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DESCRIPTION

Fansidar is an antimalarial agent, each tablet containing 500 mg N^1-(5,6-dimethoxy-4-pyrimidinyl) sulfanilamide (sulfadoxine) and 25 mg 2,4-diamino-5-(p-chlorophenyl)-6-ethylpyrimidine (pyrimethamine). Each tablet also contains corn starch, gelatin, lactose, magnesium stearate and talc.

CLINICAL PHARMACOLOGY

Fansidar is an antimalarial agent which acts by reciprocal potentiation of its two components, achieved by a sequential blockade of two enzymes involved in the biosynthesis of folinic acid within the parasites. Fansidar is effective against certain strains of *Plasmodium falciparum* that are resistant to chloroquine.

Both the sulfadoxine and the pyrimethamine of Fansidar are absorbed orally and are excreted mainly by the kidney. Following a single tablet administration, sulfadoxine peak plasma concentrations of 51 to 76 mcg/mL were achieved in 2.5 to 6 hours and the pyrimethamine peak plasma concentrations of 0.13 to 0.4 mcg/mL were achieved in 1.5 to 8 hours. The apparent half-life of elimination of sulfadoxine ranged from 100 to 231 hours with a mean of 169 hours, whereas pyrimethamine half-lives ranged from 54 to 148 hours with a mean of 111 hours. Both drugs appear in breast milk of nursing mothers.

INDICATIONS AND USAGE

Fansidar is indicated for the treatment of *P. falciparum* malaria for those patients in whom chloroquine resistance is suspected. Malaria prophylaxis with Fansidar is indicated for travelers to areas where chloroquine-resistant *P. falciparum* malaria is endemic. However, strains of *P. falciparum* may be encountered which have developed resistance to Fansidar.

CONTRAINDICATIONS

Prophylactic (repeated) use of Fansidar is contraindicated in patients with severe renal insufficiency, marked liver parenchymal damage or blood dyscrasias. Hypersensitivity to pyrimethamine or sulfonamides. Patients with documented megaloblastic anemia due to folate deficiency. Infants less than two months of age. Pregnancy at term and during the nursing period because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF FANSIDAR HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS. FANSIDAR PROPHYLAXIS SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH, IF A SIGNIFICANT REDUCTION IN THE COUNT OF ANY FORMED BLOOD ELEMENTS IS NOTED, OR UPON THE OCCURRENCE OF ACTIVE BACTERIAL OR FUNGAL INFECTIONS.

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Fansidar prophylactic regimen has been reported to cause leukopenia during a treatment of two months or longer. This leukopenia is generally mild and reversible.

PRECAUTIONS

1. *General:* Fansidar should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. As with some sulfonamide drugs, in glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. Urinalysis with microscopic examination and renal function tests should be performed during therapy of those patients who have impaired renal function.

2. *Information for the Patient:* Patients should be warned that at the first appearance of a skin rash, they should stop use of Fansidar and seek medical attention immediately. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

Patients should also be warned that the appearance of sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura, jaundice or glossitis may be early indications of serious disorders which require prophylactic treatment to be stopped and medical treatment to be sought.

Females should be cautioned against becoming pregnant and should not breast feed their infants during Fansidar therapy or prophylactic treatment.

Patients should be warned to keep Fansidar out of reach of children.

3. *Laboratory Tests:* Periodic blood counts and analysis of urine for crystalluria are desirable during prolonged prophylaxis.

4. *Drug Interactions:* There have been reports which may indicate an increase in incidence and severity of adverse reactions when chloroquine is used with Fansidar as compared to the use of Fansidar alone. Fansidar is compatible with quinine and with antibiotics. However, antifolic drugs such as sulfonamides or trimethoprim-sulfamethoxazole combinations should not be used while the patient is receiving Fansidar for antimalarial prophylaxis. Fansidar has not been reported to interfere with antidiabetic agents.

If signs of folic acid deficiency develop, Fansidar should be discontinued. Folinic acid (leucovorin) may be administered in doses of 5 mg to 15 mg intramuscularly daily, for 3 days or longer, for depressed platelet or white blood cell counts in patients with drug-induced folic acid deficiency when recovery is too slow.

