studies suggest that VDB was relatively inactive toward CMV (Gephart and Lerner, 1981).

VDB was active against hepatitis B virus (HBV) using a human hepatoblastoma cell line that continuously synthesizes HBV DNA (Ueda *et al.*, 1989). But in ducks or woodchucks chronically infected with HBV, only high, poorly tolerated doses of VDB were shown to inhibit viral replication (Omata *et al.*, 1986; Hirota *et al.*, 1987; Fourel *et al.*, 1992). VDB was inactive against HIV-1 (Balzarini *et al.*, 1986).

3. MECHANISM OF DRUG ACTION

VDB exerts its antiviral effect by inhibiting DNA synthesis. Like other nucleoside analogs VDB is a prodrug, requiring sequential intracellular phosphorylation to the triphosphate, mediated exclusively by cellular enzymes, for it to be able to inhibit viral DNA polymerases. In this respect, VDB differs in an important way from, and lacks the selectivity of, aciclovir and penciclovir, as the phosphorylation of the latter antiviral drugs is initiated only by herpesvirus thymidine kinases in infected cells, not by cellular kinases (see Chapter 213, Aciclovir and valaciclovir). As a consequence, intracellular levels of VDB triphosphate are high in all cells, causing systemic toxicity, whereas intracellular levels of aciclovir and penciclovir triphosphates are high only in herpesvirus-infected cells.

VDB triphosphate also inhibits mammalian cell DNA polymerases, but to a somewhat lesser degree than the virus-specified enzymes (Le Page, 1973; Shannon, 1975; Muller *et al.*, 1977); as a consequence, VDB is also incorporated into both cellular and viral DNA during DNA synthesis, making toxicity likely (Muller *et al.*, 1977). *In vivo*, the major antiviral activity was mediated by VDB, which had considerably more activity than arabinosyl hypoxanthine (Shannon, 1975; Sloan, 1975; Bryson and Connor, 1976; Gephart and Lerner, 1981).

Studies in ducks infected with duck hepatitis B virus have shown that the mechanism of action of VDB against hepadnavirus replication is through inhibition of the HBV DNA polymerase (which is a reverse transcriptase), resulting in a decrease in the "mature" forms of the viral DNA. There is, however, no effect on hepatitis B virus supercoiled DNA (Omata *et al.*, 1986).

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

VDB is no longer available in any form; no dosage was established for humans.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

VDB is rapidly deaminated to arabinosyl hypoxanthine within erythrocytes by the enzyme adenosine deaminase (Kinkel and Buchanan, 1975). Levels of arabinosyl hypoxanthine in erythrocytes parallel those in serum, and the cerebrospinal fluid levels are approximately 35% of serum levels. During a 12-hour infusion, arabinosyl hypoxanthine levels are in the range 3–6 μg/ml, and levels of the parent compound are < 0.4 μg/ml. The predominant route of excretion is via the kidneys, and there is no evidence of fecal excretion of VDB or its metabolites. No pharmacodynamic studies have been undertaken.

6. ADVERSE REACTIONS AND TOXICITY

Although early animal studies with VDB suggested that it might be minimally toxic, as soon as human usage became common it became evident that VDB was associated with unacceptable toxicity affecting multiple organs.

At therapeutic VDB doses of ≥ 15 mg/kg daily, neutropenia and thrombocytopenia are common and pancytopenia and megaloblastic changes can occur. Neurologic findings such as hallucinations, confusion, psychosis, tremors, ataxia, myoclonus, dysarthria, aphasia, neuralgia, seizures, and coma have been reported.; Gastrointestinal side effects include anorexia, nausea, vomiting, and diarrhea, and elevated liver enzymes have also been noted. Weakness, fatigue, weight loss, rash, and thrombophlebitis at the site of intravenous injection can occur. Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone have also been related to VDB therapy (Whitley *et al.*, 1976; Whitley *et al.*, 1982a; Whitley *et al.*, 1982b; Whitley *et al.*, 1982c; Lauter *et al.*, 1976; Ross *et al.*, 1976; Sacks *et al.*, 1979; Meyers *et al.*, 1982; Sacks *et al.*, 1982; Vilter, 1986; Feldman *et al.*, 1986; Safrin *et al.*, 1990; Safrin *et al.*, 1991; Arzuaga *et al.*, 1994; Bevilacqua, 1994). A severe and prolonged polyneuropathy occurred after a 12-week course of VDB in patients with chronic hepatitis B infection (Guardia *et al.*, 1986), and hepatic failure has been reported after VDB therapy combined with prednisolone for treatment of chronic HBV infection (Buti *et al.*, 1987).

7. CLINICAL USES OF THE DRUG

Several placebo-controlled studies of VDB treatment of HSV encephalitis showed an apparent reduction in death rates and improved long-term outcomes of treated individuals compared to placebo or no treatment; VDB also reportedly had little toxicity (Whitley *et al.*, 1977; Whitley *et al.*, 1981). However, in two randomized studies comparing VDB with aciclovir in patients with HSV encephalitis, aciclovir was found to be far superior to VDB in terms of survival and long-term morbidity; aciclovir also had fewer adverse reactions than VDB (Sköldenberg *et al.,* 1984; Whitley *et al.*, 1986). VDB-treated neonates with HSV infection had lower mortality and fewer sequelae than those treated with placebo (Whitley *et al.*, 1980), but a later study comparing aciclovir with VDB showed that these two drugs had equivalent efficacy in terms of both long-term morbidity and mortality, but the incidence of neutropenia and thrombocytopenia was five times higher in the VDB-treated group than in those receiving aciclovir (Whitley *et al.*, 1991).