EPIRUBICIN THYMOORGAN®

Epirubicin hydrochloride

DESCRIPTION

Epirubicin (Epirubicin hydrochloride) is an anthracycline antibiotic with antiblastic activity.

BIOLOGICAL ACTIVITY

The mechanism of action of Epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L 1210 and P 388 leukemias, sarcomas SA 180 (solid and ascitic forms), melanoma B 16, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

Toxicity studies in animals have indicated that Epirubicin has a better therapeutic index and less systemic and cardiac toxicity than doxorubicin.

CLINICAL PHARMACOLOGY

In patients with normal hepatic and renal function, plasma levels after i.v. injection of 75-90 mg/m² of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. Plasma levels of the drug's main metabolite, the 13-OH derivative, are constantly lower and virtually parallel to those of the unchanged drug. Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. The drug does not cross the blood-brain barrier.

INDICATIONS

Epirubicin has produced responses in a wide spectrum of neoplastic diseases including: breast carcinoma; ovarian carcinoma; lung carcinoma, gastric, hepatic, pancreatic and sigmo-rectal carcinomas; head and neck carcinomas, non-Hodgkin's lymphoma and Hodgkin's disease; soft tissue and bone sarcomas; acute leukemias and multiple myeloma. Transitional cell carcinoma of the bladder.

CONTRAINDICATIONS

Epirubicin is contraindicated in patients with marked myelosuppression induced by previous treatments with other antitumour agents or by radio-therapy, and in patients already treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.

The drug is contraindicated in patients with a current or previous history of cardiac impairment.

Hypersensitivity to hydroxybenzoates is a contraindication.

DOSAGE AND ADMINISTRATION

Conventional dose

When Epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m² body area; the drug should be injected i.v. over 3-5 minutes and, depending on the patient's haematomedullar status, the dose should be repeated at 21-day intervals.

High dose

Lung cancer

Epirubicin as a single agent for the high dose treatment of lung cancer should be administered according to the following regimens:

Small cell lung cancer (previously untreated): 120 mg/m² day 1, every three weeks.

Non-small cell lung cancer (squamous large cells and adenocarcinoma, previously untreated): 135 mg/m² day 1 or 45 mg/m² days 1, 2, 3, every 3 weeks.

Breast cancer

Doses up to 135 mg/m² as single agent and 120 mg/m in combination, every 3-4 weeks proved to be effective and well tolerated in the treatment of breast cancer. In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100 mg/m² to 120 mg/ml every 3-4 weeks are recommended.

Lower doses (60-75 mg/m²) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radio-therapy, by age, or neoplastic bone-marrow infiltration.

The total dose per cycle may be divided over 2-3 successive days. When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced. Since the major route of elimination of Epirubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4-3 mg/100 ml, or BSP retention: 9-15%) requires

a 50% reduction of dose while severe impairment (bilirubin >3 mg/100 ml or BSP retention >15%) necessitates a dose reduction of 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin excreted by this route.

Intravesical administration

For the treatment of the papillary cell carcinoma of the bladder, a therapy of 8 weekly instillations of 50 mg (in 25-50 ml of saline solution) is recommended.

In the case of local toxicity a dose reduction to 30 mg is advised. For carcinoma-in situ, depending on individual tolerability of the patient, the dose may be increased up to 80 mg. For prophylaxis of recurrences after transurethral resection of superficial tumors, 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dose are recommended.

WARNINGS AND PRECAUTIONS

Epirubicin should be administered only under the supervision of qualified physicians experienced in antiblastic and cytotoxic therapy.

Initial treatment calls for a careful baseline monitoring of various laboratory parameters and cardiac function.

Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia and generalized infections) of prior cytotoxic treatment before beginning treatment with Epirubicin.

During the first cycles of treatment with Epirubicin patients must be carefully and frequently monitored.

White and red blood cells and platelet counts should be carefully monitored. Leukopenia is usually transient with normal dosage schedules, reaching a nadir between the 10th and 14th day, but returning to normal values by the 21st day. Before starting therapy, and if possible during treatment, liver function should be evaluated (SGOT, SGPT, alkaline phosphatase, bilirubin, BSP).

Experimental animal data and results of short-term trials in man indicate that Epirubicin is less cardiotoxic than its structural analogue, doxorubicin.

