Toxic Cardiomyopathies

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ABSTRACT

Examples of toxic cardiomyopathies of various characteristics are presented. Daunomycin and doxorubicin, antineoplastic drugs, cause multifocal cardiomyopathies and intractable heart failure by cardiotoxic mechanisms; these effects are delayed and related to the cumulative dose. Cobalt caused diffuse vacuolar cardiomyopathy in chronic beer drinkers. The development of fulminant heart failure was the function of factors that increased the absorption of cobalt or sensitized the myocardium to its cytotoxic effect. Beta-adrenergic receptor stimulant bronchodilators like isoproterenol or vasodilating antihypersensitive drugs like hydralazine are able to produce focal subendocardial necroses. This lesion is due to ischemia brought about by the acute exaggerated pharmacological effects of these compounds.

Introduction

Chemically induced cardiomyopathy is a rare clinical entity, for few chemicals in use cause this condition. Iatrogenic lesions in the heart are less frequent than those in other parenchymatous organs. Even in the toxicity testing of new chemicals in experimental animals, organic changes of the myocardium are seldom encountered. Nevertheless, cardiomyopathies are of great interest in experimental medicine because they serve as models for the study of myocardial diseases in humans. They are also of clinical interest because a few chemicals are able to cause severe lesions. They are generally dose-related.

In some cases, however, a pre-existing condition increases the susceptibility to the cardiotoxic effects of the chemicals. These cardiomyopathies are produced by a direct specific cytotoxic mechanism or by an indirect mechanism, e.g., by ischemia brought about by hemodynamic effects. The action of anthracycline antineoplastic drugs and of cobalt salts in heavy beer drinkers are examples of the former; the action of sympathomimetic bronchodilators and vasodilating antihypertensive drugs are examples of the latter. The cardiotoxicity of these agents reported during the last decade is the subject of this report.

Cardiotoxicity of Daunomycin and Doxorubicin

Daunomycin (also known as daunorubicin) is an antibiotic isolated from cultures of Streptomyces peucetius. The active product is a glycoside of the anthracycline family consisting of the pigmented aglycone, daunomycinone, attached to the
amino sugar, daunosamine. Other antibiotics closely related to daunomycin were subsequently discovered; of these, doxorubicin (14-hydroxydaunomycin; Adriamycin) is of particular importance. Both daunomycin and doxorubicin have a high cytotoxic activity against normal and neoplastic cells. Initially, daunomycin was considered to be one of the most useful drugs in the treatment of acute leukemia; however, many investigators have reported that serious cardipulmonary side effects appeared during the course of therapy.

A review of the literature on the use of daunomycin indicated that cardiac toxicity occurred in 4 to 10 percent of the patients. Several characteristics of anthracycline cardiotoxicity were demonstrated in a recent controlled study of children undergoing therapy for acute lymphocytic leukemia. Heart failure developed in 9.9 percent of the children given daunomycin while none of the children receiving other drugs developed any cardiac abnormality. The total dose in patients with cardiac toxicity varied from 360 to 1260 mg per m². The study substantiates the findings of other investigators that the cardiac toxicity is dose-dependent in children, generally occurring at total doses over 500 to 600 mg per m² (17 to 20 mg per kg), but is less predictable in adults and may develop at doses as low as 55 to 220 mg per m².

Both daunomycin and doxorubicin induce cardiac toxicities that are similar clinically over a similar dose range. Two distinct types of cardiac effects have emerged. The first is characterized by electrocardiogram (EKG) alterations during or immediately following drug administration. The changes are nonspecific and include sinus tachycardia, ST segment depression, T wave flattening and ventricular premature beats. These are reversible and do not lead to the second and more serious type of abnormal cardiac activity, heart failure. Heart failure induced by these agents develops suddenly with signs of sinus tachycardia, hypotension, dyspnea, tachypnea, and gallop rhythm and is followed shortly thereafter by rapidly progressive biventricular failure and death.

The onset of these symptoms is usually not seen during the first three to six months after initiation of treatment and may not occur for weeks to months after the treatment is concluded. Prior to the development of heart failure, systolic time intervals were found to be altered. The ratio of pre-ejection time to left ventricular ejection time increased, indicating a decreased myocardial contractility.

Enlarged heart and dilated ventricles with mural thrombi were the principal gross findings. Histopathological studies have shown multifocal interstitial edema, focal myocytolysis, hyalinization and atrophy of the myocytes (figure 1). Mitochondrial myelin figures, myofibrillary lysis and disruption and proliferation of Z band material were the main ultrastructural findings. In addition, alterations in chromatin were detected in some nuclei; these consisted of transformation of chromatin into fibers and filaments and were interpreted to be the sequence of uncoiling of chromatin.