5. *Carcinogenesis, mutagenesis, impairment of fertility:* Pyrimethamine was not found carcinogenic in female mice or in male and female rats. The carcinogenic potential of pyrimethamine in male mice could not be assessed from the study because of markedly reduced life-span. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totaling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test. Testicular changes have been observed in rats treated with 105 mg/kg/day of Fansidar and with 15 mg/kg/day of pyrimethamine alone. Fertility of male rats and the ability of male or female rats to mate were not adversely affected at dosages of up to 210 mg/kg/day of Fansidar. The pregnancy rate of female rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at dosages of 31.5 mg/kg/day or higher, a dosage approximately 30 times the weekly human prophylactic dose or higher.

6. *Pregnancy:* Teratogenic effects: Pregnancy Category C. Fansidar has been shown to be teratogenic in rats when given in weekly doses approximately 12 times the weekly human prophylactic dose. Teratology studies with pyrimethamine plus sulfadoxine (1:20) in rats showed the minimum oral teratogenic dose to be approximately 0.9 mg/kg pyrimethamine plus 18 mg/kg sulfadoxine. In rabbits, no teratogenic effects were noted at oral doses as high as 20 mg/kg pyrimethamine plus 400 mg/kg sulfadoxine.

There are no adequate and well-controlled studies in pregnant women. However, due to the teratogenic effect shown in animals and because pyrimethamine plus sulfadoxine may interfere with folic acid metabolism, Fansidar therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential who are traveling to areas where malaria is endemic should be warned against becoming pregnant.

Nonteratogenic Effects: See "CONTRAINDICATIONS" section.

7. *Nursing Mothers:* See "CONTRAINDICATIONS" section.

8. *Pediatric Use:* Fansidar should not be given to infants less than two months of age because of inadequate development of the glucuronide-forming enzyme system.

ADVERSE REACTIONS

For completeness, all major reactions to sulfonamides and to pyrimethamine are included below, even though they may not have been reported with Fansidar. See WARNINGS and PRECAUTIONS (*Information for the Patient*) sections.

Blood Dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, methemoglobinemia and eosinophilia.

Allergic Reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, toxic epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal Reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea and pancreatitis.

C.N.S. Reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Respiratory Reactions: Pulmonary infiltrates.

Miscellaneous Reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

OVERDOSAGE

Acute intoxication may be manifested by anorexia, vomiting and central nervous system stimulation (including convulsions), followed by megaloblastic anemia, leukopenia, thrombocytopenia, glossitis and crystalluria. In acute intoxication, emesis and gastric lavage followed by purges may be of benefit. The patient should be adequately hydrated to prevent renal damage. The renal and hematopoietic systems should be monitored for at least one month after an overdosage. If the patient is having convulsions, the use of a parenteral barbiturate is indicated. For depressed platelet or white blood cell counts, folinic acid (leucovorin) should be administered in a dosage of 5 mg to 15 mg intramuscularly daily for 3 days or longer.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE section):

(a) *Treatment of Acute Attack of malaria*

A single dose of the following number of Fansidar Tablets is used in sequence with quinine or alone:

Adults	2 to 3 tablets
9 to 14 years	2 tablets
4 to 8 years	1 tablet
Under 4 years	½ tablet

(b) *Malaria Prophylaxis*

The first dose of Fansidar should be taken 1 or 2 days before departure to an endemic area; administration should be continued during the stay and for 4 to 6 weeks after return.

	Once Weekly	Once Every Two Weeks
Adults	1 tablet	2 tablets
9 to 14 years	¾ tablet	1½ tablets
4 to 8 years	½ tablet	1 tablet
Under 4 years	¼ tablet	½ tablet

HOW SUPPLIED

Scored tablets, containing 500 mg sulfadoxine and 25 mg pyrimethamine—Tel-E-Dose® packages of 25 (NDC-0004-0161-03). Imprint on tablets: FANSIDAR ROCHE

Revised: October 1993

Shown in Product Identification Guide, page 326

FLUOROURACIL

℞

[*flu "ro-u 'ra-sil*]

INJECTION

The following text is complete prescribing information based on official labeling in effect June 1, 1994.

WARNING

It is recommended that FLUOROURACIL be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy.

DESCRIPTION

FLUOROURACIL INJECTION, an antineoplastic antimetabolite, is a sterile, nonpyrogenic injectable solution for intravenous administration. Each 10-mL contains 500 mg fluorouracil; pH is adjusted to approximately 9.2 with sodium hydroxide.

