PRODUCT MONOGRAPH

PrVIROPTIC®
Trifluridine Ophthalmic Solution
1%

Topical Antiviral Agent

Bausch & Lomb Incorporated
1400 North Goodman Street
Rochester, NY
USA 14609

Imported and Distributed by:
Bausch + Lomb Corporation
520 Applewood Crescent
Vaughan, Ontario
L4K 4B4

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ACTION AND CLINICAL PHARMACOLOGY

Trifluridine is phosphorylated by a cellular thymidine kinase to its nucleotide monophosphate. Trifluridine monophosphate is an inhibitor of thymidylate synthetase, the target enzyme for the action of monofluorinated pyrimidines. Trifluridine has been demonstrated to combine slowly and irreversibly with thymidylate synthetase in a reaction that requires ATP.

Trifluridine monophosphate is further phosphorylated by cellular enzymes to the triphosphate which is incorporated into DNA (but not RNA) by competitively inhibiting the incorporation of the natural nucleotide, thymidine triphosphate (dTTP).

The inhibition of viral replication can be reversed by the addition of thymidine (thymidine rescue).

Viral DNA polymerase has a higher affinity for trifluridine triphosphate than does the DNA polymerase of uninfected cells, resulting in the preferential incorporation of the analogue into viral DNA.

INDICATIONS AND CLINICAL USE

VIROPTIC (trifluridine) Ophthalmic Solution, 1% is indicated for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex viruses, types 1 and 2.

VIROPTIC is also effective in the treatment of epithelial keratitis that has not responded clinically to the topical administration of idoxuridine or when ocular toxicity or hypersensitivity to idoxuridine has occurred. In a smaller number of patients found to be resistant to topical vidarabine, VIROPTIC was also effective.

NB: VIROPTIC is not indicated for the treatment of keratitis with deep stromal invasion and uveitis, ocular vaccinia, adenoviral ocular disease, prophylaxis of keratoconjunctivitis and/or recurrent epithelial keratitis, Epstein Barr virus keratitis, or ocular bacterial, fungal, or chlamydial infections.

CONTRAINDICATIONS

VIROPTIC (trifluridine) is contraindicated for patients who are known to be hypersensitive or intolerant to trifluridine or any of its non-medicinal ingredients.

WARNINGS

The recommended dosage and frequency of administration of VIROPTIC (trifluridine) should not be exceeded (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy
VIROPTIC should not be administered to pregnant women or nursing mothers unless the anticipated benefits outweigh the potential risks. The teratogenic potential of this compound in humans is unknown.

The topical application of trifluridine to the eyes of rabbits on days 6-18 of gestation produced no teratogenic effects. When administered subcutaneously to rabbits and rats, fetal toxicity has been observed at doses above 1.0 mg/kg/day (see TOXICOLOGY).

The maximum dose anticipated in a human being based on the recommended dosage is approximately 0.1 mg/kg/day, assuming a body weight of 45 kg.

PRECAUTIONS

General
VIROPTIC (trifluridine) should be prescribed only for patients who have a clinical diagnosis of herpetic keratitis.

VIROPTIC may cause mild local irritation of the conjunctiva and cornea when instilled, but these effects are usually transient.

Caution should be exercised in the use of VIROPTIC in the treatment of infections caused by strains of herpes simplex virus resistant to other antivirals. Conflicting evidence has been presented on the issue of cross-resistance to other antiviral agents. Resistance of herpes simplex virus type 1 to trifluridine has been produced in vitro and these strains are able to produce trifluridine-resistant infections in vivo. HSV-1 strains insensitive to trifluridine were also resistant to idoxuridine and adenine arabinoside. On the other hand, it has been shown that virus lacking thymidine kinase and/or DNA polymerase activity may retain complete or reduced sensitivity to trifluridine in vitro and that trifluridine is still of some benefit in rabbit eyes infected with acyclovir-resistant strains of herpes simplex virus type 1. Early work showed that rabbits infected with HSV-1 strains made resistant to idoxuridine could still be treated successfully with trifluridine.

Following re-epithelialization, VIROPTIC should not be used in an attempt to reduce the rate of recurrence of herpetic keratitis as supporting experimental and clinical data are lacking, and toxicity may occur with prolonged use.

There is no specific experience respecting efficacy and safety of use in children.

