DOXORUBICIN (Adriamycin®)

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from Streptomyces peucetius (var. caesius). It was introduced in the 1960s and immediately gained acceptance for its broad spectrum of activity. Doxorubicin is currently used in the treatment of solid mass tumors including breast cancer, bladder carcinoma, thyroid cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma and several other carcinomas. Even though this drug has anti-infective properties, its cytotoxicity precludes its use as an antibiotic.

Pharmacology & Pharmacokinetics

The antineoplastic activity of doxorubicin involves two mechanisms that work independently of one another. Doxorubicin contains a flat polyyclic aromatic ring that enables it to intercalate between base pairs on a partially uncoiled DNA strand. This alters DNA structure and interferes with proper DNA template function causing inhibition of DNA and RNA synthesis. Additionally, doxorubicin undergoes a series of reduction/oxidation reactions that generate highly reactive oxygen free radicals which induce single strand breaks in DNA leading to chromosomal damage.

Doxorubicin is only administered intravenously due to its poor bioavailability from the GI tract and its direct irritant effect on tissue membranes. It is commercially available as a hydrochloride salt to increase stability. Once injected, the drug rapidly distributes through the plasma and into organ tissues. Within 30 seconds after IV administration doxorubicin is found in the liver, lungs, heart and kidneys. The volume of distribution of the drug is 1.0 L/kg. The elimination half-life of doxorubicin is 1-3 hours and its terminal half-life is 3.3 hours for its metabolites. During phase III, the plasma half-life is prolonged to 16.7 hours for doxorubicin and 33 hours for the other metabolites due to its high affinity for plasma protein. Approximately, 70% of doxorubicin is bound to plasma protein. Doxorubicin is unable to cross the blood brain barrier or achieve a measurable concentration in the cerebrospinal fluid due to its amphoteric properties. Limited data indicate that doxorubicin and its metabolites can cross the placenta so that its use in pregnancy is contraindicated. Doxorubicin is also not recommended for lactating women since it is distributed into breast milk.

Doxorubicinol is the major active metabolite of doxorubicin which is formed by the liver enzymatic reduction: aldoke reductase. Other metabolites include aglycones and conjugates. The enzymatic reduction of the quinone structure generates a number of free radical species. It is believed that these toxic species are primarily responsible for producing cardiac toxicity by promoting lipid peroxidation in the heart. Other potential causes of the drug's cardiotoxicity include the release of histamine and prostaglandin, calcium overload, and adenogenic changes in the myocardium. The majority of doxorubicin and its metabolites (80%) are excreted in the bile by day 5. About 50% of the compound is excreted unchanged, 23% as doxorubicinol and the remainder consists of other metabolites. A minimal amount of drug (10%) is eliminated unchanged in the urine after five days. The rate of clearance is notably reduced in patients with liver impairment and in obese women.

Toxicology

Doxorubicin is a drug with a low therapeutic index. A therapeutic response is unlikely to occur without some evidence of toxicity. There are numerous symptoms of doxorubicin toxicity. The most significant dose-limiting toxicities of therapy are myelosuppression and cardiotoxicity. A single dose of doxorubicin can produce life-threatening consequences of myelosuppression including leukopenia, neutropenia, thrombocytopenia and anemia. Clinical manifestations of these can increase the risk of infection, hemorrhage, fatigue and cardiopulmonary dysfunction. Fortunately, bone marrow suppression is usually reversible. The peak effects are seen during the second week (nadir 10-14 days) of chemotherapy administration and levels return to normal by day 21. Leukocyte counts as low as 1000 have been documented with therapeutic doses of doxorubicin. The use of doxorubicin is limited by an accumulative, dose-dependent toxicity to the heart. Lifetime cumulative doses that approach 550 mg/m² or greater are strongly linked to myocardial damage. Other data suggest that doses of 450 mg/m² or less may also cause cardiotoxicity. The cardiac damage produced is irreversible. Cardiomyopathy presents in two different ways, acute or chronic, based on time of occurrence. Acute toxicity is uncommon and less problematic. It occurs immediately after a single dose or a single cycle of chemotherapy. It is characterized by abnormal ECG changes including ST - T wave changes, prolongation of the QT interval and arrhythmias (eg, sinus tachycardia and supraventricular arrhythmias). Reports of pericarditis and myocarditis are few, but often fatal. Chronic cardiotoxicity occurs months to years post treatment and is characterized by conduction disturbances (eg, AV block), systolic function alterations (eg, decreased left ventricular ejection fraction), and congestive heart failure which may be life threatening. Data reveals a decline in left ventricular ejection fraction ranging from 10 to 55%. The incidence of cardiac failure has been estimated to be 3-4% with a lifetime dose of 450 mg/m² and dramatically increases to 18% following a lifetime dose of 700 mg/m².

Doxorubicin can also affect the cell lining of the gastrointestinal tract causing nausea, vomiting, and diarrhea that usually present the day of administration. Esophagitis and stomatitis tend to occur during the second week of treatment. Reports of colon necrosis and ulceration have been noted leading to bleeding and severe infections. Alopecia, conjunctivitis and lacrimation have been reported. Doxorubicin is very toxic to the local and vascular tissues. Extravasation at the site of administration causes cellulitis, vesication, and local tissue necrosis. Local erythematous streaking along the vein proximal to infusion site is common. Facial flushing and hyperpigmentation of nail beds have been reported. Sclerosis of the vein may result when doxorubicin is injected into a small vein or previously used vein. Sensitivity reactions involving fever, chills and urticaria have been observed in patients receiving various doses of this compound.

Peripheral neurotoxicity has also been reported with intrathecal doses. Anal fissures or proctitis may occur with higher doses. Doxorubicin regimen have been shown to interfere with gonadal development and normal growth in children. Hepatotoxicity is seen in patients with pre-existing hepatic dysfunction because doxorubicin is primarily excreted by the hepatobiliary route.

Drug-Drug Interactions

Other antineoplastic agents may potentiate the toxicities commonly seen with doxorubicin therapy. Cyclophosphamide, mitoxantrone, and other anthracycline compounds enhance cardiotoxic effects. The administration of paclitaxel before doxorubicin produces a decrease in doxorubicin clearance leading to an exacerbation of leukopenia and stomatitis. 6-mercaptopurine increases hepatotoxicity. Streptozocin inhibits the hepatic metabolism of doxorubicin resulting in an increase plasma concentration.

The adjunctive use of cyclosporine may induce coma and/or seizures. In addition, this combination produces prolonged episodes of myelosuppression. High doses of prostaglandins have been reported to exacerbate doxorubicin-induced neutropenia and thrombocytopenia. Oxaliplatin has been noted to decrease digoxin and phenytoin plasma levels. The use of immunosuppressive agents is contraindicated in...
patients receiving doxorubicin therapy. The safety in using doxorubicin during pregnancy has not been determined. It is categorized in Class D.3.4 No adequate studies have been conducted in pregnant women. The potential for serious injury to the fetus is great and should be avoided at all costs.

**Treatment**

The management of doxorubicin toxicity is supportive. Activated charcoal and gastric lavage are not beneficial since the drug is not absorbed in the GI tract. Its pharmacokinetic properties (large volume of distribution, large molecular size and high protein binding) prevent use of hemodialysis. However, the early institution of hemoperfusion may enhance elimination. A study shows that plasma clearance could be enhanced up to 20-fold using this method.4 Further studies need to be conducted to determine its efficacy.

The proper management of doxorubicin-induced myelosuppression requires a complete blood count (CBC) initiated before and during drug treatment. Hematologic toxicity may require a reduction in dose, a delay in treatment, or discontinuance of chemotherapy. If a patient presents with signs of infection, antimicrobial therapy should be initiated immediately. The use of hematopoietic growth factors (G-CSF, GM-CSF) and platelet transfusions have proven to be beneficial.14

Patients with a history of hepatic impairment should have liver function tests completed prior to each dose of doxorubicin. The following levels: alkaline phosphatase, bilirubin, AST, and ALT, should be recorded and monitored frequently for abnormalities.12,13 Many of these patients require a reduction in dose.

