218

Discontinued Herpesvirus Agent: Vidarabine

Suzanne M. Crowe and John Mills

1. DESCRIPTION

Vidarabine (also known as adenine arabinoside, Ara-A, or VDB) is a purine analog that *in vitro* inhibits the replication of a wide range of DNA viruses, particularly herpes simplex and varicella-zoster, and some oncogenic RNA viruses (De Garilhe and De Rudder, 1964). The chemical name is 9-beta-D-arabinofuranosyl-adenine. The chemical structure is shown in Figure 218.1.

VDB was originally developed as an anticancer agent in 1960 (Lee *et al.*, 1960) and activity against DNA viruses was recognized in 1964. It was the first drug to have proven antiviral efficacy when given systemically to humans, effectively beginning the era of antiviral drugs, now numbering over 70 (De Garilhe and De Rudder, 1964; Whitley *et al.*, 1976). However, although VDB was reasonably efficacious against herpes simplex and varicella-zoster virus infections, the toxicity of VDB is such that it is no longer clinically useful for human use, and it was withdrawn from the market in 2001. VDB has been replaced by aciclovir and many other more potent and less toxic antiviral drugs.

A fluorinated analog of VDB, fludarabine (Fludara), is approved for the treatment of cancer (Koduvayur *et al.*, 2016).

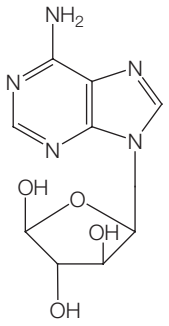

Figure 218.1. Chemical structure of vidarabine.

2. ANTIMICROBIAL ACTIVITY

The reported activity of VDB against herpes simplex (HSV) and vaccinia virus in 1964 was subsequently followed by evidence of activity against cytomegalovirus (CMV) and Rous sarcoma virus, some strains of adenovirus, and hepatitis B virus (De Garilhe and De Rudder, 1964; Miller *et al.*, 1968; Schabel, 1968; Wigand, 1979; Miller *et al.*, 1968; Schabel, 1968; Hirsch and Swartz, 1980; Hess *et al.*, 1981; Kitabayashi *et al.*, 1994).

The *in vitro* activity of VDB includes strains of HSV types 1 and 2, which are resistant to idoxuridine and bromovinyldeoxyuridine (Shannon, 1975; Wilber and Docherty, 1994; Schinazi, 1987). Against clinical isolates of HSV, VDB was less potent (50% effective concentration [EC_{50}] 11 μg/ml) than aciclovir and bromovinyldeoxyuridine (EC_{50} ranging from 0.02 to 0.9 μg/ml) (Andrei *et al.*, 1992). A more recent study showed that VDB was synergistic with aciclovir against HSV but only against strains susceptible to both agents (Suzuki *et al.*, 2006). The *in vitro* data were supported by the efficacy of VDB for the treatment of experimental HSV encephalitis in mice (Schinazi, 1987).

Using an unusual assay system, VDB was more active against varicella-zoster virus (VZV) (EC_{50} 1.0–3.5 μg/ml) than aciclovir (EC_{50} 2.5–50 μg/ml) and of similar efficacy to trifluorothymidine (EC_{50} 1.2–5.0 μg/ml); VZV was more susceptible to VDB than HSV (Berkowitz and Levin, 1985; Gephart and Lerner, 1981). It is not surprising that VDB was found to have a much lower selectivity index against VZV than aciclovir or penciclovir (Machida *et al.*, 1995). Aciclovir-resistant strains of VZV were susceptible to VDB; the mean EC_{50} of 4 clinical isolates was 1.4 μM (Schinazi *et al.*, 1986; Jacobson *et al.*, 1990).

In two studies human CMV was inhibited by VDB at low concentrations in cell culture, and foscarnet-resistant strains were also susceptible, although the therapeutic margin was narrow (Verheyden, 1988; Sullivan and Coen, 1991), but other