Drug Interactions

VIROPTIC should not be applied to the eye simultaneously with other medications. However, the following ophthalmic drugs have been administered topically and concurrently with VIROPTIC in a limited number of patients without apparent evidence of adverse interaction: antibiotics - chloramphenicol, erythromycin, polymyxin B sulfate, bacitracin, gentamicin sulfate, tetracycline hydrochloride, sodium sulfacetamide, neomycin sulfate; steroids - dexamethasone sodium phosphate, dexamethasone, prednisolone acetate, prednisolone sodium phosphate, hydrocortisone, fluorometholone; and other ophthalmic drugs - atropine sulfate, scopolamine hydrobromide, naphazoline hydrochloride, cyclopentolate hydrochloride, homatropine hydrobromide, pilocarpine, l-epinephrine hydrochloride and sodium chloride.

Carcinogenesis and Mutagenesis

See TOXICOLOGY

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. VIROPTIC Ophthalmic Solution, 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see TOXICOLOGY).

Nursing Mothers

It is unlikely that trifluridine is excreted in human milk after ophthalmic instillation of VIROPTIC because of the relatively small dosage (5.0 mg/day), its dilution in body fluids and its extremely short half-life (approximately 12 minutes). The drug should not be prescribed for nursing mothers unless the potential benefit outweighs the potential risk.

ADVERSE REACTIONS

Fifty-four of 297 (18%) patients experienced adverse reactions. The following adverse reactions were noted in controlled and open studies during the administration of VIROPTIC (trifluridine): burning upon instillation (12%); superficial punctate keratitis (2%); and eyelid edema, irritation, epithelial keratopathy, allergic reaction, increased intraocular pressure, keratitis sicca, stromal edema, blurred vision and nausea each occurred in less than 1% of the patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage by ocular instillation is unlikely because any excess solution should be quickly expelled from the conjunctival sac.

Acute overdosage by accidental oral ingestion of VIROPTIC (trifluridine) has not been reported. However, should such ingestion occur, the 75 mg of trifluridine in a single bottle of VIROPTIC would not be expected to produce adverse effects.

Single intravenous doses of 1.5 - 30 mg/kg/day in children and adults with neoplastic disease

produce reversible bone marrow depression as the only potentially serious toxic effect and only after at least 5 doses. The acute oral LD_{50} in the mouse and rat was 4379 mg/kg or higher.

DOSAGE AND ADMINISTRATION

Adult

Instill one drop of VIROPTIC (trifluridine) Ophthalmic Solution, 1% onto the cornea of the affected eye every two hours while awake. The maximum daily dosage is nine drops.

This therapeutic regimen should be continued until the herpetic lesion has completely re-epithelialized. At this time the dosage of VIROPTIC should be reduced to one drop every four hours for a maximum daily dosage of five drops. This regimen should be continued for seven days post-re-epithelialization.

If there are no signs of improvement after seven days of full therapy or complete re-epithelialization has not occurred after 14 days of full therapy, other forms of therapy should be considered.

ADMINISTRATION OF A FULL DOSAGE REGIMEN FOR PERIODS EXCEEDING 21 DAYS SHOULD BE AVOIDED BECAUSE OF POTENTIAL OCULAR TOXICITY.

Pediatric

There is no specific information relating to use in children.

PHARMACEUTICAL INFORMATION

Drug Substance

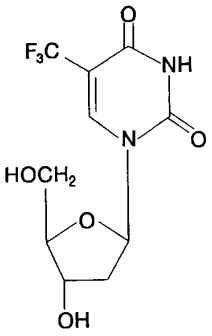
Brand Name: VIROPTIC

Common Name: Trifluridine

Chemical Name: Thymidine, α,α,α-trifluoro-[USAN]

Chemical Name: 2'-Deoxy-5-(trifluoromethyl)uridine [Chem. Abstr.]

Structural Formula:



[USAN]

Molecular Formula: $C_{10}H_{11}F_3N_2O_5$

Molecular Weight: 296.21 g/mol

Physicochemical Properties

Description: Trifluridine is a white, odorless, crystalline powder.

Melting Point: Melting point of about 186°C with decomposition.

pKa: It is a very weak base with a pKa of 7.85.

Solubility:	At 25°C, it is soluble in water to the extent of 50 mg/mL. In non-polar organic solvents, it is not soluble at the 0.2 mg/mL level.

