PRODUCT MONOGRAPH

ADRIAMYCIN® RDF®
Doxorubicin Hydrochloride for Injection USP

10mg, 50mg, and 150mg Vials

Antineoplastic Agent

Pharmacia Canada Inc
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Date of Preparation
2001.06.29

Control # 072157

NAME OF DRUG

ADRIAMYCIN® RDF®

Doxorubicin Hydrochloride for Injection USP

10 mg, 50 mg and 150 mg Vials

CAUTION:

ADRIAMYCIN (DOXORUBICIN HYDROCHLORIDE) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPY DRUGS (SEE **WARNINGS** AND **PRECAUTIONS**). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. BECAUSE OF THE EXPERIENCE WITH CARDIAC TOXICITY, A TOTAL DOSE OF ADRIAMYCIN EXCEEDING 550 MG/M^2 WITH THE 21 DAY REGIMEN AND 700 MG/M^2 WITH THE WEEKLY REGIMEN IS NOT RECOMMENDED. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, OTHER ANTHRACYCLINE OR ANTHRACENE THERAPY, WITH PRE-EXISTING CARDIAC DISEASE, OR WHO HAVE RECEIVED PRIOR ADRIAMYCIN CUMULATIVE DOSES EXCEEDING 400 MG/M^2 WITH THE 21 DAY REGIMEN AND 550 MG/M^2 UTILIZING THE WEEKLY REGIMEN.

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CLINICAL PHARMACOLOGY

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations. Animal studies have shown activity in a wide spectrum of experimental tumours, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy of testes in rats and dogs.

Pharmacokinetic studies show that the intravenous administration of normal or radiolabelled ADRIAMYCIN (doxorubicin hydrochloride) for injection is followed by rapid plasma clearance and significant tissue binding. Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the feces

in seven days. Impairment of liver function results in slower excretion, and, consequently, increased retention and accumulation in plasma and tissues. ADRIAMYCIN does not cross the blood brain barrier.

INDICATIONS AND CLINICAL USE

ADRIAMYCIN has been used successfully both as a single agent and also in combination with other approved cancer chemotherapeutic agents to produce regression in neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilm's tumour, neuroblastomas, soft tissue sarcomas, bone sarcomas, breast carcinomas, gynecologic carcinomas, testicular carcinomas, bronchogenic carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma, thyroid carcinoma, bladder carcinomas, squamous cell carcinoma of the head and neck, and gastric carcinoma.

ADRIAMYCIN has also been used by instillation into the bladder for the topical treatment of superficial bladder tumours.

A number of other solid tumours have also shown some responsiveness to ADRIAMYCIN alone or in combination with other drugs. (Refer to **Dosage and Administration**) Studies to date have shown malignant melanoma, kidney

carcinoma, large bowel carcinomas, brain tumours and metastases to the central nervous system not to be significantly responsive to ADRIAMYCIN therapy.

CONTRAINDICATIONS

ADRIAMYCIN therapy should not be started in patients who have marked myelosuppression induced by previous treatment with other antineoplastic agents or by radiotherapy. Conclusive data are not available on pre-existing heart disease as a co-factor of increased risk of ADRIAMYCIN-induced cardiac toxicity. Preliminary data suggest that in such cases cardiac toxicity may occur at doses lower than the recommended cumulative limit. It is therefore not recommended that ADRIAMYCIN be started in such cases. ADRIAMYCIN treatment is contraindicated in patients who received previous treatment with complete cumulative doses of ADRIAMYCIN and/or other anthracyclines and anthracenes.

WARNINGS

Special attention must be given to the cardiac toxicity exhibited by ADRIAMYCIN. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received a total dosage of the drug exceeding the currently recommended limit of 550 mg/m^2 body surface area for the 21 day regimen or a higher dose limit in the order of 700 mg/m^2 for the weekly regimen. These limits appear to be lower (400 mg/m^2 and 550 mg/m^2, respectively) in patients who received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of ADRIAMYCIN therapy. Children appear to be at particular risk for development of delayed doxorubicin cardiotoxicity in that doxorubicin impairs myocardial growth as they mature, leading to subsequent possible development of congestive heart failure during early adulthood.