Daunomycin and doxorubicin have produced cardiac changes in experimental animals. Daunomycin given to rats on six consecutive days at a total dose of 283 mg per m² produced electron microscopic changes in the myocardium similar to those seen in patients treated with this agent. Hamsters given large single or multiple doses of daunomycin developed congestion of myocardial capillaries, intramyocardial hemorrhages, mural thrombosis, coagulation necrosis of myocardial fibers, and myocarditis; there was an indication of cumulative cardiotoxicity.
Rabbits have proved to be the most useful animal model so far because in several studies cardiomyopathies were found after dosage regimens similar to those used clinically. Myocardial lesions frequently occurred at total doses of 250 to 350 mg per m² or larger and some of these animals had congestive heart failure with cardiomegaly, pulmonary and hepatic congestion and serious effusions.

Histological examination of the hearts showed vacuolar degeneration and atrophy of muscle cells and interstitial fibrosis. The pathogenesis of anthracycline heart failure is still unsettled. Although histologic changes were demonstrated, they were moderate; similar alterations in cardiac muscle as a result of injury have been described in a variety of cardiomyopathies. The biological activity of both daunomycin and doxorubicin is directly related to their ability to interact with deoxyribonucleic acid (DNA), to which they bind by intercalation between adjacent base pairs of double-helix DNA. As a consequence, both DNA replication and ribonucleic acid (RNA) synthesis on the DNA template are inhibited.

The uncoiling of the chromatin, as seen by electron microscopic examination, is most likely related to these events. Daunomycin and doxorubicin leave the cell very slowly and, since the cardiac muscle cell cannot reproduce itself, any inhibition of a specific nucleic acid function might be long-lasting. Under these conditions cellular functions are inhibited. For example, changes in Z substance can be interpreted as a sign of impaired differentiation into myofilaments. Such an event inhibits growth of the fiber mass and adaptation to an overload and leads to heart failure.

Cardiotoxicity of Cobalt

An alarming incidence of cardiomyopathy of similar clinical and postmortem characteristics occurred among beer drinkers during the mid 1960's in a few North American cities and in Belgium. Patients were in good health from 3 months up to a week prior to admission to hospitals. Anorexia, nausea, and diarrhea were often their first
symptoms. Dyspnea and cyanosis, epigastric pain, cardiac enlargement, sinus tachycardia, gallop rhythm, low blood pressure, severe venous distention and ankle edema were the principal clinical findings. Polycythemia, acidosis, elevated serum lactic and pyruvic acids and, in severe cases, very high activities of serum enzymes of hepatic origin were the laboratory findings.

The severity of the disease varied from mild congestive heart failure, which responded to therapy, to cardiogenic shock with low cardiac output that resulted in a high mortality. Eighteen to 47 percent of the patients died within a day after admission to hospitals in the different cities. In the survivors, the course of the disease varied from sudden recovery to chronic congestive heart disease.2,36,44

At autopsies, the heart was enlarged and the chambers were dilated. The myocardium was flabby and pale; mural thrombi were frequent findings. Pericardial and pleural effusions, thromboembolism, ascites and centriflobular hepatic congestion or necroses were often present. The thyroid showed follicular hyperplasia and scanty colloid in several cases. Histologic examination of the heart revealed hyaline necroses and vacuolar degeneration in each chamber. Multiple small vacuoles or a number of large vacuoles and empty sarcosomal sheets gave the muscle a moth-eaten appearance.

Vacuolization has been attributed to lipid droplets, myocytolysis, swollen mitochondria, or elements of sarcoplasmic reticulum. In a few instances interstitial fibrosis was seen. Electron microscopic findings consisted of loss of myofibrils, focal accumulation of glycogen and lipid, dilatation of sarcoplasmic reticulum and T tubules, and various mitochondrial changes.11,25,50,53

The patients from the various cities consumed a specific brand of beer produced locally and had been heavy drinkers for several years. The disease started to occur about a month after the use of a cobalt salt in the beer as a foam stabilizer in a concentration of about one part per million, i.e., one mg per liter. Cardiotoxicity has been experienced only rarely with the use of much larger doses of cobalt (100 mg per day) in various anemias.2,25

Some of the extracardiac findings in the beer drinkers, (polycythemia, thyroid changes), could be attributed to the cobalt effect. In the cardiac muscles of eight victims examined, the cobalt concentrations were elevated ten times over normal; manganese, zinc, and magnesium concentrations were low.55 All these findings, as well as the fact that no new cases were seen a month after cobalt was no longer used in the local beers, favored the role of cobalt in the etiology of this cardiomyopathy.43,44

