ADLEY

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

ADRIB

INJECTION

DOXORUBICIN HYDROCHLORIDE INJECTION IP

DOXORUBICIN HYDROCHLORIDE INJECTION IP 10 mg./5ml 50mg./25ml

Each ml. contains:

Doxorubicin Hydrochloride IP	2mg	
Sodium Chloride IP	0.9%	w/v
Water for Injections IP	qs	

INDICATIONS:

Doxorubicin is indicated in the treatment of acute leukemia, soft tissue and bone sarcomas, breast cancer, ovarian cancer, Hodgkin's and non Hodgkin's lymphomas, small cell lung cancer, gastric carcinoma and bladder carcinoma.

CONTRAINDICATIONS:

Doxorubicin is contraindicated in patients with marked Myelosuppression induced by previous chemotherapy or Radiotherapy, in case of pre-existing heart disease, or previous treatment with doxorubicin or any other anthracyclin with completion of cumulative dose.

MODE OF ACTION:

There are several hypothesis concerning the mode of action of doxorubicin. The best documented mechanism is its ability to interact with DNA, presumably by interaction of the planner aglycone, moiety between two adjacent base pairs. This may result in inhibition of DNArepair mechanism.

Another mechanism of action may be binding to cell membranes, resulting in altered permeability properties. A third mechanism involves formation of free radicals. Reduction of doxorubicin may result in formation of semiquinolone radicals, which in turn give rise to variety or oxygen species (superoxide and hydroxyl radicals and hydrogen peroxide) These reactive species can damage cell membranes and organelles, but may also interact with DNA. There is evidence that free radical formulation may have a role in the mutagenicity and cardiotoxicity of doxorubicin.

PHARMACOKINETICS:

The intravenous administration of doxorubicin is followed by rapid plasma clearence and significant tissue binding. After doses of 30-60 mg./m^2 initial plasma concentrations are approximately 2-8 um Doxorubicin Kinetics are generally adequately described by a three compartmental kinetic model, withcorresponding half lives 11/12 a/4-8 min, 11/2 b 0.7-1.6 h and t 1/2 g 25-35 h. Volume of distribution is high, ranging from 800-3500/ Lm^{2}Doxorubicin is metabolized extensively. Three types of metabolic reactions occur: Ketoreduction, cleavage reaction with aglycone formation, and conjugation, some metabolities (e.g. 7 hydroxyaglycones) have been correlated with cardiotoxicity in humans. Elimination of doxorubicin, unchanged or metabolized, occurs primarily via the liver and billiary system. Billiary excertion may be as high as 40-50% in 5-7 days. Approximately 10% of the total dose administered is excreted in the urine, in about 5-7 days.

ADVERSE EFFECTS:

Myelosuppression and cardiotoxicity are the dose - limiting toxicities. Other adverse reactions are as follows.

Cutaneous:

Reversible and complete alopecia may occur. Hyperpigmentaiton of nailbeds and dermal creases, primarily in children, and onycholysis in a few cases has been reported. Recall of skin reaction due to prior radiotherapy may occur with doxorubicin administration.

Gastorintestinal:

Acute nausea and vomiting occurs frequently which may be alleviated by antimetic therapy. Mucositis (stomatitis and esophagilis) may occur 5-10 days after administration and may be severe with dose regimen consisting of administration of doxorubicin on three consecutive days. The effect may lead to ulceration and represent a cite of origin for severe infection. Ulceration and necrosis of the colon, especially the cecum may occur leading to bleeding or severe infections, which can be fatal This has been reported in ANLL patients being treated with a three day course inclusive of doxorubicin combined with cylarabine. Anorexia and diarrhoea have been occassionally reported.

Vascular:

Phlebosclerosis has been reported especially when small veins are used or a single vein is used for repeated administration Facial flushing may occur if the injection is given too rapidly.

Local:

Severe cellulities, vesication and tissue necrosis will occur if doxorubicin is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported.

Hypoersensitivity:

Fever, chills and urticaria have been reported occassionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Other: Conjunctivities and lacrimation occur rarely.