Composition
VIROPTIC is an aqueous, 1% trifluridine solution. It also contains sodium chloride, acetic acid, sodium acetate and benzalkonium chloride as preservative.

Stability and Storage Recommendations
VIROPTIC should be stored under refrigeration (2° to 8° C).

AVAILABILITY OF DOSAGE FORMS

VIROPTIC Ophthalmic Solution, 1% is supplied as a sterile ophthalmic solution in a plastic drop-dose dispenser bottle of 7.5 mL.

VIROLOGY

Trifluridine is active against the following DNA viruses: herpes simplex types 1 and 2, varicella zoster, adenovirus and vaccinia virus.

Using plaque inhibition assays, plaque reduction assays and inhibition of cytopathic effect (CPE) in Vero cells, activity was demonstrated against clinical isolates of HSV-1 and HSV-2. The concentrations of antiviral required to reduce the plaque count or yield of virus by 50% (ED_{50}'s) ranged from 0.75 mcM to 19.5 mcM for HSV-1 and 0.87 mcM to 44.7 mcM trifluridine for HSV-2, depending on the assay employed. Two of the HSV-2 isolates proved to be resistant to trifluridine up to concentrations which produced cellular toxicity. These data have been reproduced in other studies in which ED_{50}'s ranging from 0.4 mcg/mL to 1.0 mcg/mL trifluridine for HSV-1 and 0.3 mcg/mL to 1.0 mcg/mL trifluridine for HSV-2 were found. In addition, the activity of trifluridine against vaccinia virus and a thymidine kinase deficient (TK^-) isolate of HSV-1 has been assessed. These viruses had ED_{50}'s of 0.2 mcg/mL and 0.5 mcg/mL trifluridine, respectively. An HSV-1 isolate (McKrae strain) made resistant to idoxuridine was still sensitive to trifluridine.

Adenovirus, a clinical isolate and two reference strains, were tested in human embryonic kidney cells and Flow 4000 cells; activity was scored by inhibition of CPE and reduction in virus yield. With standard concentrations of 0.05 mg/mL or 0.07 mg/mL trifluridine, a reduction in virus yield anywhere from 10-fold to 10 000-fold could be demonstrated, depending on the strain tested.

The major degradation product of trifluridine, 5-carboxy-2'-deoxyuridine, showed minimal activity in a plaque reduction assay with Vero cells and HSV-1.

In Vivo Studies
Animal studies have demonstrated the effectiveness of trifluridine in the treatment of keratitis and iritis caused by herpes simplex and by vaccinia viruses.

The animal model most commonly employed was the New Zealand White rabbit model of keratitis. The rabbits' eyes were scarified, and infection produced by topical instillation of infective material. Treatment was commonly begun on the third day following infection. By this time ulcers were usually demonstrable using fluorescein staining and slit lamp examination. Using this system, it was shown that the severity of ulceration was much less marked in trifluridine-treated animals than in controls. Scores were 0.2 ± 0.3 and 2.0 ± 0.9, respectively. In another study, the following 4 treatment groups were employed:

1. Drops every 2 hours for 8 hours/day in one eye, the other eye was left untreated, treatment commenced on day 3.

2. Treatment as in group 1 but started on day 5.

3. Following infection, the eyes were treated with prednisolone and subsequently, on day 3, with trifluridine or further steroid.

4. Treatment with trifluridine or steroid beginning on day 3.

Treatment was assessed on day 8 and groups 1 and 4 showed acceptable clinical cure in the trifluridine-treated eyes. In groups 2 and 3 treatment was effective but did not always prevent deep involvement of the stroma.

In other experiments, keratitis or iritis was produced by local instillation of herpesvirus (McKrae strain) or by injection into the anterior chamber of the eyes of New Zealand White rabbits. Treatment with trifluridine 5 times/day was significantly better than placebo in clearing the eye of the keratitis; topical treatment was effective in iritis when applied every two hours around the clock.

PHARMACOLOGY

Animal Studies

Penetration of trifluridine (TFT) into the aqueous humour of herpesvirus-infected and uninfected rabbit eyes following topical application has been studied. The following table summarizes the

Concentration of TFT in Aqueous Humour

	30 minutes	60 minutes	90 minutes
Normal rabbit eyes	5-6 mcg/mL	5-6 mcg/mL	5-6 mcg/mL
Diseased eyes	37 mcg/mL	3.4 mcg/mL	not detectable

Penetration of trifluridine into the aqueous humour has been shown to be a linear function of concentration and time, and not a saturable process. Penetration of trifluridine across the cornea is not likely to be carrier-mediated. Studies on excised rabbit cornea confirmed that trifluridine could penetrate the cornea, and that the absence of the corneal epithelium enhanced its penetration approximately 2-fold.

Intravenous and intraperitoneal pharmacokinetic studies in animals (dogs, monkeys, tumour-bearing and normal mice) reveal that 60-93% of the drug is excreted in the urine within 24 hours, mainly as the ultimate metabolite, 5-carboxy-2'-deoxyuridine, with traces of its intermediates. The plasma half-life in dogs and monkeys is approximately 30 minutes There is some difference in the rates of metabolism and excretion among species. Following sacrifice of the animals at 24 hours, small amounts of unchanged drug (2-30 mcg/g) were detectable in the tissues. The greatest amounts were found in the bone marrow (dogs and monkeys), lymph nodes (dogs) and tumour tissue (mice); of this, a significant portion appeared to be protein bound.

Human Studies

Intraocular penetration of trifluridine was evaluated in 5 patients undergoing intraocular surgery. One drop of 1% trifluridine was instilled into the affected eye four times at 10-minute intervals, the last dose being administered 5 minutes before sterile preparation for surgery. Penetration of the drug was demonstrated in 4 of the 5 patients in concentrations ranging from 3.1-43.9 mcM with a mean value of 16.75 mcM which exceeds the ED_{50}'s for most clinical isolates of HSV-1. There appeared to be a correlation between the degree of corneal integrity and the degree of penetration of trifluridine into the aqueous humour as evidenced by the fact that patients with corneal thinning had higher drug levels (mean 21.3 mcM) than did the single patient with an intact cornea (3.1 mcM). The major metabolite of trifluridine (5-carboxy-2'-deoxyuridine) was not detected in any of the eyes.

The pharmacokinetics of trifluridine in humans is similar to that of animals. The plasma half-life in human cancer patients following intravenous administration of the drug is short and dose-independent (see table).

	Dose of Trifluridine	T1/2
Patient 1	27 mg/kg	18 minutes
Patient 2	15 mg/kg	28 minutes
Patient 3	5 mg/kg	14 minutes

Following intravenous administration trifluridine is excreted in the urine largely as 5-carboxy-2'-deoxyuridine, with trace amounts of its intermediates and unchanged drug. Evidence indicates minimal tissue protein binding both in animals and man.

Samples from 12 volunteers who received topical 1% trifluridine did not reveal detectable serum levels of the drug, indicating that systemic absorption from the eye is minimal.

TOXICOLOGY

Acute Studies

The acute LD_{50} values in animals are as follows:

Species	Dosage	Route
Mouse	3598 mg/kg	I.V.
Mouse	5282 mg/kg	P.O.
Rat	4379 mg/kg	P.O.

Subchronic Subcutaneous Studies

Rats
Groups of 15 male and 15 female Long-Evans rats were given subcutaneous injections for 32-33 consecutive days of either 0.0, 1.5, 6.0 or 15.0 mg/kg/day of trifluridine as 3 equally divided doses. At the end of dosing, 10 males and 10 females per treatment group were sacrificed; the remaining 5 of each sex sacrificed following a 16-day postdose drug-free period. Data were collected on antemortem observations, hematology, clinical chemistry, ophthalmology and post-mortem examinations. No drug-related changes were observed in clinical signs, hematology, clinical chemistry and ophthalmic observations or measurements. Testicular effects (atrophy, decreased absolute organ weight and presence of giant cells) were noted in the 15.0 mg/kg/day dose groups, but were absent in animals held for a 16-day postdose drug-free period.

Dogs
Groups of 4 male and 4 female Beagle dogs were given subcutaneous injections for 29-30 consecutive days of either 0.0, 1.5, 6.0 or 15.0 mg/kg/day of trifluridine as 3 equally divided doses. At the end of dosing, 3 male and 3 female dogs per treatment group were sacrificed; the remaining male and female dogs were sacrificed following a 20-day postdose drug-free period. Data were collected from antemortem observations, hematology, clinical chemistry, ophthalmology, electrocardiograms and post-mortem examinations.

Administration of trifluridine to the dog at 6.0 mg/kg/day resulted in body weight loss, reduced appetite, emesis, soft or watery feces, decreased total leukocyte counts, thrombocytopenia, a mild normocytic normochromic anemia, hypoplasia of the bone marrow, lymphoid depletion in the lymph nodes and thymus, reduced mitotic activity of the intestinal epithelium and the presence of

many spermatidic giant cells in the testes. Similar changes, usually more severe, occurred at 15.0 mg/kg/day and probably accounted for all dogs being sacrificed in a moribund condition or dying between dose days 7-25. Several serum chemistry parameters (glucose, urea nitrogen, total protein, albumin, globulin, SGPT and BSP retention) were increased only at the 15.0 mg/kg/day dose level and were believed to be secondary to the deteriorated health state of these animals. Emesis, alterations in fecal consistency, a marginal decrease in total leukocyte counts and the presence of a few spermatidic giant cells in the testes were noted in dogs at 1.5 mg/kg/day.

Subchronic Intravenous Studies

Dogs
Eleven adult male and female Beagle dogs were administered a single daily intravenous injection of trifluridine with 2 animals at each level of 6.25, 12.5, 25, 50 and 100 mg/kg and 1 dog at 200 mg/kg for an attempted duration of 14 days. Deaths occurred in the dog at doses of 50mg/kg/day or greater. At all dosage levels, body weight losses occurred and varied from severe, at 25 mg/kg and above, to moderate at lower dosage levels. Doses of 12.5 mg/kg/day or greater resulted in leukopenia and hematuria. Histopathological changes occurred in the liver (reduction in liver glycogen and increased organ weight), kidney (swelling and focal necrosis of the proximal tubules), gastrointestinal tract (intestinal focal congestion and hemorrhage), lymphoid tissue (focal hypoplasia in the spleen and regional lymph nodes) and bone marrow hypoplasia.

Monkeys
Eleven adult male and female Rhesus monkeys were administered a single daily intravenous injection of trifluridine: 4 animals at 50 mg/kg, 3 at 100 mg/kg and 150 mg/kg, and 1 at 200 mg/kg for an attempted duration of 14 days. Deaths occurred in the monkeys at doses of 150 mg/kg/day or greater.

At 100 mg/kg/day or greater, there was pronounced leukopenia, transient erythropenia with concurrent decreases in hematocrit and hemoglobin values, increases in SGPT and BUN values, hematuria and proteinuria. Histopathological changes occurred in liver (focal necrosis and congestion), kidney (focal cloudy swelling and fat deposition) and bone marrow hypoplasia.

In a 90-day study, 27 adult male and female Rhesus monkeys were administered daily or weekly intravenous doses of trifluridine.

In animals receiving a daily dose, 3 monkeys in each group received 12.5, 25 or 50 mg/kg/day and 5 animals were used as controls. In animals receiving a weekly dose, 3 monkeys in each group received 200, 400 or 800 mg/kg/week, 1 animal received 1200 mg/kg and 3 animals were used as controls. Each group consisted of males and females.

In the daily-dosed animals, one death occurred in the control group and in the 50 mg/kg/day group. In the weekly-dosed animals, a single death occurred in each of the following groups: control, 400 mg/kg and 1200 mg/kg. There were 2 deaths in the 800 mg/kg group.

Once-a-week dosing at levels greater than 200 mg/kg was more toxic than lower doses given

once daily. Toxicity was minimal or reduced at the 12.5 mg/kg/day dose level. Toxic signs included reduced erythrocyte counts, transient leukopenia, decreased hematocrit and/or hemoglobin values, increased SGPT and BUN values and hypoglycemia.

Histopathologic changes occurred in the liver (decreased glycogen, microgranules and increased neutral lipids) and lipid nephrosis of the kidney.

Subchronic Ocular Studies

Rabbits
Five groups each consisting of 6 New Zealand White rabbits were administered one drop of test solution into one eye, 5 times per day for a period of 21 consecutive days. The test solutions were 0.9% saline control, vehicle control, and 1.0%, 2.0% and 4.0% trifluridine. There were 2 male and 4 female rabbits in each group except for the 1% trifluridine group, which had an equal number of males and females. The untreated eye of each rabbit was used as a self-control.

No drug-related abnormal clinical signs or gross signs of irritation were observed. Biomicroscopic findings included corneal, vitreous and/or lens opacities in all groups including the control eyes. There was no clear relationship to drug treatment. Histological examination revealed slight thinning of the cornea only in the 1% trifluridine group. There were no histological changes observed in any animals sacrificed 14 days after the termination of dosing.

In a second study, 3 groups of 12 (5 male and 7 female) New Zealand White rabbits each were administered one drop of vehicle, 2.0% or 4.0% trifluridine solution, 5 times daily for 21 consecutive days. The untreated eye of each rabbit was used as a self-control.

No gross signs of eye irritation were observed in this study. Biomicroscopic and funduscopic examinations revealed no drug-related abnormalities. Histologic examination of eyes from rabbits sacrificed 14-15 days after the end of treatment showed no changes in any of the groups.

Chronic Ocular Study
New Zealand White rabbits were treated either intermittently or daily for one year with a balanced saline solution, 1% trifluridine solution or 1% trifluridine ointment. Two groups, each consisting of 8 males and 8 females, were dosed with either one drop of trifluridine 1% solution or one cm of 1% ointment respectively. These groups were dosed 5 times daily for an initial 3-week period, then for two 2-week periods, followed by a final 3-week period. They were not dosed during the three 10-11-week periods between the four dosing periods.

An additional 2 groups consisting of 10 males and 10 females, and 8 males and 8 females, were dosed with balanced saline and 1% trifluridine solution, respectively. These 2 groups were dosed 5 times daily for 6 consecutive weeks; the dosing schedule then decreased to once daily for 7 consecutive weeks. This pattern of alternate dosing was continued for a period of 12 months. In addition, a control group of 10 male and 10 female rabbits served as an untreated control group.

No drug-related effects were observed in body weight gain, food consumption, general health status, slit lamp biomicroscopy or gross and histopathologic eye examinations. A greater

frequency of mild chemosis and conjunctivitis occurred early in the study and only with the 1% ointment group. No signs of eye irritation were observed with 1% trifluridine solution.

Corneal Wound Healing

A study in New Zealand White rabbits (17 eyes per group, treated with 1% trifluridine solution vs. saline control) indicated that trifluridine does not significantly retard closure of epithelial eye wounds. A reduction in the mean tensile strength of wounds in 8 trifluridine-treated eyes was evident compared with controls but the difference was not statistically significant.

Teratogenicity

Trifluridine is teratogenic when injected into the yolk sac of developing chick embryos on days 1 through 4. Skeletal abnormalities included cleft palate, absence of whole extremities, and absence, shortening or curvature of single bones in the extremities. Fetal mortality was high. Doses which produced teratogenic changes increased with the developing maturity of the embryo: e.g., 0.1-0.5 mcg on day 2, 0.75-1.75 mcg on day 3, and 2.4-3.1 mcg on day 4.

Trifluridine (0.0, 1.0, 2.5 and 5.0 mg/kg/day) was not teratogenic when administered subcutaneously to rats on days 6-15 of gestation. There were 17-23 rats per dose level. Fetal toxicity was seen at the 2.5 mg/kg/day and was more marked at the 5.0 mg/kg/day dose levels. It was manifested by an increase in the incidence of reduced ossification of the first sternebra, unossified second sternebra and thin parietal, interparietal and supraoccipital bones.
Similar results were observed when trifluridine was administered subcutaneously to rabbits at doses of 0.0, 1.0, 2.5 and 5.0 mg/kg/day on days 16-18 of gestation. The number of female New Zealand White rabbits per group ranged from 12-16. There were no obvious teratogenic effects at any of the doses, but fetal toxicity was observed at the 2.5 mg/kg/day level. Notable findings included an increase in the number of dead and resorbed fetuses, an increase in the number of supernumerary 13th ribs, and reduced ossification in the first cervical vertebra and the first and third sternebrae. Increasing the dose of trifluridine to 5.0 mg/kg/day produced maternal toxicity as well as fetal damage, evidenced by decreased maternal weight during dosing and pregnancy, spontaneous abortion in one doe and only 3/16 does having viable fetuses at time of sacrifice on day 29 of gestation.

The effect of topically administered trifluridine was studied in Japanese albino rabbits. Eight rabbits received 1 drop of 1% trifluridine 6 times daily on the 6th day of gestation, and 4 times daily from the 7th to the 18th day of gestation. All rabbits were sacrificed on day 28 and the fetuses were examined for external, skeletal or histologic changes. No teratogenic or toxic effects were observed.