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4 (1*H*,3*H*)-pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water. The molecular weight of fluorouracil is 130.08.

CLINICAL PHARMACOLOGY

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid rate.

Following intravenous injection, fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. In spite of its limited lipid solubility, fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

Seven percent to 20% of the parent drug is excreted unchanged in the urine in 6 hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The

catabolic metabolism of fluorouracil results in degradation products (eg, CO_2, urea and α-fluoro-β-alanine) which are inactive. The inactive metabolites are excreted in the urine within the next 3 to 4 hours. When fluorouracil is labeled in the 6-carbon position, thus preventing the ^{14}C metabolism to CO_2, approximately 90% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position approximately 90% of the total radioactivity is excreted in expired CO_2. Ninety percent of the dose is accounted for during the first 24 hours following intravenous administration.

Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an intravenous injection.

INDICATIONS AND USAGE

Fluorouracil is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

CONTRAINDICATIONS

Fluorouracil therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function, those with potentially serious infections or those with a known hypersensitivity to Fluorouracil.

WARNINGS

THE DAILY DOSE OF FLUOROURACIL IS NOT TO EXCEED 800 MG. IT IS RECOMMENDED THAT PATIENTS BE HOSPITALIZED DURING THEIR FIRST COURSE OF TREATMENT.

Fluorouracil should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function.

In a small number of patients, deficiency of dihydropyrimidine dehydrogenase has been reported.[1] This condition may lead to prolonged elevated blood levels of 5-fluorouracil and enhanced toxicity in patients receiving 5-fluorouracil, particularly when administered in combination with other antineoplastic agents.

Pregnancy: Teratogenic effects: Pregnancy category D. Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil has been shown to be teratogenic in laboratory animals. Fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10 to 40 mg/kg on day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12 to 37 mg/kg given to rats between days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg given to hamsters between days 8 and 11 of gestation were teratogenic. Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 1 to 3 times the maximum recommended human therapeutic dose. In monkeys, divided doses of 40 mg/kg given between days 20 and 24 of gestation were not teratogenic.

There are no adequate and well-controlled studies with Fluorouracil in pregnant women. While there is no evidence of teratogenicity in humans due to Fluorouracil, it should be kept in mind that other drugs which inhibit DNA synthesis (eg, methotrexate and aminopterin) have been reported to be teratogenic in humans. Women of childbearing potential should be advised to avoid becoming pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be told of the potential hazard to the fetus. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Combination Therapy: Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of Fluorouracil.

PRECAUTIONS

General: Fluorouracil is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised, since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of Fluorouracil despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

Stomatitis or esophagopharyngitis, at the first visible sign.

Leukopenia (WBC under 3500) or a rapidly falling white blood count.

Vomiting, intractable.

Diarrhea, frequent bowel movements or watery stools.

Gastrointestinal ulceration and bleeding.

Thrombocytopenia (platelets under 100,000).

Hemorrhage from any site.

The administration of 5-fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. This syndrome has been characterized as a tingling sensation of hands and feet which may progress over the next few days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Although pyridoxine has been reported to ameliorate the palmar-plantar erythrodysesthesia syndrome, its safety and effectiveness have not been established.

Information for Patients: Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

Laboratory Tests: White blood counts with differential are recommended before each dose.

Drug Interactions: Leucovorin calcium may enhance the toxicity of fluorouracil.

Also see WARNINGS section.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate the carcinogenic potential of fluorouracil have not been conducted. However, there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses of 0.01, 0.3, 1 or 3 mg per rat 5 days per week for 52 weeks, followed by a 6-month observation period. Also, in other studies, 33 mg/kg of flourouracil was administered intravenously to male rats once a week for 52 weeks followed by observation for the remainder of their lifetimes with no evidence of carcinogenicity. Female mice were given 1 mg of fluorouracil intravenously once a week for 16 weeks with no effect on the incidence of lung adenomas. On the basis of the available data, no evaluation can be made of the carcinogenic risk of fluorouracil to humans.

Mutagenesis: Oncogenic transformation of fibroblasts from mouse embryo has been induced in vitro by fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. Fluorouracil has been shown to be mutagenic to several strains of *Salmonella typhimurium*, including TA 1535, TA 1537 and TA 1538, and to *Saccharomyces cerevisiae*, although no evidence of mutagenicity was found with *Salmonella typhimurium* strains TA 92, TA 98 and TA 100. In addition, a positive effect was observed in the micronucleus test on bone marrow cells of the mouse, and fluorouracil at very high concentrations produced chromosomal breaks in hamster fibroblasts in vitro.

