

Rubicin

Daunorubicin Injection

COMPOSITION

Rubicin Injection: Each vial contains Daunorubicin Hydrochloride USP equivalent to Daunorubicin 20 mg (as lyophilized powder).

DESCRIPTION

Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline glycoside antibiotic produced by *Streptomyces coeruleorubidus*.

CLINICAL PHARMACOLOGY

Mode of Action

Daunorubicin hydrochloride is an antibiotic of the anthracycline group.

Daunorubicin hydrochloride is a highly potent antileukaemic agent, which appears to act on the nucleic acids of the neoplastic cell, particularly the DNA.

In addition to its antimetabolic activity, Daunorubicin hydrochloride possesses antibacterial and some immunosuppressive properties.

Pharmacodynamics/Kinetics:

After intravenous administration of Daunorubicin hydrochloride, the plasma concentration of Daunorubicin falls in a biphasic pattern where an initial rapid clearance is followed by a prolonged elimination. Daunorubicin becomes concentrated in the heart, kidneys, liver, lungs and spleen. It does not appear to cross the blood-brain barrier.

Daunorubicin is mainly metabolised in the liver and excreted mostly in the bile. The major metabolite is daunorubicinol, which is also cytotoxic. About 5-18% of Daunorubicin is excreted unchanged in the urine within 24 hours and 12-29% over 7 days. A further 20% has been recovered from the faeces over 7 days.

INDICATIONS

It is used in the treatment of acute leukaemia and some effect has been demonstrated in disseminated neuroblastoma and rhabdomyosarcoma.

Acute Myeloblastic Leukaemia:

Daunorubicin hydrochloride alone or in association with other cytotoxic medicines (e.g. cytarabine) is indicated in the treatment of this disease at all stages.

Acute Lymphoblastic Leukaemia:

Daunorubicin hydrochloride is a very active remission-producing agent in this condition but because it is toxic and since other forms of treatment are available, its use is chiefly indicated in those cases, which have proved resistant to treatment with other medication. A combined treatment regimen of Daunorubicin hydrochloride, a steroid and vincristine has however been used at an early stage in the disease.

DOSAGE AND ADMINISTRATION

The dosage in each individual injection may vary from 0.5 to 3 mg per kg. Doses of 0.5 - 1 mg per kg may be repeated at intervals of one or more days; doses of 2 mg per kg should be spaced four or more days apart; doses of 2.5 or 3 mg per kg, if used, should be given at 7-14 day intervals.

The number of injections required varies widely from patient to patient and must be determined in each case according to response and tolerance. One injection has sometimes sufficed, commonly 3-6 injections have been necessary, occasionally up to 10 injections in one series have been used.

When second or subsequent injections are to be given, the doses and the time intervals depend on the effect of the previous doses and must be the subject of careful deliberation, examination of the peripheral blood and, under some circumstances, of the marrow.

The effect of Daunorubicin hydrochloride on the disease process and on the normal blood precursors cannot be exactly predicted for any particular case. The differences between incomplete treatment, a satisfactory remission and overdosage with possible irreversible aplasia of the marrow depends on the correct choice of dosage, time intervals and total number of doses.

In acute myeloblastic leukaemia, unless given with other cytotoxic agents, each dose should be about 2 mg per kg according to effect, repeated at four to seven day intervals. Doses of over 2 mg per kg should be employed with extra caution and at intervals of a week or longer. In acute lymphoblastic leukaemia, doses of 1 mg per kg may be repeated according to tolerance and effect at one to four day intervals.

Rubicin injection vial should be reconstituted with 4 ml of Sterile Water for Injection and agitated gently until the material has completely dissolved. The sterile vial contents provide 20 mg of Daunorubicin, with 5 mg of Daunorubicin per ml. The desired dose is withdrawn into a syringe containing 10 ml to 15 ml of 0.9% Sodium Chloride Injection and then injected into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose Injection, or 0.9% Sodium Chloride Injection. Rubicin should not be administered mixed with other drugs or heparin. This method is used to avoid stasis of the antibiotic in the vein and to minimise reaction due to accidental extravasation. It is recommended that solutions are freshly prepared, but no significant decrease in potency has occurred after storage of a freshly prepared solution away from bright light, at room temperature for 24 hours.

When administered with other cytotoxic medicines, which also have a tendency to depress the marrow, dosage should be suitably reduced.

In the treatment of ALL, Prednisolone 100 mg per square metre daily, with Vincristine 1.5 mg per square metre on the first day and Daunorubicin hydrochloride 20 mg per square meter on the first and the second days of each week, have been used until remission occurred.

In adult AML, repeated intermittent courses of Daunorubicin hydrochloride and cytarabine have been used. Each course (which lasts five days) consists of the intravenous injection of both Daunorubicin hydrochloride 1.5 mg per kg and cytarabine 2 mg per kg on the first day. The dose of cytarabine only is then repeated daily for a further four days. An average of two to three such courses at 10-day intervals is required to induce remission.

CONTRAINDICATIONS

1. In patients who have marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy.
2. In patients with impaired cardiac function.
3. In patients who have previously received the full cumulative dose of daunorubicin and doxorubicin. In patients who are pregnant.
4. Patients with previous hypersensitivity to daunorubicin.

PRECAUTIONS

Each patient should be subjected to a clinical and bacteriological examination to determine whether infection is present and infections should be adequately eliminated before treatment with Daunorubicin hydrochloride which might depress the bone marrow to the point where anti-infective agents would no longer be effective.

If facilities are available, patients should be treated in a germ-free environment or, where this is not possible, reversed-barrier nursing and aseptic precautions should be employed.

Rapid destruction of a large number of leukaemia cells may cause a rise in the blood uric-acid or urea and so it is a wise precaution to check the blood uric acid and urea levels three or four times a week during the first week of treatment, for fluids to be pushed and allopurinol to be used in severe cases to prevent the development of hyperuricaemia.

Anti-infective therapy should be employed in the presence of demonstrated or suspected infection and during a phase of aplasia it should be continued for some time after the marrow has regenerated.

Patients with heart disease should not be treated with this potentially cardiotoxic drug. Cardiotoxicity, if it occurs, is likely to be heralded by either a persistent tachycardia or by minor changes in the electrocardiogram and for this reason the electrocardiogram examination should be made at regular intervals during treatment.

It is recommended that Daunorubicin hydrochloride be used under the direction of those conversant with the management of acute leukaemia and cytotoxic chemotherapy and that haematological monitoring of patients be carried out.

Pharmaceutical precautions

Handling guidelines

1. Daunorubicin should be prepared for administration only by professionals who have been trained in the safe use of the preparation.
2. Operations such as reconstitution of powder and transfer to syringes should be carried out only in the designated area.
3. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.
4. Pregnant personnel are advised not to handle chemotherapeutic agents.

Contamination

1. In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline (0.9% sodium chloride injection). A bland cream may be used to treat the transient stinging of skin. Medical advice should be sought if the eyes are affected.
2. In the event of spillage, operators should put on gloves and mop up the spilled material with a sponge kept in the area for that purpose. Rinse the area twice with water. Put all solutions and sponges into a plastic bag and then seal it. The bag should be prominently labelled with the words "Cytotoxic Waste" or similar.

Pregnancy and Lactation

Category D. This category includes drugs, which have caused an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Daunorubicin hydrochloride may cause foetal harm when administered to a pregnant woman because of its teratogenic potential. Women of childbearing potential should be advised to avoid becoming pregnant.

Although it is not known if daunorubicin hydrochloride is distributed into breast milk, breast feeding is not recommended while daunorubicin is being administered because of the risks to the infant.

Effects on ability to drive and use machines

Daunorubicin Hydrochloride Injection may be likely to produce minor or moderate adverse effects that may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

Other

Daunorubicin is potentially mutagenic and carcinogenic.

OVERDOSE

Clinical features of overdosage are likely to be an extension of daunorubicin's pharmacological action. Possible symptoms of toxicity are those listed under **ADVERSE REACTIONS**.

Management

Symptomatic supportive measures should be instituted. Particular attention should be given to prevention and treatment of possible severe haemorrhages or infections secondary to severe, persistent bone marrow depression.

ADVERSE EFFECTS

A number of side effects may arise:

Subcutaneous Extravasation

Subcutaneous extravasation of the agent during intravenous administration will cause a severe local reaction, and if Daunorubicin is not adequately flushed into the venous system after its introduction, phlebitis may occur.

Marrow Depression

In every patient the bone marrow will be depressed by treatment with Daunorubicin hydrochloride and, in a variable proportion of cases, a severe aplasia will develop. This must be anticipated in every case by eliminating infection before the treatment, by isolating the patient from infection during the treatment and by the use of supportive therapy, including the continuous administration of anti-infective agents, the administration of platelet-rich plasma or fresh whole blood transfusion and under some circumstances, the transfusion of white cell concentrates.

Cardiotoxicity

Daunorubicin hydrochloride has a cardiotoxic effect, which can be manifested under two distinct sets of circumstances. Firstly, if a large dose (2 mg per kg or more) is administered at daily intervals, transient reversible ECG changes will be noted in a proportion of cases. This can be avoided by administering the medicine at longer intervals. Secondly, if during the course of a long treatment, or after repeated treatment a total dosage of 20 mg per kg of Daunorubicin hydrochloride has been exceeded, the patient may develop heart failure with very little warning and after only a short period of tachycardia. For this reason, a total dosage of 20 mg per kg should never be exceeded and it is therefore unwise to use the medicine for maintenance therapy.

Gastrointestinal Side-effects

Moderate, or sometimes severe, nausea and vomiting; stomatitis.

Other

Alopecia can occur. Rarely facial flushing, conjunctivitis and lachrymation may occur. Transient red colouration of the urine may occur.

Nephrotoxic, hepatotoxic and neurotoxic effects have not been reported.

DRUG INTERACTIONS

Allopurinol, colchicine, probenecid or sulfinpyrazone: Daunorubicin may raise the concentration of blood uric acid. Dosage adjustment of antigout agents may be necessary to control hyperuricaemia and gout. Allopurinol may be preferred to prevent or reverse daunorubicin-induced hyperuricaemia because of the risk of uric acid nephropathy with uricosuric antigout agents.

Other bone marrow depressants: Dosage reduction of daunorubicin may be required.

Cyclophosphamide: Concurrent use with daunorubicin may result in increased cardiotoxicity. It is recommended that the total dose of daunorubicin not exceed 400 mg/m² of BSA when given concurrently with cyclophosphamide.

Doxorubicin: Previous treatment with doxorubicin increases the risk of daunorubicin-induced cardiotoxicity. Daunorubicin should not be used in patients who have previously received complete cumulative doses of doxorubicin.

Hepatotoxic medications: Concurrent use may increase the risk of hepatotoxicity.

Vaccines, live virus: Due to its immunosuppressive properties, concurrent use of daunorubicin with a live virus vaccine may potentiate the replication of the vaccine virus, increase the adverse effects of the vaccine virus, or decrease the patient's antibody response to the virus.

PHARMACEUTICAL INFORMATION

Storage condition

Store the vial in original carton at 15°C - 30°C. Protect from light. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration. It should be protected exposure to sunlight. Retain in carton until time of use.

Packaging

Rubicin Injection: Each commercial box contains a vial containing Daunorubicin 20 mg as lyophilized powder.