Available evidence appears to indicate that cardiotoxicity is cumulative across members of the anthracycline and anthracene class of drugs. Patients who have previously received other anthracyclines and anthracenes are at particular risk for possible cardiotoxic effects of ADRIAMYCIN at a lower total dose than previously untreated patients and, therefore, should be carefully monitored.

Cardiac failure is often not favourably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug-induced heart failure appears to be essential for successful treatment with digitalis,

diuretics, low salt diet, and bed rest. Reduction of afterload with vasodilating agents appears to be beneficial in refractory ADRIAMYCIN-induced heart failure. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. Transient EKG changes consisting of T-wave flattening, S-T depression and arrhythmias lasting for up to two weeks after a dose or course of ADRIAMYCIN are presently not considered indications for suspension of ADRIAMYCIN therapy. ADRIAMYCIN cardiomyopathy has been reported to be associated with a persistent reduction in the voltage of QRS wave, a prolongation of the systolic time interval and a reduction of the left ventricular ejection fraction (LVEF) as determined by echocardiography or radionuclide angiography (MUGA scan). None of these tests have yet been confirmed to consistently identify those individual patients who are approaching their maximally tolerated cumulative dose of ADRIAMYCIN. If test results indicate change in cardiac function associated with ADRIAMYCIN, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

BECAUSE OF THE EXPERIENCE WITH CARDIAC TOXICITY, A TOTAL DOSE OF ADRIAMYCIN EXCEEDING 550 mg/m^2 WITH THE 21 DAY REGIMEN AND 700 mg/m^2 WITH THE WEEKLY REGIMEN, IS NOT RECOMMENDED.

Acute life-threatening arrhythmias have been reported to occur during or within a few hours after ADRIAMYCIN administration.

There is a high incidence of bone marrow supression, primarily of leukocytes, requiring careful haematologic monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir 10-14 days after treatment with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm^3 are to be expected during treatment with appropriate doses of ADRIAMYCIN. Red blood cell and platelet levels should also be monitored since they may also be supressed. Haematologic toxicity may require dose reduction or suspension or delay of ADRIAMYCIN therapy. Persistent severe myelosuppression may result in superinfection or haemorrhage.

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

Toxicity to recommended doses of ADRIAMYCIN is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin. (See **Dosage and Administration**).

Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of ADRIAMYCIN given by I.V. push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

On intravenous administration of ADRIAMYCIN, extravasation may occur with or without an accompanying stinging or burning sensation, and even if blood returns well on aspiration of the infusion needle. (See **Dosage and Administration**). If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein.

ADRIAMYCIN and related compounds have also been shown to have mutagenic and carcinogenic properties when tested in experimental models.

ADRIAMYCIN RDF may impart a red colouration to the urine for 1 to 2 days after administration and patients should be advised to expect this during active therapy.

Use in Pregnancy - There is no conclusive information about doxorubicin adversely affecting human fertility, or causing teratogenesis; however, ADRIAMYCIN is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. Therefore, women of childbearing potential should be advised to avoid pregnancy.

If ADRIAMYCIN is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the fetus. Mothers should be advised not to breast-feed while undergoing chemotherapy with ADRIAMYCIN.

PRECAUTIONS

Initial treatment with ADRIAMYCIN RDF requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, ADRIAMYCIN RDF may induce hyperuricemia secondary to rapid lysis of neoplastic cells, particularly in patients with leukemia. The clinician should monitor the patient's serum chemistry and blood uric acid level and be prepared to use such

supportive and pharmacologic measures as might be necessary to control this problem.

ADRIAMYCIN RDF is not an anti-microbial agent.

ADVERSE REACTIONS

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity (See **Warnings**). Other reactions reported are:

Cutaneous - Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in children, have been reported in a few cases. Recall of skin reaction due to prior radiotherapy has occurred with ADRIAMYCIN RDF administration.

Gastrointestinal - Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur 5-10 days after administration. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dose regimen consisting of administration of ADRIAMYCIN on three successive days results in the greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or

severe infections which can be fatal. This reaction has been reported in patients with acute non-lymphocytic leukemia treated with a 3-day course of ADRIAMYCIN combined with cytarabine. Anorexia and diarrhea have been occasionally 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 cellulitis, vesication and tissue necrosis will occur if ADRIAMYCIN is extravasated during administration. Erythematous streaking along the vein proximal to the site of the injection has been reported. (See **Dosage and Administration**)

Bladder, local - Instillation of ADRIAMYCIN RDF into the bladder may cause pain, hemorrhage and occasionally decreased bladder capacity.

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

Hematological - The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been reported rarely in patients concurrently

treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 years) latency period.

Other - Conjunctivitis and lacrimation occur rarely.

OVERDOSAGE

Acute overdosage with ADRIAMYCIN RDF enhances the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

Chronic overdosage with cumulative doses exceeding 550 mg/m^2 increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics. The use of peripheral vasodilators has been recommended.

DOSAGE AND ADMINISTRATION

REFER TO GUIDELINES FOR SAFE PREPARATION AND HANDLING

Dosage

A variety of dose schedules has been used. The following recommendations are for use as a single agent only.

The most commonly used dosage schedule is 60-75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is weekly doses of 20 mg/m^2 which has been reported to produce a lower incidence of congestive heart failure. 30 mg/m^2 on each of three successive days repeated every 4 weeks has also been used. ADRIAMYCIN dosage must be reduced if the bilirubin is elevated as follows: Serum Bilirubin 1.2-3.0 mg/dL -- give ½ normal dose, > 3 mg/dL -- give ¼ normal dose.

When ADRIAMYCIN RDF is instilled intravesically for the treatment of superficial bladder carcinomas, the usual dose employed ranges from 50-80 mg in a total volume of 50-100 mL of 0.9% Sodium Chloride Injection USP with a contact time of 1-2 hours. Care should be taken to ensure that the tip of the catheter is in the

bladder cavity before instilling the ADRIAMYCIN solution. Instillation is repeated weekly for 4 weeks and subsequently at monthly intervals. Therapy may continue for one year or longer as no significant systemic toxicity has been reported. Care should be exercised in the handling and disposal of the voided urine. (Refer to **Guidelines for Safe Preparation and Handling**). PVC gloves should be worn and the urine should be inactivated by decolourizing it with 10 mL or more or sodium hypochlorite solution (household bleach).

Other methods of administration have been investigated including intra-arterial administration and also continuous or long term intravenous infusion utilizing appropriate infusion pumps.

Clinical studies support the efficacy of ADRIAMYCIN used concurrently with other chemotherapeutic agents. Listed below are tumour types and drugs used concurrently with ADRIAMYCIN:

Acute lymphocytic leukemia in adults: ADRIAMYCIN with vincristine and prednisone or with cytosine arabinoside, vincristine and prednisone.

Acute lymphocytic leukemia in children: ADRIAMYCIN with L-asparaginase, vincristine and prednisone.

Acute non-lymphocytic leukemia: ADRIAMYCIN with cytosine arabinosyl or with arabinosyl cytosine, vincristine and prednisone.

Carcinoma of the breast: ADRIAMYCIN with 5-fluorouracil and/or cyclophosphamide or with vincristine with or without cyclophosphamide.

Bronchogenic carcinoma, non-small cell: ADRIAMYCIN with cyclophosphamide, methotrexate and procarbazine or with cyclophosphamide and cisplatinum. Bronchogenic carcinoma, small cell: ADRIAMYCIN with vincristine or etoposide (VP-16) and cyclophosphamide.

Hodgkin's disease: ADRIAMYCIN with bleomycin, vincristine and dacarbazine.

Non-Hodgkin's lymphoma: ADRIAMYCIN with cyclophosphamide, vincristine and prednisone, or bleomycin, cyclophosphamide, vincristine and prednisone.

Carcinoma of the ovary: ADRIAMYCIN with cisplatinum.

Soft tissue sarcoma: ADRIAMYCIN with dacarbazine, or with dacarbazine, cyclophosphamide and vincristine.

Carcinoma of the bladder: ADRIAMYCIN with methotrexate, vinblastine and cisplatinum or cisplatinum and cyclophosphamide or with 5-fluorouracil.

Carcinoma of the stomach: ADRIAMYCIN with 5-fluorouracil and mitomycin-C.

ADMINISTRATION:

Care in the administration of ADRIAMYCIN RDF will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of ADRIAMYCIN RDF, extravasation may occur with or without an accompanying stinging or burning sensation even if the blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein.

If it is known or suspected that subcutaneous extravasation has occurred, the following steps are recommended:

1. Attempt aspiration of the infiltrated ADRIAMYCIN solution.

2. Local intermittent application of ice for up to 3 days.

3. Elevation of the affected limb.

4. Close observation of the lesion.

5. Consultation with a plastic surgeon familiar with drug extravasations if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

ADRIAMYCIN RDF 10 mg, 50 mg and 150 mg vials should be reconstituted with 5 mL, 25 mL and 75 mL respectively of 0.9% Sodium Chloride Injection USP to give a final concentration of 2 mg/mL of doxorubicin hydrochloride. Bacteriostatic diluents are not recommended.

After adding the diluent, the vial should be shaken until the contents are dissolved. A slight suspension may form which will completely dissolve on further shaking. The vials are under negative pressure and care should be taken to avoid a pressure build up. The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration 2-8°C. The solution should be protected from exposure to direct light. For single dose vials, any unused solution should be discarded.

ADRIAMYCIN RDF should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP (0.9%) or 5% Dextrose Injection USP. The tubing should be attached to a Butterfly® needle, or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic

drainage. The rate of administration is dependent on the size of the vein and the dosage, however, the dosage should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration.

Unless specific compatibility data are available, the mixing of ADRIAMYCIN solutions with other drugs is not recommended. Precipitation occurs with 5-fluorouracil and heparin.

GUIDELINES FOR SAFE PREPARATION AND HANDLING

Preparation and Handling

1. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Personnel handling ADRIAMYCIN solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If ADRIAMYCIN contacts the skin or mucosa, the area should be washed with soap and water immediately.

3. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

4. Directions for Dispensing from Pharmacy Bulk Vial

   The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only.

Entry into the vial must be made with a sterile dispensing device such as the Econ-O-Set® Sterile Transfer System[1]. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as increasing the potential for microbial and particulate contamination.

Swab the vial stopper with an antiseptic solution. Following carefully the manufacturer's instructions, insert the device into the vial. Withdraw contents of vial into syringes, using aseptic technique. Discard any unused portion within eight hours of initial entry.

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[1] Distributed by International Medication Systems of Canada, Ltd.

Disposal

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials which have come in contact with doxorubicin should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, ADRIAMYCIN may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolourize the doxorubicin, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

Needles, syringes, disposable and non-disposable equipment:

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution in the sewer system with running water and discard disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

Spillage/Contamination:

Wear gloves, mask, protective clothing. Treat spilled powder or liquid with sodium hypochlorite solution. Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again and place in polyethylene bag; seal, double bag and mark as hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean-up should wash with soap and water.

PHARMACEUTICAL INFORMATION

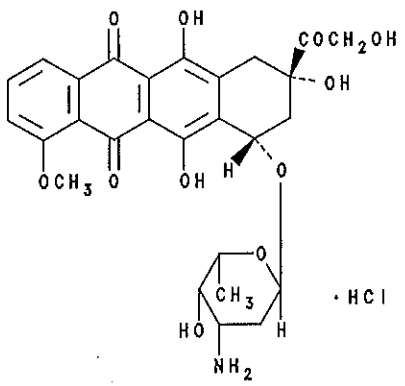
CHEMISTRY

Trade Name: ADRIAMYCIN® RDF®

Proper Name: Doxorubicin Hydrochloride

Chemical Name: (8S:10S)-10[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride (USAN).

