Myocardial protection by L-carnitine in children treated with adriamycin

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The aim of this study was to evaluate the possible cardioprotective effects of l-carnitine used in children treated with adriamycin for the treatment of several types of tumors. Adriamycin cardiotoxicity was compared in two groups of patients: one group (N=20) was treated only with adriamycin, non-protected group, and a second group (N=108), protected group, was treated with adriamycin plus l-carnitine. These groups were studied according to a protocol which includes X-ray, electrocardiography and echocardiography, stressing on shortening fraction and ejection fraction, clinical and laboratory parameters, especially CK-MB. In the non-protected group, two patients developed marked myocardial toxicity, one of them developing also a severe congestive heart failure (CHF IV, NYHA) which did not responded to standard treatment. This child recovered to CHF I, NYHA after three months of l-carnitine treatment. Patients in the protected group received 1-2 g l-carnitine IV on the same day they received adriamycin, and 175 mg/kg/day l-carnitine PO up to one year after the end of adriamycin treatment.
The protective effect of l-carnitine against adriamycin cardiotoxicity, shown for the first time in children in a clinical setting, is very encouraging. Further studies are necessary to establish l-carnitine as a cardioprotective agent in cancer chemotherapy patients.

Key words: *Myocardial protection. I-carnitine in children, adriamycin.*

En este trabajo se evalúa la posible acción cardioprotectora de la L-carnitina en niños tratados con adriamicina por diferentes tipos de neoplasias. La cardiotoxicidad por adriamicina fue comparada en dos grupos de pacientes: un grupo (N=20) fue tratado sólo con adriamicina, grupo no protegido; un segundo grupo (N=108), grupo protegido, fue tratado con adriamicina y carnitina. El protocolo de estudio incluyó: RX, electro y ecocardiografía (fracciones de eyección y de acortamiento), parámetros clínicos y de laboratorio especialmente CK-MB. En el grupo no protegido, dos pacientes presentaron importante cardiotoxicidad, uno de ellos severa ICC (IV de la NYHA) que no respondió al tratamiento usual. Este niño se recuperó (ICC I de la NYHA) con L-carnitina durante 3 meses. El grupo protegido recibió 1-2 g IV de L-carnitina el mismo día de la dosis de adriamicina y 175/mg/kg/día PO, hasta 1 año después del tratamiento con adriamicina. No hubo evidencia de cardiotoxicidad en este grupo. Por primera vez se presenta evidencia de la acción cardioprotectora de la L-carnitina en niños con cáncer que reciben adriamicina.

Palabras clave: ***protección miocárdica, L-carnitina en niños, adriamicina.***

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The major risk in using doxorubicin hydrochloride (Adriamycin) to treat some types of neoplasic diseases is cardiotoxicity, which is dose-dependent. Cardiotoxicity may range between early, mild, reversible alterations and a late, severe irreversible myocardiopathy. Recently, cases of «very late toxicity», appearing up to 6 to 10 years after chemotherapy, have been reported[1,2]. Adriamycin induced myocardial toxicity has also been experimentally[3-5] and clinically[6,7] studied.

Early detection of myocardial damage is of the utmost importance for discontinuing chemotherapy.[8,9] Several authors have developed methods for diagnosing myocardial damage[10-12]; nevertheless, research on prevention has not been the main concern. Recently, some drugs have been used in order to prevent cardiotoxicity[13-16]. One of them, l-carnitine, has demonstrated to be really effective as shown experimentally[17,18], and in clinical trials in adults[19-23].

The aim of this trial was to ascertain, for the first time, the l-carnitine protective effect against cardiotoxicity caused by adriamycin in children with neoplasic diseases.

PATIENTS AND METHODS

One hundred and twenty eight children, ages 1-12 years old, with neoplasic diseases (table 1) received 30-60 mg/kg/dose adriamycin (ADM) intravenously (X:40 mg) once a week in 4 weeks cycles. Total doses ranged between 260 and 420 mg/m²/BSA. Thirteen patients received repeated cycles. Other drugs such as cytosar, platinol, vinblastin, oncovin, prednisone and methotrexate, were also used.

Children were divided in two groups, one group (N=20) received only adriamycin, non-protected group, and a second group (N=108) received adriamycin plus l-carnitine, protected group, according to the protocol, as follows.

Non-protected group

Twenty children, monitored until 1986, received only adriamycin. In 15 patients, a complete cardiovascular evaluation was performed at least once during ADM treatment. Three patients were subjected to close and periodic control because of electrocardiogram alterations. Two patients (No. 12 and No. 15) developed signs of myocardial toxicity, so ADM was discontinued.

