to genital lesions; this is more frequent with first episodes of genital herpes than with recurrent episodes and is more frequent in women than in men (Corey *et al.*, 1982a). In general, topical application to genital lesions is well tolerated (Fiddian *et al.*, 1983). Mild superficial punctate epithelial staining can occur after treatment with the ophthalmic ointment, but this disappears a few days after the drug is discontinued (Laibson *et al.*, 1982).

6h. Embryotoxicity

Administration of very high doses (50–100 mg/kg) of aciclovir to pregnant rats can result in a high rate of resorptions of fetuses, and malformations of the skull, vertebral column, and tail (Chahoud *et al.*, 1988; Stahlmann *et al.*, 1988). Lower doses of aciclovir have been associated with abnormal development of the fetal thymus (Foerster *et al.*, 1992; Stahlmann *et al.*, 1992). The GlaxoSmithKline registry of pregnancy outcomes after prenatal maternal exposure to aciclovir was closed in 1999 after enrolling 1246 cases, with 756 exposures to aciclovir occurring in the first trimester. Aciclovir doses ranged from 200 to 2800 mg p.o. daily and up to 45 mg/kg i.v. daily. Only 2% of infants had a birth defect (similar to surveillance data in pregnancies with no aciclovir exposure) and no specific pattern was noted (GlaxoSmithKline, 1999). Although virtually all reports of the use of aciclovir during pregnancy suggest no toxicity, one case of fetal diastematomyelia, a rare spinal condition, was diagnosed in a fetus exposed to aciclovir at the time of implantation (Gubbels *et al.*, 1991).

6i. Other side effects

Because aciclovir for injection has a relatively high pH (9–11), local irritation occurs if it extravasates into surrounding tissues (Keeney *et al.*, 1982; Robbins *et al.*, 1993). Thrombophlebitis and local inflammation at the site of injection are reported in 9% of the patients receiving intravenous aciclovir (GlaxoSmithKline, 2003). Experience in one patient indicated that a high-concentration infusion of aciclovir (12 mg/ml) may have caused vesiculation at the infusion site (Sylvester *et al.*, 1986). Fever, pulmonary infiltrates, and a pleural effusion have been described in an elderly man after commencement of aciclovir; cessation of the drug resulted in clinical improvement (Pusateri and Muder, 1990).

6j. Aciclovir overdoses

In reported cases of aciclovir overdose, including in neonates, no toxicity has been observed (McDonald *et al.*, 1989). The major exception is when aciclovir levels accumulate due to poor renal function; there have been a number of cases of neurotoxicity associated with elevated aciclovir plasma levels in patients with renal failure (Gill and Burgess, 1990; Davenport *et al.*, 1992; Leikin *et al.*, 1995).

7. CLINICAL USES OF THE DRUG

Aciclovir, or its prodrug valaciclovir, are highly effective and very safe for treatment or prevention of all HSV and VZV infections. Intravenous aciclovir is indicated for the treatment of severe primary genital HSV infections in immunocompetent persons, for primary or recurrent mucocutaneous infections in immunocompromised patients, for HSV encephalitis, for life-threatening HSV infections in neonates, and for treatment of VZV in immunocompromised patients or severe VZV in any patient. Although not FDA-approved indications (off-label use), intravenous aciclovir is also effective for treatment of other serious HSV and VZV infections, such as eczema herpeticum.

Oral aciclovir and valaciclovir are indicated for the treatment of genital herpes—primary or recurrent disease or chronic suppression (chemosuppression) of recurrences—for immunocompetent patients with herpes zoster (shingles), and for the treatment of VZV in immunocompetent patients (Mylan Pharmaceuticals, 2012; GlaxoSmithKline, 2013). Aciclovir is also indicated for prevention of herpes labialis recurrences triggered by sun or possibly by other stimuli. Valaciclovir is also now indicated for treatment of herpes labialis. Several off-label or investigational uses for aciclovir and valaciclovir have been described in the literature and include treatment or prevention of recurrent HSV infections at nongenital sites (e.g. orofacial) and prevention of HSV reactivation in HIV-positive patients, hematopoietic stem cell transplant patients, and during periods of neutropenia in patients with acute leukemia.

7a. Herpes simplex infections

MUCOCUTANEOUS HERPES SIMPLEX INFECTIONS

Genital infections

Initial or primary episodes of genital herpes. For initial episodes of genital herpes, aciclovir is very effective when administered intravenously at a dose of 5 mg/kg every 8 hours for 4–5 days (Mindel *et al.*, 1982; Corey *et al.*, 1983a; Peacock *et al.*, 1988; Figure 213.4). The duration of viral shedding, time to complete healing of lesions, and duration of local and systemic symptoms were all markedly decreased by aciclovir therapy if the treatment begins with 7 days of lesion onset. Formation of new genital lesions was also dramatically reduced after therapy was initiated and the complications of the disease were reduced. Neither intravenous nor oral aciclovir treatment of initial genital HSV infections influenced the frequency or duration of subsequent reactivation, indicating that the treatment of first-episode disease occurs too late to have an effect on ganglionic latency (Corey *et al.*, 1983b; Mertz *et al.*, 1984).

Managing recurrent HSV infections with aciclovir, whether by episodic treatment or long-term chemoprophylaxis, also does not influence the natural history of the disease. Neither the interval between recurrences nor their