Structural Formula:



Molecular Formula: $C_{27}H_{29}NO_{11}.HCl$

Molecular Weight: 579.98

Description: Doxorubicin hydrochloride is the hydrochloric acid salt of a glycoside antibiotic produced by S. peucetius var. caesius. It is a red-orange, almost odourless, hygroscopic powder, m.p. 205°C (dec.), $(\alpha)^{20}_{D}$ + 248°(c = 0.1 methanol), and soluble in water and dilute alcohols.

Composition:

ADRIAMYCIN RDF is a sterile, red-orange lyophilized powder. Methylparaben is added to enhance dissolution.

10 mg Vials - Each vial contains 10 mg of Doxorubicin Hydrochloride USP, 50 mg of lactose NF and 1 mg of methylparaben NF.

50 mg Vials - Each vial contains 50 mg of Doxorubicin Hydrochloride USP, 250 mg of lactose NF and 5 mg of methylparaben NF.

150 mg Pharmacy Bulk Vial - Each vial contains 150 mg of Doxorubicin Hydrochloride USP, 750 mg of lactose NF and 15 mg of methylparaben NF.

Incompatibility:

Unless specific compatibility data are available, ADRIAMYCIN RDF should not be mixed with other drugs. Precipitation occurs with 5-fluorouracil and heparin.

RECONSTITUTION

Solutions for Reconstitution

0.9% Sodium Chloride Injection USP

(without bacteriostatic agent)

RECONSTITUTION TABLE

Vial Size	Diluent Added to Vial (mL)	Approximate Available Volume (mL)	Approximate Concentration (mg/mL)
10 mg	5	5	2
50 mg	25	25	2
150 mg	75	75	2

See **Preparation of Solution** for instructions.

DOSAGE FORMS

Availability:

ADRIAMYCIN RDF (DOXORUBICIN HYDROCHLORIDE FOR INJECTION) is supplied as a sterile lyophilized powder. The following single dose vial sizes are available:

10 mg vials supplied in 10 vial cartons.

50 mg vials supplied in single vial cartons.

Pharmacy Bulk Vial:

150 mg vials supplied in single vial cartons.

NOTE:

THE USE OF PHARMACY BULK VIALS IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM. THE PHARMACY BULK VIAL IS INTENDED FOR SINGLE PUNCTURE, MULTIPLE DISPENSING AND FOR INTRAVENOUS USE ONLY.

Entry into the vial must be made with a suitable, sterile transfer or dispensing device. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as it may increase the potential for microbial and particulate matter contamination.

In a suitable work area such as a laminar flow hood, swab the vial stopper with an antiseptic solution. Insert the device into the vial. Withdraw contents of the vial into sterile syringes using strict aseptic techniques. Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of the initial entry because of the potential for microbial contamination. Discard any unused portion. The contents of the syringes filled from the Pharmacy Bulk Vial should be used within 24 hours at room temperature or 48 hours when refrigerated from the time of the initial entry into the Pharmacy Bulk Vial.

Storage:

Store ADRIAMYCIN RDF sterile lyophilized powder for injection at 15-30°C and protected from light.

Stability of Solution

The reconstituted solution is stable for 24 hours at room temperature or for 48 hours under refrigeration. The solution should be protected from exposure to direct light and any unused solution should be discarded.

Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of initial entry because of the potential for microbial contamination.

PHARMACOLOGY

ADRIAMYCIN, when administered i.v., is rapidly cleared from the plasma of rodents, with concentration of the drug being seen in the liver, spleen, kidney, lung and heart. Drug excretion is prolonged and occurs predominantly via the liver.

