Hydroxyurea Capsules USP, 500 mg

DESCRIPTION

Hydroxyurea Capsules USP are an antineoplastic agent available for oral use as capsules containing 500 mg hydroxyurea. Hydroxyurea is 1H-2-azirine, 2-OH, 1H-2-azirine-1-oxide. The molecular formula is C4H4N2O. The molecular weight is approximately 146.1.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and humans lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor without interfering with the synthesis of deoxyribonucleic acid or of proteins. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. In vitro studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radiosensitive S-stage cells, and (2) reduces further cell cycle progression of cells already in S phase.

Absorption

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUC values are observed.

Pharmacokinetics

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water. Placenta to ascs fluid ratios range from 2:1 to 7:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

Hydroxyurea is 50% bound to plasma proteins.

Metabolism

Up to 60% of an oral dose undergoes conversion through metabolic pathways that have not been fully characterized. One metabolite of hydroxyurea, 2-aminopyrimidine, has been noted in the urine of some patients with sickle cell disease treated with hydroxyurea and resulting in action of leucocytes from hydroxyurea.

Excretion

The elimination of hydroxyurea in humans is likely a linear first-order renal process.

Special Populations

Geriatric, Gender, Race

Distribution is similar regardless of pharmacokinetic differences due to age, gender or race.

Pregnancy

No adequate and well-controlled studies in pregnant women. Drug used in pregnancy only if the benefit to the mother clearly outweighs the potential risk to the fetus. Pregnancy category B.

Nursing Mothers

No adequate and well-controlled studies in nursing women. Hydroxyurea crosses the placenta and may appear in breast milk. Hydroxyurea concentration in breast milk is lower than in plasma.

Pediatric

No adequate and well-controlled studies in pediatric patients treated with hydroxyurea.

Renal Insufficiency

As with all drug elimination pathways of elimination, consideration should be given to the degree of hydroxyurea dose reduction in renal impairment.

Non-renal dose modifications are recommended. Patients in the study with normal renal function (creatinine clearance [CrCl] >90 mL/min), mild (CrCl 50-80 mL/min), moderate (CrCl <30 <50 mL/min), or severe (<30 mL/min) renal impairment received hydroxyurea as a single oral dose of 15 mg/kg, achieved by using combinations of the 200 mg, 300 mg, or 400 mg capsules.

Drug Interactions

Drug Interactions

There are no concomitant use of hydroxyurea with other drugs in children.

Animal Pharmacology and Toxicology

The oral LD50 of hydroxyurea is 7330 mg/kg in mice and 5780 mg/kg in rats, given at a single dose. In subacute and chronic toxicology studies, the most consistent pathological findings were an apparent dose-related mild to moderate decrease in bone marrow, changes in liver function, and occasional deaths in the lungs. At the highest doses (1260 mg/kg/day for 37 days then 2350 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis was observed. The testicular atrophy occurred in animals that survived the study. Acute toxicity in dogs and monkeys was observed. Acute toxicity in the dog, mild to marked bone marrow depression with anemia and thrombocytopenia was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, diastolic hypertension, EKG changes) and hematological changes (slight leukopenia, slight anemia) were noted and delayed in some species of laboratory animals at doses exceeding clinical levels.

INDICATIONS AND USAGE

Significant tumor response to Hydroxyurea capsules, USP has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinoma of the head and neck or in the palliation of a recurrent carcinomatous state of the head and neck.

CONTRAINdications

Hydroxyurea is contraindicated in patients with marked bone marrow depression, leukopenia (WBC <5000 WBC) or thrombocytopenia (platelet count <100,000), or severe anemia.

Hydroxyurea is contraindicated in patients who have demonstrated a pre-existing intolerance to any component of its formulation.

WARNINGS

Treatment with hydroxyurea should not be initiated if bone marrow function is to be restored. Cautiously administer hydroxyurea to patients with evidence of myelosuppression. The relationship between myelosuppression and leukopenia is generally first and its most consistent manifestation. These patients appear to have a significantly lower incidence of myelosuppression than a previously reported study, but are seldom seen without a preceding leukopenia. However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiation or chemotherapy agents; hydroxyurea should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema.

In HIV-infected patients during therapy with hydroxyurea and didanosine, peripheral neuropathy, myelosuppression, pancreatitis, and skin rash have occurred. In patients treated with didanosine alone, hematologic abnormalities, peripheral neuropathy, and rash have occurred. There have been reports of pancreatitis in patients treated with hydroxyurea and other antiretroviral agents. Fetal hepatic events were reported most often in patients treated with the combination hydroxyurea, didanosine, and stavudine. This combination should be avoided.

Peripheral neuropathy, is severe in some cases, has been reported in patients treated with hydroxyurea alone or combined with other antiretroviral agents, including didanosine, with or without stavudine. Severe anemia must be corrected before initiating therapy with hydroxyurea.

Erythrocyte abnormalities: macrocytosis and megaloblastic anemia, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The macrocytic change resembles pernicious anemia, but is not related to vita-
An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with hydroxyurea, and in particular, in combination with danidine and stavudine. This combination should be avoided.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

See WARNINGS for Carcinogenesis and Mutagenesis information.

Impairment of Fertility

Hydroxyurea administered to male rats at 60 mg/kg/day (about the maximum recommended human daily dose on a mg/m² basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

Pregnancy

Pregnancy Category D (See WARNINGS.)