Impairment of Fertility: Fluorouracil has not been adequately studied in animals to permit an evaluation of its effects on fertility and general reproductive performance. However, doses of 125 or 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil did not produce any abnormalities at oral doses of up to 80 mg/kg/day. In female rats, fluorouracil, administered intraperitoneally at weekly doses of 25 or 50 mg/kg for 3 weeks during the pre-ovulatory phases of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and postimplantation embryos, increased the incidence of pre-implantation lethality and induced chromosomal anomalies in these embryos. In a limited study in rabbits, a single 25 mg/kg dose of fluorouracil or 5 daily doses of 5 mg/kg had no effect on ovulation, appeared not to affect implantation and had only a limited effect in producing zygote destruction. Compounds such as fluorouracil, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Nonteratogenic Effects: Fluorouracil has not been studied in animals for its effects on peri- and postnatal development. However, fluorouracil has been shown to cross the placenta and enter into fetal circulation in the rat. Administration of fluorouracil has resulted in increased resorptions and embryolethality in rats. In monkeys, maternal doses higher than 40 mg/kg resulted in abortion of all embryos exposed to fluorouracil. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Nursing Mothers: It is not known whether fluorouracil is excreted in human milk. Because fluorouracil inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy.

Leukopenia usually follows every course of adequate therapy with Fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of treatment, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range.

Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. It is generally reversible and usually responsive to symptomatic treatment.

Other adverse reactions are:

Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia.

Cardiovascular: myocardial ischemia, angina.

Gastrointestinal: gastrointestinal ulceration and bleeding.

Allergic Reactions: anaphylaxis and generalized allergic reactions.

Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.

Dermatologic: dry skin; fissuring; photosensitivity, as manifested by erythema or increased pigmentation of the skin; vein pigmentation, palmar-plantar erythrodysesthesia syndrome, as manifested by tingling of the hands and feet followed by pain, erythema and swelling.

Ophthalmic: lacrimal duct stenosis, visual changes, lacrimation, photophobia.

Psychiatric: disorientation, confusion, euphoria.

Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails).

OVERDOSAGE

The possibility of overdosage with Fluorouracil is unlikely in view of the mode of administration. Nevertheless, the anticipated manifestations would be nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of Fluorouracil should be monitored hematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilized.

The acute intravenous toxicity of fluorouracil is as follows:

Species	LD_{50} (mg/kg±S.E.)
Mouse	340±17
Rat	165±26
Rabbit	27±5.1
Dog	31.5±3.8

DOSAGE AND ADMINISTRATION

General Instructions: Fluorouracil Injection should be administered only intravenously, using care to avoid extravasation. No dilution is required.

All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

It is recommended that prior to treatment each patient be carefully evaluated in order to estimate as accurately as possible the optimum initial dosage of Fluorouracil.

Dosage: 12 mg/kg are given intravenously once daily for 4 successive days. The daily dose should not exceed 800 mg. *If no toxicity is observed,* 6 mg/kg are given on the 6th, 8th, 10th and 12th days *unless toxicity occurs.* No therapy is given on the 5th, 7th, 9th or 11th days. *Therapy is to be discontinued at the end of the 12th day, even if no toxicity has become apparent.* (See WARNINGS and PRECAUTIONS sections.)

Poor risk patients or those who are not in an adequate nutritional state (see CONTRAINDICATIONS and WARNINGS sections) should receive 6 mg/kg/day for 3 days. *If no toxicity is observed,* 3 mg/kg may be given on the 5th, 7th and 9th days *unless toxicity occurs.* No therapy is given on the 4th, 6th or 8th days. The daily dose should not exceed 400 mg.

A sequence of injections on either schedule constitutes a "course of therapy."

Maintenance Therapy: In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules:

1. Repeat dosage of first course every 30 days after the last day of the previous course of treatment.
2. When toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dosage of 10 to 15 mg/kg/week as a single dose. Do not exceed 1 gm per week.