Mutagenicity

A variety of in vitro test systems and organisms have been employed in an attempt to assess the mutagenic potential of trifluridine. These test systems include the Ames Salmonella assay (plate incorporation and pre-incubation assay), an E. coli DNA-repair assay and two loci in cultured mouse lymphoma cells.

Results from the microbial studies have been conflicting. The Ames plate incorporation assay, at concentrations of 0.1, 1.0, 10.0, 100.0 and 500.0 mcg/plate, did not demonstrate any mutagenic potential. The pre-incubation assay, which maximizes contact between test compound and indicator strain, was performed at the following concentrations of trifluridine: 80, 400, 2000, 4000, and 8000 mcg/plate. Positive results were seen at concentrations of 400 mcg/plate trifluridine and above.

The E. coli DNA repair test demonstrated that trifluridine could induce, in particular bacterial strains, repairable DNA damage at the lowest concentration employed, 125 mcg/well (range of doses 0, 125, 500 and 1000 mcg/well).

Testing in the mammalian cell system (L5178Y mouse lymphoma) did not demonstrate any trifluridine-induced mutagenic changes at the HGPRT locus at concentrations of 0.5, 1, 4, 16, 32, 63 and 125 mcg/mL. Interpretation of the study at the thymidine kinase (TK) locus (0.5, 1.5, 5.0 mcg/mL trifluridine) was confounded by the selective toxicity of trifluridine to the parent cell population.

The effect of trifluridine has also been assessed in synchronous and asynchronous Chinese hamster cells. These studies employed a wide range of concentrations, from 3×10^{-3} mM to 1 mM trifluridine. No mutagenic effects were noted in asynchronous cultures, but a weak mutagenic effect could be seen in synchronous cells.

Carcinogenicity

Lifetime carcinogenicity bioassays in rats and mice given daily subcutaneous doses of trifluridine have been performed. Rats tested at 1.5, 7.5 and 15 mg/kg/day had increased incidences of adenocarcinomas of the intestinal tract and mammary glands, hemangiosarcomas of the spleen and liver, carcinosarcomas of the prostate gland and granulosathecal cell tumors of the ovary. Mice were tested at 1, 5 and 10 mg/kg/day; those given 10 mg/kg/day trifluridine had significantly increased incidences of adenocarcinomas of the intestinal tract and uterus. Those given 10 mg/kg/day also had a significantly increased incidence of testicular atrophy as compared to vehicle control mice.

BIBLIOGRAPHY

1. Reyes P, Heidelberger C: Fluorinated pyrimidines. XXVI. Mammalian thymidylate synthetase: its mechanism of action and inhibition by fluorinated nucleotides. Mol Pharmacol 1965; 1(1):14-30.

2. Heidelberger C: On the molecular mechanism of the antiviral activity of trifluorothymidine. Ann NY Acad Sci 1975; 255:317-25.

3. Coster DJ, McKinnon JR, McGill JI, et al. Clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of corneal ulcers caused by herpes simplex virus. J Infect Dis 1976; 133(Suppl):A173-A177.

4. Laibson PR, Arentsen JJ, Mazzanti WD, et al. Double controlled comparison of IDU and trifluorothymidine in thirty-three patients with superficial herpetic keratitis. Tr Am Ophth 1977; Soc LXXV:316-24.

5. Laibson PR, Pavan-Langston D: Trifluorothymidine in the treatment of herpes simplex keratitis. Drug Symposium, sponsored by ARVO and AAOO, Dallas, October 1977.

6. McKinnon JR, McGill JI, Jones BR: A coded clinical evaluation of adenine arabinoside and trifluorothymidine in the treatment of ulcerative herpetic keratitis. In: Pavan-Langston D, Buchanan RA, Alford CA, Jr. (eds), Adenine Arabinoside: An Antiviral Agent, Raven Press, New York, 1975, pp. 401-410.

7. Pavan-Langston D, Foster CS: Trifluorothymidine and idoxuridine therapy of ocular herpes. Am J Ophthal 1977; 84(6):818-25.

8. Pavan-Langston D, Foster CS: Trifluorothymidine therapy of herpetic keratitis: double-blind and open clinical study. Invest Ophthal 1977; 16(Suppl):75. (abstract)

9. Travers JP, Patterson A: A controlled trial of adenine arabinoside and trifluorothymidine in herpetic keratitis. J Int Med Res 1978; 6:102-04.

10. Wellings PC, Awdry PN, Bors FH, et al. Clinical evaluation of trifluorothymidine in the treatment of herpes simplex corneal ulcers. Am J Ophthal 1972; 73(6):932-42.

11. Itoi M, Gefter JW, Kaneko N, et al. Teratogenicities of ophthalmic drugs. I. Antiviral ophthalmic drugs. Arch Ophthalmol 1975; 93(1):46-51.

12. Gauri KK: Anti-herpesvirus polychemotherapy. Adv Ophthalmol 1979; 38:151-63.

13. Field H, McMillan A, Darby G: The sensitivity of acyclovir-resistant mutants of herpes simplex virus to other antiviral drugs. J Infect Dis 1981; 143(2):281-85.

14. O'Brien WJ, Taylor JL: Chemotherapy of herpetic keratitis induced by acyclovir-resistant strains of herpes simplex virus type 1. Am J Med 1982; 73(1A):294-99.

15. Kaufman HE, Heidelberger C: Therapeutic antiviral action of 5-trifluoromethyl-2'-deoxyuridine in herpes simplex keratitis. Science 1964; 145(3652):585-86.

16. Kaufman HE: In vivo studies with antiviral agents. Ann NY Acad Sci 1965; 130:168-80.

17. Collins P, Bauer DJ: Relative potencies of anti-herpes compounds. Ann NY Acad Sci 1977; 284:49-59.

18. Lennette DA, Eiferman RA: Inhibition of adenovirus replication in vitro by trifluridine. Arch Ophthalmol 1978; 96:1662-63.

19. De Clercq E, Descamps J, Verhelst G, et al. Comparative efficacy of antiherpes drugs against different strains of herpes simplex virus. J Inf Dis 1980; 141(5):563-74.

20. Kaufman HE, Varnell ED, Centifanto YM, et al. Effect of 9-(2-hydroxyethoxymethyl)guanine on herpesvirus-induced keratitis and iritis in rabbits. Antimicrob Agents Chemother 1978; 14(6):842-45.

21. Sugar J, Varnell E, Centifanto Y, et al. Trifluorothymidine treatment of herpetic iritis in rabbits and ocular penetration. Invest Ophthalmol 1973; 12(7):532-34.

22. O'Brien WJ, Edelhaus HF: The corneal penetration of trifluoro-thymidine, adenine arabinoside, and idoxuridine: a comparative study. Invest Ophthalmol Visual Sci 1977; 16(12):1093-1103.

23. Rogers WI, Hartman AC, Palm PE, et al. The fate of 5-trifluoromethyl-2'-deoxyuridine in monkeys, dogs, mice and tumor-bearing mice. Cancer Res 1969; 29(4):953-961.

24. Heidelberger C, Boohar J, Kampschroer B: Fluorinated pyrimidines. XXIV. In vivo metabolism of 5-trifluoromethyluracil-2-C^{14} and 5-trifluoromethyl-2'- deoxyuridine-2-C^{14}. Cancer Res 1965; 25(4):377-81.

25. Dexter D, Wolberg W, Ansfield F, et al. The clinical pharmacology of 5-trifluoromethyl-2'-deoxyuridine. Cancer Res 1972; 32:247.

26. Foster CS, Pavan-Langston D: Corneal wound healing and antiviral medication. Arch Ophthalmol 1977; 95(11):2062-67.

27. Kury G, Crosby RJ: The teratogenic effect of 5-trifluoromethyl- 2'-deoxyuridine in chicken embryos. Toxicol Appl Pharmacol 1967; II(1):72-80.

28. Huberman E, Heidelberger C: The mutagenicity to mammalian cells of pyrimidine nucleoside analogs. Mutat Res 1972; 14(1):130-32.

29. Aebersold PM: Relative mutagenicity of nucleoside virostatic drugs in Chinese hamster ovary cells. Adv Ophthalmol 1979; 38:214-21.

30. Heidelberger C, Dexter DL, Wolberg WH. Clinical pharmacology of 5-trifluoromethyl-2'-deoxyuridine (F-TDR). Pro. Amer. Assoc. Cancer Res. 1970;11:35.