Nursing Mothers

Hydroxyurea is excreted in human milk.

Because of the potential for serious adverse reactions with hydroxyurea, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen.

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION: Renal Insufficiency).

Drug Interactions

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events. (See WARNINGS and ADVERSE REACTIONS.)

Studies have shown that there is an analytical interference of hydroxyurea with the enzymes (urase, uricase, and lactate dehydrogenase) used in the determination of uric acid and lactic acid, rendering falsely elevated results of these in patients treated with hydroxyurea.

Information for Patients

Hydroxyurea is a medication that must be handled with care. People who are not taking HYDROXYUREA should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling HYDROXYUREA or bottles containing HYDROXYUREA capsules. Anyone handling HYDROXYUREA should wash their hands before and after contact with the bottle or capsule. If the powder from the capsule is spilled, it should be wiped up immediately with a damp disposable towel and discarded in a closed container, such as a plastic bag. The medication should be kept away from children and pets. Contact your doctor for instructions on how to dispose of outdated capsules.

ADVERSE REACTIONS

Reported adverse reactions are bone marrow depression (leukopenia, anemia, and thrombocytopenia), gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological disorders (dermatomyositis-like skin changes, peripheral and facial erythema). Hypoglycemia, atrophy of skin and nails, scaling and violaceous papules have been observed in some patients after several years of long-term daily maintenance therapy with hydroxyurea. Skin cancer has been reported. Cutaneous vasculitic lesions, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported to be the result of pruritis, which may often be associated with hydroxyurea treatment (see WARNINGS). Dysuria and alopecia have been reported.

Large doses may produce moderate depression. Coagulation parameters may be affected by an increase in the serum level of vitamin B6 and by increased fibrinogen levels. Abnormal bromsulphalein (BSP) retention has been reported. Fever, chills, malaise, edema, anemia, and elevation of hepatic enzymes have also been reported.

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastrointestinal, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy developed cutaneous leukopenia. Mucositis is observed almost universally during concurrent irradiation and is usually severe. Severe gastric distress, nausea, vomiting, and anorexia, resulting from combined therapy may be controlled by temporary interruption of hydroxyurea administration.

When hydroxyurea is administered concomitantly with antiretroviral agents, in particular, didanosine plus stavudine, fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported. Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir in Study ACTG 5035 showed a median decline in CD4 cells of approximately 100/mm³. (See WARNINGS and PRECAUTIONS.)

OVERDOSE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, vomiting, edema, edema of the skin and soles followed by scaling of hands and feet, severe generalized hyperpigmentation of the skin, and stomatitis have also been observed.

DOSAGE AND ADMINISTRATION

Procedures for proper handling and disposal of cytotoxic drugs should be followed. Several guidelines on this subject have been published.1 To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing HYDROXYUREA capsules. HYDROXYUREA capsules should not be opened. Personnel should avoid exposure to crushed or opened capsules. If contact with crushed or opened capsules occurs, wash immediately and thoroughly. More information is available in the references listed below.

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, cutaneous T-cell lymphoma, anemia and leukopenia, and carcinomas of the head and neck in pediatric patients, dosage regimens have not been established.

All dosages should be based on the patient's actual or ideal weight, whichever is less. Concurrent use of hydroxyurea with other myelosuppressive agents may require adjustment of dosages.

Since hydroxyurea may raise the serum acid level, dosage adjustment of uricosuric medication may be necessary.

SOLID TUMORS

Intermittent Therapy

80 mg/kg administered orally as a single dose every third day

Continuous Therapy

20 to 30 mg/kg administered orally as a single dose every third day

Concomitant Therapy with Irradiation

Carcinoma of the head and neck - 80 mg/kg administered orally as a single dose every third day

Administration of hydroxyurea should begin at least seven days before initiation of irradiation and continued during radiotherapy as long as indenitely afterwards provided that the patient may be kept under adequate observation and evidences no unusual or severe reactions.

RESISTANT CHRONIC MYELOCYTIC LEUKEMIA

Until the intermittent therapy regimen has been evaluated, CONTINUOUS therapy (20 to 30 mg/kg administered orally as a single dose daily) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxyurea is six weeks of therapy. When there is regression in tumor size or arrest in tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below 2500/mm³ or the platelet count below 100,000/mm³. In these cases, the counts should be re-evaluated after three days, and therapy resumed when the counts return to acceptable levels. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined hydroxyurea capsules, USP and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare. Radiotherapy has usually been continued using the recommended dosage and technique. Severe anemia, if it occurs, should be corrected before interrupting hydroxyurea therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxyurea be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (xerostomia) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, hydroxyurea therapy may be temporarily interrupted. If it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. However, it may not be necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may be controlled by temporary interruption of hydroxyurea administration.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDROXYUREA in patients with renal impairment. (See PRECAUTIONS and CLINICAL PHARMACOLOGY.) Close monitoring of hematologic parameters is advised in these patients.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

HOW SUPPLIED

Hydroxyurea capsules USP 500 mg are dark green opaque (cap) printed ‘HYDROXYUREA’ and white opaque (body) printed ‘500’. They are supplied in bottles of 100 (NDC# 48884-724-01).

Dispense in a tight container as defined in the USP.

Storage - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). (See USP Controlled Room Temperature). Keep tightly closed.

REFERENCES


Manufactured by:

PAR PHARMACEUTICAL COMPANIES, INC.

Spring Valley, NY 10977

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