The cardiotoxicity of cobalt has also been substantiated in animal experiments. A single oral dose of CoSO4 given to rats at 100 mg per kg caused fatty changes and hyaline necrosis in the heart.53 In an eight week study in which cobalt was given orally to rats (100 mg per kg as the first dose, followed by 26 mg per kg daily), the cardiac lesions were characterized by edematous separation of cells, fat droplets, decreases in the number of myofibrils, and minimal cellular response.23,24 Subcutaneous injections of CoCl2 at 15 to 20 mg per kg for 10 to 15 days produce extensive myocardial necroses in rats. The cobalt concentration in the heart increased 100-fold and calcium decreased to one-half.34 Similar doses given to rabbits caused focal myocardial degeneration.27 Guinea pigs dosed orally with cobalt at 20 mg per kg for five weeks developed cardiomegaly, pericardial effusion and myocardial degeneration. The myocytes had reduction of fibrillar material, multiple vacuoles, and increased lipid and glycogen.16
Experiments were performed to examine the significance of factors that sensitize the myocardium to the effect of cobalt. When rats were kept on a low-protein diet and given cobalt orally at 4 to 12.5 mg per kg for two weeks, vacuolar dystrophic cardiomyopathy of a dose-related severity developed (figure 2). This lesion was similar to that observed in man. Amino acids provided protection, since both amino and sulfhydryl groups complex with Co ions and decrease their absorption. Among other factors examined in rats, pre-existing myocardial lesion, thyroidectomy, thiamine-deficient diet, or beer as the only source of fluid aggravated the cardiotoxicity of cobalt.

These findings implied that the increased absorption of cobalt brought about by a protein-deficient diet, which also existed among the patients, might not be the only mechanism of enhancing cobalt toxicity. The role of ethanol in a direct cardiac mechanism has not been well substantiated, although ethanol has been shown to increase cobalt uptake in the heart in humans.

There are a number of possible ways that cobalt may produce its cardiac toxicity. Cobalt specifically reacts with SH groups of dihydrolipoic acid, thus inactivating the coenzyme required for the oxidative decarboxylation of pyruvate to acetyl coenzyme A and of alpha-ketoglutarate to succinate in the citric acid cycle. Cobalt may lower the effective calcium concentration in cytosol and mitochondria. This could impair excitation-contraction coupling by blocking the calcium-dependent adenosine triphosphatase system, which in turn would limit the ability of cardiocytes to utilize high-energy phosphate and thus reduce the ability to sustain mechanical tension in a state of excitation. Cobalt might also compete successfully with other metal ions for absorption from the gastrointestinal tract, thereby producing a deficiency of essential ions such as iron, zinc, magnesium and other trace metals necessary for the integrity of the myocardium.

**Cardiotoxicity of Bronchodilators and Vasodilating Antihypertensives**

Sympathomimetic bronchodilators such as isoproterenol, metaproterenol and salbutamol act primarily on bronchial beta-receptors. In decreasing order, they also act on cardiac and vascular beta-receptors and, therefore, cause tachycardia and vasodilation in some areas. Antihypertensive drugs that decrease the peripheral resistance by their direct effect on the vascular smooth muscle cause reflex tachycardia. Hydralazine and minoxidil belong to this class. Drugs of both classes cause signs of myocardial hypoxia. The occurrence and intensity of the effect may be a function of the degree of cardiac receptor affinity for the bronchodilators or of the length of action of the antihypertensive agents.
In humans, pressurized aerosol isoproterenol occasionally caused palpitation, tachycardia, flushing, EKG signs of angina and, in a few instances, also myocardial infarction. The extreme abuse of this product caused deaths which, in some cases, might be related to the effects described previously, e.g., when arrhythmia preceded death. Clinical reports indicated that hydralazine, diazoxide, and minoxidil caused tachycardia and signs of angina. EKG signs of subendocardial ischemia and myocardial infarction have been observed with hydralazine and diazoxide treatments in a few instances.

Animal experiments were of heuristic value in the understanding of the pathogenesis of adverse cardiac effects induced by drugs of these two pharmacologic classes. To study the cardiotoxicity of a pressurized aerosol bronchodilator, a commercial product of isoproterenol was administered through an endotracheal tube to conscious dogs at a rate of five sprays per minute during inhalation. This route mimicked the oral inhalation used in man.

Five sprays produced marked tachycardia, and higher doses also produced ST segment depressions and ventricular arrhythmia. Treatments on two consecutive days produced subendocardial necroses that were most prominent in the left ventricular papillary muscles. Histologically, these lesions showed loss of striation, myofibrillar fragmentation, and sarcolemmal proliferation. Electron microscopic studies of isoproterenol-induced lesions revealed that the earliest changes were myofibrillar and consisted of irregular contraction and myofilament homogenization.

