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Didanosine

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1. DESCRIPTION

Didanosine (2′,3′-dideoxyinosine, ddI) is a synthetic purine nucleoside analog that is active against HIV-1 and HIV-2, including strains of HIV that are resistant to zidovudine and lamivudine. It was the second drug licensed for the treatment of HIV infection and was initially used as monotherapy, but since 2010 it is no longer recommended by WHO, the European AIDS Clinical Society, and the US Department of Health and Human services (DHHS) for either initial or second-line treatment of HIV infection because of its unfavorable safety profile and the availability of better options. It is no longer used in the USA, Europe, or Australia but continues to have use in low- and middle-income countries, including Russia and Ukraine. Although international guidelines no longer contain didanosine-containing regimens in preferred first- or second-line antiretroviral therapy, there is no guidance for management of patients who remain on didanosine. In 2012 at least 20 countries spent a total of $1 to $2 million on purchasing didanosine (Dziuban *et al.*, 2015).

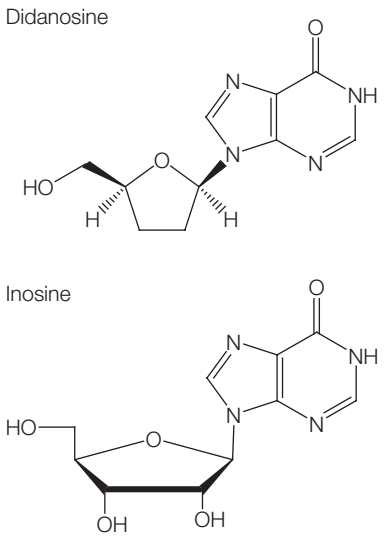

Figure 226.1. Chemical structure of didanosine and inosine.

The drug is marketed by Bristol-Myers Squibb under the trade names Videx and Videx EC (Bristol-Myers Squibb, 2007). The availability of didanosine as enteric-coated capsules (Videx EC) has greatly improved the gastrointestinal tolerability of the drug. In India didanosine is marketed by a number of pharmaceutical companies. Cipla markets didanosine as Dinex (100 mg), DinexEC (250 and 400 mg), and as a fixed-dose combination of didanosine, efavirenz, and lamivudine as Odivir.

The molecular formula of didanosine is $C_{10}H_{12}N_4O_3$, its molecular weight is 236.2, and its chemical structure is shown in Figure 226.1. The concentration can be expressed as in micromolars or micrograms per milliliter (1 μg/ml is approximately equivalent to 5 μM).

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

HUMAN IMMUNODEFICIENCY VIRUS

Didanosine has generally been found to be less potent as an inhibitor of HIV than zidovudine and lamivudine (Hitchcock, 1993; Mathez *et al.*, 1993), but to have a much higher *in vitro* selectivity ratio (Coplan and Nolan, 1991). Didanosine is effective against both HIV-1 and HIV-2 (Richman, 1987; Mitsuya and Broder, 1988; Connolly and Hammer, 1992).

A compound that is closely related to didanosine, 2′,3′-dideox-yadenosine (ddA) was first synthesized in 1964 (Robins and Robins, 1964). In 1985, Mitsuya and Broder (1986, 1987) demonstrated the activity of both didanosine and ddA against HIV replication. Both didanosine and ddA inhibit HIV replication in T-lymphocytes and macrophages that are exposed to the drug at the time of infection with HIV (Mitsuya and Broder, 1986; Perno *et al.*, 1988). In macrophages, the activity of didanosine against HIV is similar to or greater than that of zidovudine (Hitchcock, 1993).

The half-maximal inhibitory concentration (IC_{50}) of didanosine for HIV ranges from 2.5 to 10 μM (0.5 to 2 μg/ml) in activated T-lymphocytes and from 0.01 to 0.1 μM in