WARNINGS AND PRECAUTIONS:

Special attention must be given to the cardiac toxicity exhibited by doxorubicin. Although uncommon, acute left ventricular failure has occured, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 g/m^2. The limit appears to be lower in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. The total dose of doxorubicin administered to the individual patient should also take into account a previous or concomitant therapy with related compounds such as daunorubicin. Congestive heart failure and / or cardiomyopathy may be encountered several weeks after discontinuation of doxorubicin therapy. Cardiac failure is often not favourably affected by presently known edical or physical therapy for cardiac support. Early Clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitals, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes. A base line ECG and ECGs performed prior to each dose or course after 300 mg/m^2 cumulative dose has been given is suggested. Transient ECG changes consiting of T-wave flattering, S-T depression and arrhythmias lasting up to two weeks after a dose or course of doxorubicin are presently not considered indications for suspension of doxorubicin therapy. Doxorubicin cardiomyopathy has been reported to be associated with a presistent reduction in the voltage of the QRS w ave, a prolongation of the systolic time interval and a reduction of the ejection fraction as determined by echocardiogra phy or radionuclide angiography. None of these tests have yet been confirmed to consistently identify those individua patients that are approaching their maximally tolerated cumulative

dose of doxorubicin. If test results indicate change in cardiac function associated with doxorubicin the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage. Acute life threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

There is a high incidence of bone marrow depression, primarily of leukocytes, requiring careful hematologic monitoring. With the recommended dose schedule, leukopenia is usually transient, reaching its nadir at 10-14 days after treatment with recovery usually occuring by the 21st day.

White blood cell counts as low as 1,000/mm^3 are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or haemorrhage.

Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment, therefore prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory test, such as SGOT, SGPT, alkaline phosphatase and bilirubin. (See Dosage and Administration). Necrotizing colitis manifested by typhilitis (cecal inflammation, bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin given i. v. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of doxorubicin extravasation may occur with or without an accompanying stinging or burning sensation and even if blood returns well on aspiration of the infusion needle . If any signs or symptoms and extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and plastic surgery consultation obtained. Early wide excision of the involved area should be considered.

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It is recommended, therefore, that patients, be hospitalized at least during the first phase of the treatment. Like other cytotoxic drugs, doxorubicin may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use supportive and pharmacologic measures as might be necessary to control this problem. Doxorubicin imparts are coloration to the urine 1-2 days after administration and patients should be advised to expect this during active therapy.

USE DURING PREGNANCY AND LACTATION:

Doxorubicin can cause fetal harm when administered to a pregnant woman. Doxorubicin was terotogenic and embryotoxic at doses of 0.8 mg/kg/day and greater (about 1/13 the recommended human dose on a body surface area basis) when administered during the period of organogenesis in rats. Teratogenicity and embryotoxicity were also seen using discrete periods of treatment. The most susceptible was the 6 - to 9- day gestation period at doses of 1.25 mg/kg/day and greater. Characteristic malformations included esophageal and intestinal atresia, tracheoesophageal fistula, hypoplasia of the urinary bladder, and cardiovascular anomalies. Doxorubicin was embryotoxic (increase in embryofetal deaths) and abortifacient at 0.4 mg/kg/day (about 1/14 the recommended human dose on a body surface area basis) in rabbits when administered during the period of organogenesis.

There are no adequate and well - controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

INTERACTIONS:

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced cystitis and enhancement of 6-mercaptopurine hepatotoxicity have been reported. Radiation induced toxicity to the myocardium, mucosae, skin and liver has been reported to be increased by the administration of doxorubicin.

DOSAGE AND ADMINISTRATION:

ADRIB 10 MG INJECTION :

Doxorubicin Hydrochloride IP 10mg / 5ml.

ADRIB 50 mg. INJECTION:

Doxorubicin Hydrochloride IP 50mg / 25ml.

The most commonly used dosage schedule is 60-75 mg/m^2 as a single intravenous injection administered at 21 days intervals. Lower doses may be required in patients with inadequate marrow reserves.

An alternative dosage schedule of 20 mg. /m^2 weekly has been reported to produce a lower incidence of congestive heart failure. Doxorubicin dosage should be reduced if the bilirubin is elevated as follows: serum bilirubin 1.3 to 3.0 mg/dl give 1/2 normal dose, bilirubin > 3.0 mg/dl give 1/4 normal dose.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

Acute Overdosage of doxorubicin enhances the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patients and granulocyte transfusions and sympomatic treatment of mucositis. Chronic overdosage with cumulative dosage exceeding 550 mg/m^2 increase the risk of cardiomyopathy and results congestive heart failure. Treatment consist of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

INCOMPATIBILITIES:

Doxorubicin should not be mixed with 5-fluorouracil or heparin, Until specific compatibility data are available, it is recommended not to mix doxorubicin with other drugs.

STORAGE :

STORE BETWEEN 2°C - 8°C.

PROTECT FROM LIGHT.

PRESENTATION :

Each Pack Contains

Doxorubicin Hydrochloride 10 mg / 5ml , 50mg/25ml

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