The patient's reaction to the previous course of therapy should be taken into account in determining the amount of the drug to be used, and the dosage should be adjusted ac-

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Roche Laboratories—Cont.

cordingly. Some patients have received from 9 to 45 courses of treatment during periods which ranged from 12 to 60 months.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Although the Fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F and shaking vigorously; allow to cool to body temperature before using.

HOW SUPPLIED

For intravenous use—10-mL single-use vials, boxes of 10 (NDC 0004-1977-01). Each 10 mL contains 500 mg fluorouracil in a colorless to faint yellow aqueous solution, with pH adjusted to approximately 9.2 with sodium hydroxide.

Store at room temperature (59° to 86°F; 15° to 30°C). Protect from light.

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Revised: October 1993

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STERILE
FUDR
[*ef-u-dee-are*]
(floxuridine)

FOR INTRA-ARTERIAL INFUSION ONLY

The following text is complete prescribing information based on official labeling in effect June 1, 1994.

WARNING

It is recommended that FUDR be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and intra-arterial drug therapy and is well versed in the use of potent antimetabolites.

Because of the possibility of severe toxic reactions, all patients should be hospitalized for initiation of the first course of therapy.

DESCRIPTION

Sterile FUDR (floxuridine), an antineoplastic antimetabolite, is available as a sterile, nonpyrogenic, lyophilized powder for reconstitution. Each vial contains 500 mg of floxuridine which is to be reconstituted with 5 mL of sterile water for injection. An appropriate amount of reconstituted solution is then diluted with a parenteral solution for intra-arterial infusion (see DOSAGE AND ADMINISTRATION section).

Floxuridine is a fluorinated pyrimidine. Chemically, floxuridine is 2′-deoxy-5-fluorouridine with an empirical formula of $C_9H_{11}FN_2O_5$. It is a white to off-white odorless solid which is freely soluble in water.

The 2% aqueous solution has a pH of between 4.0 to 5.5. The molecular weight of floxuridine is 246.19.

CLINICAL PHARMACOLOGY

When FUDR is given by rapid intra-arterial injection it is apparently rapidly catabolized to 5-fluorouracil. Thus, rapid injection of FUDR produces the same toxic and antimetabolic effects as does 5-fluorouracil. The primary effect is to interfere with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibit the formation of ribonucleic acid (RNA). However, when FUDR is given by continuous intra-arterial infusion its direct anabolism to FUDR-monophosphate is enhanced, thus increasing the inhibition of DNA.

Floxuridine is metabolized in the liver. The drug is excreted intact and as urea, fluorouracil, α-fluoro-β-ureidopropionic acid, dihydrofluorouracil, α-fluoro-β-guanidopropionic acid and α-fluoro-β-alanine in the urine; it is also expired as respiratory carbon dioxide. Pharmacokinetic data on intra-arterial infusion of FUDR are not available.

INDICATIONS AND USAGE

FUDR is effective in the palliative management of gastrointestinal adenocarcinoma metastatic to the liver, when given by continuous regional intra-arterial infusion in carefully selected patients who are considered incurable by surgery or other means. Patients with known disease extending beyond an area capable of infusion via a single artery should, except in unusual circumstances, be considered for systemic therapy with other chemotherapeutic agents.

CONTRAINDICATIONS

FUDR therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function or those with potentially serious infections.

WARNINGS

BECAUSE OF THE POSSIBILITY OF SEVERE TOXIC REACTIONS, ALL PATIENTS SHOULD BE HOSPITALIZED FOR THE FIRST COURSE OF THERAPY.

FUDR should be used with extreme caution in poor risk patients with impaired hepatic or renal function or a history of high-dose pelvic irradiation or previous use of alkylating agents. The drug is not intended as an adjuvant to surgery.

FUDR may cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in the chick embryo, mouse (at doses of 2.5 to 100 mg/kg) and rat (at doses of 75 to 150 mg/kg). Malformations included cleft palates; skeletal defects; and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 4.2 to 125 times the recommended human therapeutic dose.

There are no adequate and well-controlled studies with FUDR in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Combination therapy: Any form of therapy which adds to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of FUDR.

PRECAUTIONS

General: Sterile FUDR is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of FUDR despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

Myocardial ischemia
Stomatitis or esophagopharyngitis, at the first visible sign
Leukopenia (WBC under 3500) or a rapidly falling white blood count
Vomiting, intractable
Diarrhea, frequent bowel movements or watery stools
Gastrointestinal ulceration and bleeding
Thrombocytopenia (platelets under 100,000)
Hemorrhage from any site

Information For Patients: Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

Laboratory Tests: Careful monitoring of the white blood count and platelet count is recommended.

