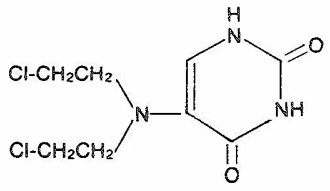
Upjohn

Uracil Mustard Capsules, USP

DESCRIPTION

Uracil Mustard, 5-[bis (2-chloroethyl) amino] uracil, has the following chemical structure:



Uracil Mustard is an off-white, odorless crystalline compound which is slightly soluble in methanol and in acetone. It is unstable in the presence of water and reacts with many organic substances, including the carbonyl and amino groups of proteins including, in all probability, the nucleoproteins of the cell nucleus.

Uracil Mustard Capsules contain the following inactive ingredients: erythrosine sodium, FD&C Blue No. 1, FD&C Yellow No. 5, FD&C Yellow No. 6, gelatin, lactose, mineral oil, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Uracil Mustard is an orally active alkylating agent belonging to the class of substances known as nitrogen mustards. Clinically Uracil Mustard, like other nitrogen mustards, has been found to be of value in the palliative treatment of certain neoplasms affecting the reticuloendothelial system.

INDICATIONS AND USAGE

Chronic lymphocytic leukemia: Uracil Mustard is usually effective in the palliative treatment of symptomatic chronic lymphocytic leukemia.

Non-Hodgkin's lymphomas: Uracil Mustard is effective for palliative treatment of lymphomas of the histiocytic or lymphocytic type.

Chronic myelogenous leukemia: Uracil Mustard may be effective in the palliative treatment of patients with chronic myelogenous luekemia. It is not effective in the acute blastic crisis or in patients with acute leukemia.

Other conditions: Uracil Mustard may be effective in the palliative treatment of early stages of polycythemia vera before the development of leukemia or myelofibrosis. It may also be beneficial as palliative therapy in mycosis fungoides.

CONTRAINDICATIONS

Uracil Mustard should not be given to any patient with severe leukopenia or thrombocytopenia.

WARNINGS

Usage in pregnancy: Drugs of the nitrogen mustard group have been shown to produce fetal abnormalities in experimental animals when given during pregnancy. Uracil Mustard should not be used during pregnancy unless in the opinion of the physician the potential benefits outweight the possible hazards.

Alkylating agents are carcinogenic in animals and suspect as carcinogens in humans. Their possible effect on fertility should be considered; amenorrhea and impaired spermatogenesis have been reported following therapy with alkylating compounds.

Uracil Mustard has a cumulative toxic effect against the hematopoietic system. Blood counts including platelet counts should be done once or twice weekly.

PRECAUTIONS

Patients receiving Uracil Mustard must be followed carefully to avoid the possibility of irreversible damage to the bone marrow. Therapy with this agent should be discontinued if severe depression of the bone marrow occurs, as indicated by sharp diminution in any of the formed blood elements.

While therapy with Uracil Mustard need not be discontinued following initial depression of blood counts, it should be realized that maximum depression of bone marrow function may not occur until 2 to 4 weeks after discontinuance of the drug, and that as the total accumulated doses approach 1 mg/Kg there is real danger of producing irreversible damage to the bone marrow.

While there is no specific therapy for severe depression of the bone marrow, frequent blood and blood component transfusions, with antibiotics to combat secondary infection, may sustain the patient until recovery has occurred.

This preparation contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

In addition to its toxic effects on the hematopoietic system (see PRECAUTIONS and CONTRAINDICATIONS) evidence of toxicity may be manifested by nausea, vomiting or diarrhea of varying degrees of severity. These are related to the size of the dose, ie, the greater the dose, the more severe the symptoms. Other side reactions, some of which may not be related to administration of the drug, include nervousness, irritability or depression and various skin reactions such as pruritus, dermatitis and some loss of hair. Frank alopecia has not been reported to date.

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DOSAGE AND ADMINISTRATION

Uracil Mustard should not be administered until about 2 or 3 weeks after the maximum effect of any previous X-ray or cytotoxic drug therapy upon the bone marrow has been obtained. An increasing white blood cell count is probably the best criterion for determining that such maximum effect has subsided. Some investigators prefer to wait until the blood count has returned to normal before beginning a new course of therapy. In the presence of pronounced leukopenia, thrombocytopenia, or aplastic anemia, Uracil Mustard should not be administered. In the presence of bone marrow infiltrated with malignant cells, hematopoietic toxicity may be increased and judicious care must be used during administration.

The following are suggested dosage schedules:

Adults: A single weekly dose of 0.15 mg/Kg of body weight should be given for 4 weeks to provide an adequate trial.

Children: A single weekly dose of 0.30 mg/Kg of body weight should be given for 4 weeks to provide an adequate trial.

If response occur, the same dose may be continued weekly until relapse. These dosages must be carefully individualized and the dose reduced or discontinued in accordance with the severity of depression of bone marrow function.

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.

HOW SUPPLIED

Uracil Mustard Capsules are available in 1 mg, yellow-dark blue capsules in bottles of 50—NDC 0009-0949-01.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA, March 15, 1985.
3. National Study Commission on Cytotoxic Exposure. Recommendations for Handling Cytotoxic Agents. Available from L.P. Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy St., Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents, MedJ Australia 1:426-428, 1983.
5. Jones, RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca-A Cancer Journal for Clinicians Sept/Oct., 1983. pp 258-263.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic drugs in hospitals. AmJ Hosp Pharmacists 42:131-137, 1985.

ANIMAL PHARMACOLOGY AND TOXICITY

Pharmacologic studies have shown that Uracil Mustard is readily absorbed following oral administration, the orally effective dose in certain rat tumors being almost the same as the parenteral dose. In rats the LD_{50}'s are 7.5 mg/Kg orally, 6.2 mg/Kg subcutaneously and 3.7 mg/Kg intraperitoneally. Thus, the oral and subcutaneous toxicities appear to be about one-half the intraperitoneal toxicity.

Subacute and chronic oral toxicity studies in animals indicate that Uracil Mustard produces toxic effects characteristic of nitrogen mustards. These effects include depression of the hematopoietic system as indicated initially by severe thrombocytopenia, granulocytic and lymphocytic leukopenia and later by depression of the erythrocyte count and hemoglobin values. Other evidence of toxicity in laboratory animals included anorexia, weight loss, bleeding from the gastrointestinal tract, muscular weakness and moribund states.

Experimental studies have shown that Uracil Mustard is a highly potent inducer of malignant lung tumors in A-strain mice.

Caution: Federal law prohibits dispensing without prescription.

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