To study the cardiotoxicity of vasodilating antihypertensive drugs, a series of experiments were performed. The initial finding that hydralazine HCl given orally to beagle dogs at a dose of 10 mg per kg on five consecutive days caused papillary muscle necroses indicated the need for cardiotoxicity studies of related agents. Diazoxide (10, 20 or 40 mg per kg) given intravenously and minoxidil (1, 3 or 10 mg per kg) given orally caused marked tachycardia at each dose and ST junctional depression during the peak effect at the highest doses. Both compounds, except for diazoxide at the lowest dose, caused myocardial necroses of dose-related severity.
The primary site of the lesion was the left ventricular papillary muscles. At the highest dose of each compound, the right ventricular papillary muscles and the subendocardial left ventricular wall was also involved. Microscopically, the myocardial fibers were separated, fragmented and vacuolated. Sarcolemmal proliferation and a slight round cell infiltration were also seen (figure 3). Subepicardial and subendocardial hemorrhages were frequent in minoxidil-dosed dogs.7,8

The focal subendocardial myocardial lesions are considered to be the sequence of hemodynamic changes brought about by the pharmacological effect of the drugs, and they are most likely of ischemic origin. The EKG finding is consistent with this concept. The site of the lesion is the main indirect evidence. The left ventricular subendocardium is the most susceptible area to ischemia, because the perfusion pressure is the lowest at this site.28,42 Perfusion occurs only during diastole, the period which decreases during tachycardia when the demand for oxygen increases. Thus an oxygen deficiency develops, particularly in the papillary muscles where the demand is even greater because they perform the most mechanical work.15,49

Tachycardia, itself, does not produce ischemia; however, the concurrent hypotension, with its effects on coronary circulation and on pulmonary gas exchanges causing hypoxemia, impairs the blood supply. Beta-adrenoreceptor blocking agents prevent development of the isoproterenol effect in experimental animals.19 Administration of propranolol with either diazoxide or minoxidil reduced the incidence and severity of lesions in dogs.7,8 Finally, increased lactate production was elicited by isoproterenol in the human heart and was shown to be the consequence of myocardial ischemia.37

Conclusion

These examples of chemically induced cardiomyopathies have illustrated their diverse pathogenesis and the toxicologic responses.

The beta-adrenergic stimulant bronchodilators and the vasodilating antihypertensives increased the oxygen demand and decreased the supply, and consequently produced myocardial hypoxia. This state has also been recognized in the clinical setting. Multiples of pharmacologic doses, by exaggerating this effect, produced ischemic subendocardial necroses in experimental animals. This condition serves as an example of myocardial ischemia not related to coronary artery disease.

The beer drinkers developing heart failure ingested less than one-tenth of the daily dose of cobalt used for therapeutic purposes. Some of the predisposing factors not yet identified might have sensitized the myocytes to the toxic effect of cobalt. Among these, the role of chronic alcoholism cannot be dismissed. Cobalt cardiotoxicity exemplifies the concept that the toxicity of one chemical can be modified by another agent or various conditions.

Cardiomyopathy induced by anthracycline antineoplastics is attributed at least in part to the mechanism of their chemotherapeutic effect, the inhibition of DNA function. The delayed and cumulative characters of their cardiotoxicity, as well as the severe clinical condition with a moderate underlying pathology, favor a pathomechanism of this nature. It is a novel mechanism in the pathogenesis of a heart failure.

There are major differences in the progression of the various cardiomyopathies and therefore in the clinical course of the disease. Bronchodilator and antihypertensive-induced lesions were peracute, of the focal ventricular endocardial type and recovery was un-
eventful. Following the injury induced by bronchodilators and antihypertensive agents, the lesion healed by scar and did not recur during continued dosing. Metabolic adaptations, e.g., induction of the glycolytic pathway and of the hexose monophosphate shunt, have been demonstrated following such an ischemic injury. Cobalt-induced lesions in beer drinkers were a rapidly developing, dilated ventricular type, and led to heart failure or were responsive to therapy. From animal experiments, there is no evidence of adaptation to the cardiotoxic effect of cobalt. However, the recovery of most patients indicates that there is no interference with repair. Anthracycline-induced cardiomyopathy is insidious, slowly developing, intractable and the repair is handicapped.

These characteristics of interactions between the agent and the organism indicate the need for continuous monitoring of drug effects, both in preclinical studies and in a clinical setting. The ischemic changes described are detected only during the early exposure; if examinations are made later this potential toxicity might be overlooked. Signs of anthracycline-induced cardiotoxicity might be detected by cardiac function tests prior to the development of heart failure.

References


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