Drug Interactions: See WARNINGS section.

Carcinogenesis, Mutagenesis, Impairment Of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate the carcinogenic potential of floxuridine have not been conducted. On the basis of the available data, no evaluation can be made of the carcinogenic risk of FUDR to humans.

Mutagenesis: Oncogenic transformation of fibroblasts from mouse embryo has been induced in vitro by FUDR, but the relationship between oncogenicity and mutagenicity is not clear. Floxuridine has also been shown to be mutagenic in human leukocytes in vitro and in the *Drosophila* test system. In addition, 5-fluorouracil, to which floxuridine is catabolized when given by intra-arterial injection, has been shown to be mutagenic in in vitro tests.

Impairment Of Fertility: The effects of floxuridine on fertility and general reproductive performance have not been studied in animals. However, because floxuridine is metabolized to 5-fluorouracil, it should be noted that 5-fluorouracil has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats at doses of 125 or 250 mg/kg, administered intraperitoneally.

Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. In female rats, fluorouracil, administered intraperitoneally at doses of 25 or 50 mg/kg during the preovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of preimplantation lethality and induced chromosomal anomalies in these embryos. Compounds such as FUDR, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

Pregnancy: Teratogenic Effects: Pregnancy category D. See WARNINGS section. Floxuridine has been shown to be teratogenic in the chick embryo, mouse (at doses of 2.5 to 100 mg/kg) and rat (at doses of 75 to 150 mg/kg). Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 4.2 to 125 times the recommended human therapeutic dose.

There are no adequate and well-controlled studies with FUDR in pregnant women. While there is no evidence of teratogenicity in humans due to FUDR, it should be kept in mind that other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. FUDR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Floxuridine has not been studied in animals for its effects on peri- and postnatal development. However, compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Nursing Mothers: It is not known whether FUDR is excreted in human milk. Because FUDR inhibits DNA and RNA synthesis, mothers should not nurse while receiving this drug.

Pediatric use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to the arterial infusion of FUDR are generally related to the procedural complications of regional arterial infusion.

The more common adverse reactions to the drug are nausea, vomiting, diarrhea, enteritis, stomatitis and localized erythema. The more common laboratory abnormalities are anemia, leukopenia, thrombocytopenia and elevations of alkaline phosphatase, serum transaminase, serum bilirubin and lactic dehydrogenase.

Other adverse reactions are:

Gastrointestinal: duodenal ulcer, duodenitis, gastritis, bleeding, gastroenteritis, glossitis, pharyngitis, anorexia, cramps, abdominal pain; possible intra- and extrahepatic biliary sclerosis, as well as acalculous cholecystitis.

Dermatologic: alopecia, dermatitis, nonspecific skin toxicity, rash.

Cardiovascular: myocardial ischemia.

Miscellaneous Clinical Reactions: fever, lethargy, malaise, weakness.

Laboratory Abnormalities: BSP, prothrombin, total protein, sedimentation rate and thrombopenia.

Procedural Complications of Regional Arterial Infusion: arterial aneurysm; arterial ischemia; arterial thrombosis; embolism; fibromyositis; thrombophlebitis; hepatic necrosis; abscesses; infection at catheter site; bleeding at catheter site; catheter blocked, displaced or leaking.

The following adverse reactions have not been reported with FUDR but have been noted following the administration of 5-fluorouracil. While the possibility of these occurring following FUDR therapy is remote because of its regional administration, one should be alert for these reactions following the administration of FUDR because of the pharmacological similarity of these two drugs: pancytopenia, agranulocytosis, myocardial ischemia, angina, anaphylaxis, generalized allergic reactions, acute cerebellar syndrome, nystagmus, headache, dry skin, fissuring, photosensitivity, pruritic maculopapular rash, increased pigmentation of the skin, nail pigmentation, lacrimal duct stenosis, visual changes, lacrimation, photophobia, disorientation, confusion, euphoria, epistaxis and nail changes, including loss of nails.

OVERDOSAGE

The possibility of overdosage with FUDR is unlikely in view of the mode of administration. Nevertheless, the anticipated manifestations would be nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis).