pigs with cutaneous HSV infection (Burkhardt and Wigand, 1983). In rabbits, trifluridine was less effective than aciclovir in treating experimental herpetic keratitis (Bauer, 1982). In another study, trifluridine was found to be more effective in the rabbit model of herpetic keratitis than penciclovir and similar to cidofovir (Kaufman *et al*., 1998). And a later, careful study of topical cidofovir, aciclovir, and trifluridine for experimental herpes simplex ocular keratitis in rabbits showed that 1% cidofovir was generally superior to 3% aciclovir and 1% trifluridine, with aciclovir being slightly better than trifluridine at those concentrations (Romanowski *et al.,* 1999; Table 221.1).

VARICELLA-ZOSTER VIRUS

Trifluridine was among the first antiviral drugs shown to be active against varicella-zoster virus (De Clercq and Field, 2006). Bromovinyldeoxyuridine (brivudin) had additive antiviral activity with trifluridine against several strains of varicella-zoster when assessed by plaque reduction or infectious center assays (Biron and Elion, 1982).

CYTOMEGALOVIRUS

The half-maximal inhibitory concentration (IC_{50}) values of trifluridine for murine and human CMV have been reported as 0.22 and 0.012 μM, respectively, with an *in vitro* therapeutic ratio of 108 (Wingard *et al*., 1981). However, there are large variances in the reported trifluridine IC_{50} values for CMV. Other investigators have found that trifluridine did not inhibit the viral cytopathic effect of CMV in a plaque reduction assay at concentrations below 50 μM (Lang and Cheung, 1982), and another study reported a high IC_{50} value of 0.57 μM against clinical isolates and 2.1 μM against the AD169 laboratory-adapted strain (Spector *et al*., 1983). Aciclovir and foscarnet have been found to be additive or synergistic when used in combination with trifluridine against laboratory-adapted and clinical strains of human CMV *in vitro*, and they were found additive with human fibroblast interferon (at a concentration of 25 U/ml) (Spector *et al*., 1982; Spector *et al*., 1983).

CANCER

The anticancer activity of trifluridine in animals was discovered contemporaneously with the antiviral activity of the drug (Heidelberger and Anderson, 1964), with its antitumor activity in humans being demonstrated less than a decade later (Dexter *et al.,* 1972). Relatively recently a novel formulation of trifluridine combined with the trifluridine-metabolizing enzyme inhibitor tipiracil hydrochloride to increase trifluridine blood levels (TAS-102), has been shown to have significant anticancer activity in humans (Overman *et al*., 2008; Yoshino *et al.,* 2012; Mayer *et al*., 2015).

2b. Emerging resistance and cross-resistance

Resistance to drugs with a mechanism of action similar to that of trifluridine has been seen in patients treated with aciclovir and penciclovir–famciclovir. However, there are no data on resistance specifically to trifluridine used to treat ocular herpes infections.

3. MECHANISM OF DRUG ACTION

Trifluridine, like other nucleoside analogs, is a prodrug that must be phosphorylated intracellularly to the triphosphate form before it becomes active. Trifluridine is monophosphorylated by a cellular thymidine kinase, and then further converted to the triphosphate, likewise by cellular enzymes. In this respect, trifluridine differs significantly from idoxuridine (Chapter 222, Idoxuridine), aciclovir (Chapter 213, Aciclovir and valaciclovir) and penciclovir–famciclovir (Chapter 214, Famciclovir and penciclovir), all of which are monophosphorylated efficiently only in herpesvirus-infected cells by the virus-specified thymidine kinase. This difference is potentially a positive—for example, trifluridine inhibits replication of CMV, which lacks a traditional thymidine kinase, thereby confirming that phosphorylation of trifluridine depends wholly on host cell kinases (Wingard *et al*., 1981). However it is also a negative because the drug is active in both normal and virus-infected cells, potentially leading to more toxicity than drugs like aciclovir.

Trifluridine monophosphate is an inhibitor of thymidylate synthetase, resulting in depletion of intracellular thymidine nucleotides. This slows viral and host cell DNA syntheses. In addition, trifluridine specifically inhibits viral replication through inhibiting viral DNA polymerases by two separate

Table 221.1. Comparative efficacy of cidofovir, aciclovir, and trifluridine for treatment of experimental HSV-1 keratitis in rabbits[a]

	1% cidofovir	0.5% cidofovir	3% aciclovir	1% trifluridine	Control vehicle
Mean ocular titer of HSV-1 (pfu/ml)	50[b]	250[b]	230[b]	1,500[b]	140,000
% of days with HSV-1 detected	28[c]	36[c]	60[c]	176	127
Mean days of HSV-1 shedding	4.1[d]	5.1[d]	8.2	9.7	9.6
Mean keratitis score	0.0[c]	0.3	0.3	0.7	2.3
Mean days to resolution of keratitis	4.5[d]	5.3[d]	7.0	7.9	13.2

[a]A total of 80 rabbits were used; they were dosed twice daily, starting 2 days after infection.
[b]Better than control ($p < 0.05$).
[c]Better than trifluridine or control ($p < 0.05$).
[d]Better than aciclovir, trifluridine and control ($p < 0.05$).
Source: Data from Romanowski *et al*. (1999).