract irritation. Because ribavirin is mutagenic, teratogenic, and embryotoxic, its use is generally contraindicated in pregnancy. Its administration as an aerosol poses a risk to pregnant health care workers. Because clearance of ribavirin is primarily renal, dose reduction is required in the setting of significant renal dysfunction.

AGENTS OF INVESTIGATIVE INTEREST

DAS181 is an investigational antiviral agent with activity against influenza A and B and parainfluenza viruses. It is a sialidase linked to a respiratory epithelium–anchoring domain. This agent cleaves the terminal sialic acid residues on human respiratory cells, reducing the binding of the aforementioned respiratory viruses. DAS181 is administered by oral inhalation and is being evaluated in the treatment of parainfluenza type 3 infections in recipients of lung and stem cell transplants.

ANTIVIRAL DRUGS ACTIVE AGAINST HERPESVIRUS INFECTIONS

ACYCLOVIR AND VALACYCLOVIR

Acyclovir is a highly potent and selective inhibitor of the replication of certain herpesviruses, including herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV). It is relatively ineffective in the treatment of human cytomegalovirus (CMV) infections; however, some studies have indicated effectiveness in the prevention of CMV-associated disease in immunosuppressed patients. Valacyclovir, the L-valyl ester of acyclovir, is converted almost entirely to acyclovir by intestinal and hepatic hydrolysis after oral administration. Valacyclovir offers pharmacokinetic advantages over orally administered acyclovir: it exhibits significantly greater oral bioavailability, results in higher blood levels, and can be given less frequently than acyclovir (two or three rather than five times daily).

The high degree of selectivity of acyclovir is related to its mechanism of action, which requires that the compound first be phosphorylated to acyclovir monophosphate. This phosphorylation occurs efficiently in herpesvirus-infected cells by means of a virus-coded thymidine kinase. In uninfected mammalian cells, little phosphorylation of acyclovir occurs, and the drug is therefore concentrated in herpesvirus-infected cells. Acyclovir monophosphate is subsequently converted by host cell kinases to a triphosphate that is a potent inhibitor of virus-induced DNA polymerase but has relatively little effect on host cell DNA polymerase. Acyclovir triphosphate can also be incorporated into viral DNA, with early chain termination.

Acyclovir is available in IV, oral, and topical forms, while valacyclovir is available in an oral formulation. IV acyclovir is effective in the treatment of mucocutaneous HSV infections in immunocompromised hosts, in whom it reduces time to healing, duration of pain, and virus shedding. When administered prophylactically during periods of intense immunosuppression (e.g., related to chemotherapy for leukemia or transplantation) and before the development of lesions, IV acyclovir reduces the frequency of HSV-associated disease. After prophylaxis is discontinued, HSV lesions recur. IV acyclovir is also effective in the treatment of HSV encephalitis.

Because VZV is generally less sensitive to acyclovir than is HSV, higher doses of acyclovir must be used to treat VZV infections. In immunocompromised patients with herpes zoster, IV acyclovir reduces the frequency of cutaneous dissemination and visceral complications and—in one comparative trial—was more effective than vidarabine. Acyclovir, administered at oral doses of 800 mg five times a day, had a modest beneficial effect on localized herpes zoster lesions in both immunocompromised and immunocompetent patients. Combination of acyclovir with a tapering regimen of prednisone appeared to be more effective than acyclovir alone in terms of quality-of-life outcomes in immunocompetent patients over age 50 with herpes zoster. A comparative study of acyclovir (800 mg PO five times daily) and valacyclovir (1 g PO three times daily) in immunocompetent patients with herpes zoster indicated that the latter drug may be more effective in eliciting the resolution of zoster-associated pain. Orally administered