It has been shown, in a comparative study that the ratio of cumulative doses, which lead to the same reduction in cardiac function, is of the order of 2:1. In addition, in patients previously untreated with doxorubicin, congestive heart failure has only been reported after cumulative doses exceeding 1000 mg/m².

However, cardiac function must be carefully monitored during treatment to minimize the risk of heart failure of the type described for other anthracyclines.

This heart failure can appear even several weeks after discontinuing treatment, and may prove unresponsive to specific medical treatment.

The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radio-therapy to the mediastinal pericardial area. In establishing the maximal cumulative doses of Epirubicin any concomitant therapy with potentially cardiotoxic drugs should be taken into account. It is recommended that an ECG before and after each treatment cycle should be carried out. Alterations in the ECG tracing, such as flattening or inversion of the T wave, depression of the S- T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment.

Cardiomyopathy induced by anthracyclines, and by doxorubicin in particular, is associated with a persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction.

Cardiac monitoring of patients receiving Epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques such as ECG, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography. Like other cytotoxic agents, Epirubicin may induce hyperuricemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be carefully checked so that this phenomenon may be controlled pharmacologically As with other cytotoxic agents, thromboflebitis and thromboembolic phoenomena, including pulmonary embolism (in some cases fatal have been coincidentally reported with the use of Epirubicin.

To date there is no conclusive information as to whether this drug may adversely affect human fertility, or cause teratogenic or other harmful effects to the foetus; experimental data, however, suggest that Epirubicin may reduce foetal viability its use in pregnancy is therefore not recommended.

Like most other antitumoral and immunosuppressant agents, Epirubicin, under particular experimental conditions, has mutagenic properties and is carcinogenic in laboratory animals.

Epirubicin may impart a red colour to the urine for 1-2 days after administration.

PHARMACEUTICAL PRECAUTIONS

Personnel handling Epirubicin should wear protective clothing including goggles and disposable gloves and masks. Pregnant staff should be excluded from working with this drug. All items used for administration or cleaning should be disposed of with appropriate care.

Accidental contact with the skin or eyes should be treated immediately by copious lavage with water or soap and water: medical attention should be sought. The conjunctiva should be washed with saline solution.

Spillage or leakage should be treated with dilute sodium hypochlorite solution, preferably by soaking, and then water.

SIDE EFFECTS

Apart from myelosuppression and cardiotoxicity the following side effects have been described:

- Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males;
- mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the sides of the tongue and on the sublingual mucosa;
- Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea;
- Hyperpyrexia.

Fever, chills and urticaria have been rarely reported, anaphylaxis may occur.

The occurrence of secondary acute myelogenous leukemia, with or without a pre-leukemic phase, has been reported rarely in patients treated with Epirubicin in combination with other DNA-damaging antitumor agents. These leukemias could have a short latency period.

Directions for administration

Epirubicin should be administered by intravenous and intravesical injection

It is not active when given orally and should not be injected intramuscularly or intrathecally Epirubicin should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

Epirubicin can be used in combination with other antitumour agents, but it is not recommended that it is mixed with these drugs in the same syringe.

Intravenous administration

It is advisable to give the drug via thee tubing of a freely running i.v. saline infusion after checking that the needle is well placed in the vein. This method minimize the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Epirubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclercsis may result from injection into small vessels or repeated injections into the same vein.

Intravesical administration

Epirubicin to be instilled using a catheter, should be retained intravesically for 1 hour. The patients should be instructed to void at the end of this time.

STORAGE

Store between 2 - 8°C, away from light.

PRESENTATIONS

Vials:

EPIRUBICIN THYMOORGAN 10 mg:	10 mg Epirubicin hydrochloride / 5 ml.
EPIRUBICIN THYMOORGAN 20 mg:	20 mg Epirubicin hydrochloride / 10 ml.
EPIRUBICIN THYMOORGAN 50 mg:	50 mg Epirubicin hydrochloride / 25 ml.
EPIRUBICIN THYMOORGAN 200 mg:	200 mg Epirubicin hydrochloride / 100 ml.

Excipients: sodium chloride, sodium lactate solution, hydrochloric acid, water for injection.

THYMOORGAN Pharmazie GmbH

Manufactured by:
Thymoorgan Pharmazie GmbH, Germany
For:
Hikma Pharmaceuticals, Amman - Jordan

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of the reach of children

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