Effective management of doxorubicin-induced cardiotoxicity requires early detection and intervention. The potential for cardiotoxicity should be recognized before therapy is initiated. Screening and modifying risk factors, watching for signs and symptoms during drug administration, and monitoring patient after therapy completion can prevent it. Risk factors associated with cardiotoxicity are as follows: age, female gender, preexisting cardiac disorders, prior mediastinal radiation and adjunctive treatment with other cytotoxic agents (especially cyclophosphamide).1,5,13 Continuous monitoring of serum electrolytes and cardiac enzymes are recommended. Screening tests should be completed before, during, and after chemotherapy administration. These methods allow physicians to determine if a patient has adequate heart function to tolerate additional chemotherapy when signs of injury are evident.

The best method to detect cardiotoxicity at an early stage in an effort to prevent severe tissue destruction, is still unknown. Today, there are several non-invasive and invasive imaging procedures used to obtain baseline and regular measurements of cardiac function. An electrocardiogram (ECG) is the most convenient and conventional procedure available, but it lacks specificity. An echocardiogram (ECHO) and multigated radionuclide angiography (MUGA) are frequently used to measure decreases in left ventricular ejection fraction (LVEF) due to afterload and contractility abnormalities.1,2,6,14 A significant drawback is that these methods can only identify cardiotoxicity in its chronic stage, not at an early stage. Endomyocardial biopsy (EM) is considered the only definitive predictor for CHF. Even though it is the most sensitive and specific method for diagnosing the severity myocardial damage, its use is limited by its invasiveness.15 Currently, new methods, including evaluating heart rate variability, identifying biochemical markers, anti-myosin scintigraphy and radioactive monoclonal antibodies have been proposed to help identify early signs of CHF.16,17 The use of radioactive methylidobenzyl quanine has been shown to be beneficial in detecting early adrenergic changes in the heart, which manifest later as CHF.18 Limited data and research prevent the clinical use of these newer methods at this time.

The administration rate and dosing schedule play a crucial role in preventing myocyte destruction. Data suggest that a lower cumulative dose and a weekly schedule of administration cause less injury. Additionally, the continuous infusion of doxorubicin (given over 24-48hrs) compared to a bolus dose given every third week produced less histopathologic changes on the EM biopsy.3,14

There is no antidote available to reverse the cardiac damage produced by doxorubicin.4 However, the use of dexrazoxane, a potent iron chelator, has shown promising results as a cardioprotective agent. In the presence of oxygen, the Fe3+ is oxidized to Fe2+ forming superoxide (O2··). Dextrazoxane chelates the iron molecules that are responsible for the formation of oxygen free radicals, which act as oxidizing agents in the heart. Dextrazoxane should be given 30 minutes prior to doxorubicin dose. It is usually administered in a 10:1 ratio. Thus a typical dose is 500 mg/m2 of dextrazoxane for every 50 mg/m2 of doxorubicin.13,15,16 Clinical studies indicate that dextrazone may reduce cardiotoxicity up to 90%.17 It may even allow for the administration of higher cumulative doses of doxorubicin. There are some concerns that dextrazone may decrease the effectiveness of chemotherapy. The FDA has only approved this agent for use in metastatic breast cancer patients who have already received a cumulative doxorubicin dose of 300 mg/m2.18 There is little evidence to support the use of dextrazone as concomitant therapy with doxorubicin for all tumor cell lines.

Treatment of doxorubicin-induced congestive heart failure should involve cardiac glycosides (e.g. digoxin), diuretics, afterload reducers, angiotensin converting enzymes, bed rest, and a modified diet. Additionally, calcium channel blockers and beta-blockers have been efficacious in reducing cardiac work and afterload.19 Heart transplants are reserved for patients with severe cardiac deterioration.

The formulations of several analogues of doxorubicin have been developed in an effort to eliminate cardiac toxicity. Both valrubicin and irinotecan appear to cause less cardiotoxicity. A recent study reports that a pegylated liposomal form of doxorubicin may carry a smaller risk for cardiomyopathy.19 The endomyocardial biopsies of patients who were treated with this form of doxorubicin have provided reassuring evidence, but more data must be collected before clinicians can draw any conclusions.

Much progress has been made over the past decade to ameliorate doxorubicin toxicity. The use of alternative dosing schedules, cardioprotective agents, new analogues and cardiac imaging technology have considerably reduced the incidence of myocardial damage. Hopefully the combination of these treatment strategies along with ongoing studies will eliminate the limited-dose restriction on doxorubicin administration. Until then, healthcare professionals must be adequately educated to ensure that appropriate preventive measures are carried out.

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**References:** (First Author Only)