In man, ADRIAMYCIN has also been shown to have a rapid plasma clearance and a large volume of distribution that suggests an extensive drug distribution into the tissues. Urinary excretion is minimal, with only 5% of the drug excreted during the first five days as measured by fluorimetric methods, suggesting prolonged tissue binding. After an injection of 1.5 mg/kg of tritium labelled ADRIAMYCIN approximately 50% of the administered radioactivity was detected in the feces in seven days, while in patients with impaired liver function, the fecal excretion accounted for only 20%. ADRIAMYCIN is metabolized predominantly by the liver to adriamycinol and several aglycone derivatives; approximately half of the drug excreted in bile was unchanged ADRIAMYCIN and 30% conjugates. Biliary excretion of ADRIAMYCIN was measured in one patient. A total of 40% of the administered dose was recovered as fluorescent material in the bile over a one week period.

The predominant fluorescent material in both urine and bile was ADRIAMYCIN followed by adriamycinol. Pharmacokinetic studies in patients with hepatic dysfunction show significant and prolonged plasma levels of ADRIAMYCIN metabolites associated with exaggerated clinical cytotoxicity. These observations are the basis of a requirement for dose de-escalation in patients with impaired hepatic function.

Neither ADRIAMYCIN nor any of its fluorescent metabolites were detectable in human cerebrospinal fluid obtained at varying intervals after drug administration in a variety of patients, including some with meningeal leukemia and cerebral metastasis, situations in which the blood brain barrier might be expected to be altered.

ANIMAL TOXICITY

Toxicology

The acute toxicity of ADRIAMYCIN in Swiss mice varies greatly according to the route of administration. The LD_{50} is 8.5 mg/kg by the intra-peritoneal route, 21.1 mg/kg by the intravenous route, and greater than 750 mg/kg by the oral route.

Chronic toxicity was studied in the rabbit and in the dog. ADRIAMYCIN when administered i.v. for three months at a daily dose of 0.125 mg/kg of body weight did not cause mortality or any measurable morphologic and functional changes in either species. At a dose of 0.25 mg/kg/day a few lesions were observed in the rabbit and more serious lesions in the dog, where the mortality rate reached 30%. The 0.5 mg/kg/day dose produced death in 40% of the treated rabbits within two months, and in 100% of the treated dogs within 10 days. Organs affected were gastrointestinal mucosa, hemopoietic tissues, and testes in both species, kidneys in the rabbit and skin (alopecia and melanosis) in the dog.

Teratology

ADRIAMYCIN when administered intravenously to rats at doses of 0.8 mg/kg/day during the period of organogenesis, resulted in an increased incidence of fetal resorption and fetal skeletal and soft tissue malformations. Rats treated intraperitoneally with doses of 1 mg/kg/day or greater also demonstrated skeletal and soft tissue malformations. The intravenous administration of ADRIAMYCIN to rabbits at doses of 0.1 mg/kg/day interfered with implantation and caused fetal resorption and at doses of 0.6 mg/kg/day was abortifacient. In addition, high single doses of 2 or 4 mg/kg in rabbits were shown to block implantation when administered on day 3 of pregnancy, to be embryotoxic when administered on day 7 of pregnancy, and to be abortifacient when administered on days 11, 15 or 20 of pregnancy.

Carcinogenicity

ADRIAMYCIN has been shown to be carcinogenic in the rat. The drug caused the appearance of breast fibroadenomas after a single i.v. dose of 8.0 mg/kg at an average of 33 weeks in 6 of 25 animals. Another animal developed a breast adenocarcinoma.

General

ADRIAMYCIN RDF was compared to the regular ADRIAMYCIN lyophilized formulation administered I.P. in P388 leukemic mice and I.V. to Gross leukemic mice. No difference in activity or toxicity was noted between the two formulations.

In local tolerance studies conducted in mice, rats, rabbits, and dogs, either by the intravenous or intradermal routes, the lesions induced by the ADRIAMYCIN RDF formulation appeared to be similar to those obtained with the ADRIAMYCIN lyophilized formulation.

In other tests using ADRIAMYCIN RDF, there was no evidence of incompatibility with human blood, plasma or serum.

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