Case No. 12. This was a 12 years old boy with rhabdomyosarcoma, admitted in November 1985 because of severe myocardiopathy of sudden onset during the first month on chemotherapy. He previously had been subjected to mediastinal irradiation. He was in CHF IV, NYHA: anasarca, orthopnea, gallop rhythm, muffled heart sounds. X-rays revealed a severe heart enlargement, cardiothoracic ratio (CT-R): 0.66 (fig. 1-A. ECG: low voltage P, QRS and T waves in all leads, and ST-T segment alterations (fig. 2A). Echocardiogram disclosed an important heart chambers dilatation, specially of left atrium and ventricle, and reduced ventricular function and motion: EF:35% and ShF: 18% (fig. 3A, A'). Treatment consisted of digoxin, a diuretic and a vasodilator agent, besides general maintenance procedures. An endomyocardial biopsy was also performed (figs. 4A, B and C).

Table 1. **Diagnosis our 128 cases**

Diagnosis	Non prot.	Prot.	(m/f)
Megaloblastic anemia		1	0/1
Angioneuroblastoma		1	0/1
Ganglioneuroblastoma		2	0/2
Hitiocytosis		5	1/4
Hodgkin lymphoma	2	17	13/4
Cutaneous lymphoma		1	1/0
ALL	11	54	34/20
AML	2	5	4/1
Non Hodgkin lymphoma	2	8	5/3
Neuroblastoma		2	1/1
Rabdomyosarcoma		1	1/0
Retinoblastoma		1	0/1
Osteosarcoma	1		
Wilms tumor	1	6	0/6
Ewing's tumor	1	4	2/2
Total	20	108	

ALL: Acute lymphoid leukemia; AML: Acute myeloid leukemia; Non prot.: non protected; Prot.: protected

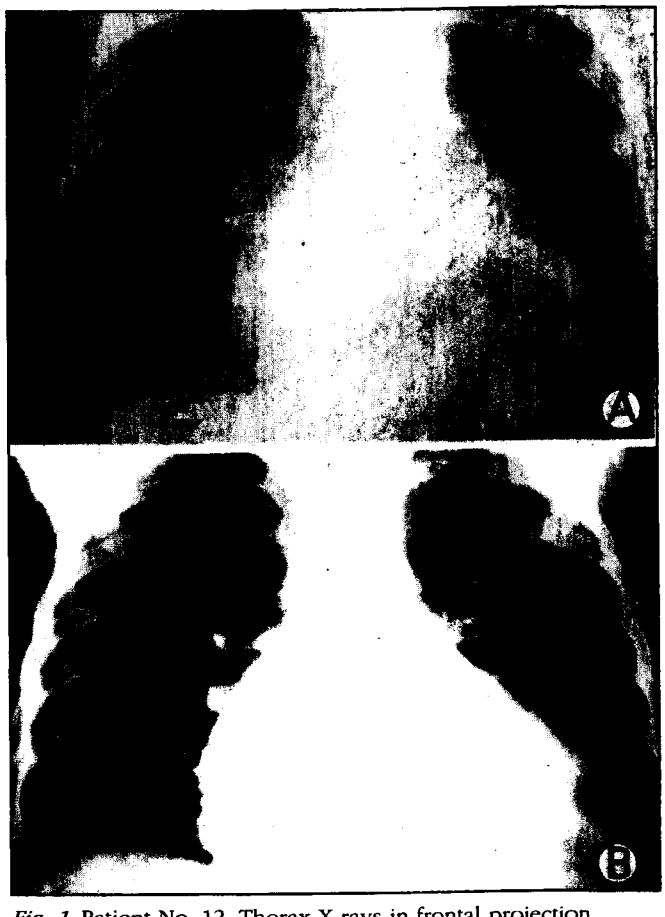

Fig. 1. Patient No. 12. Thorax X-rays in frontal projection, before (A) and after (B) l-carnitine treatment for three months. A: an important heart enlargement and signs of pulmonary venous-capillary hypertension. B: a moderate reduction of cardiomegaly, and no pulmonary venous-capillary hypertension are observed. This figure is reproduced from the volume «Role of L-carnitine in cardiomyopathies in infancy» presented in the World Congress of Pediatric Cardiology and Cardiac Surgery, Paris, June 21-25, 1993, with the kind autorization of Dr. J. P. Bonnefont of the Hopital Necker enfants-malades of Paris, and Sigma Tau of Rome.

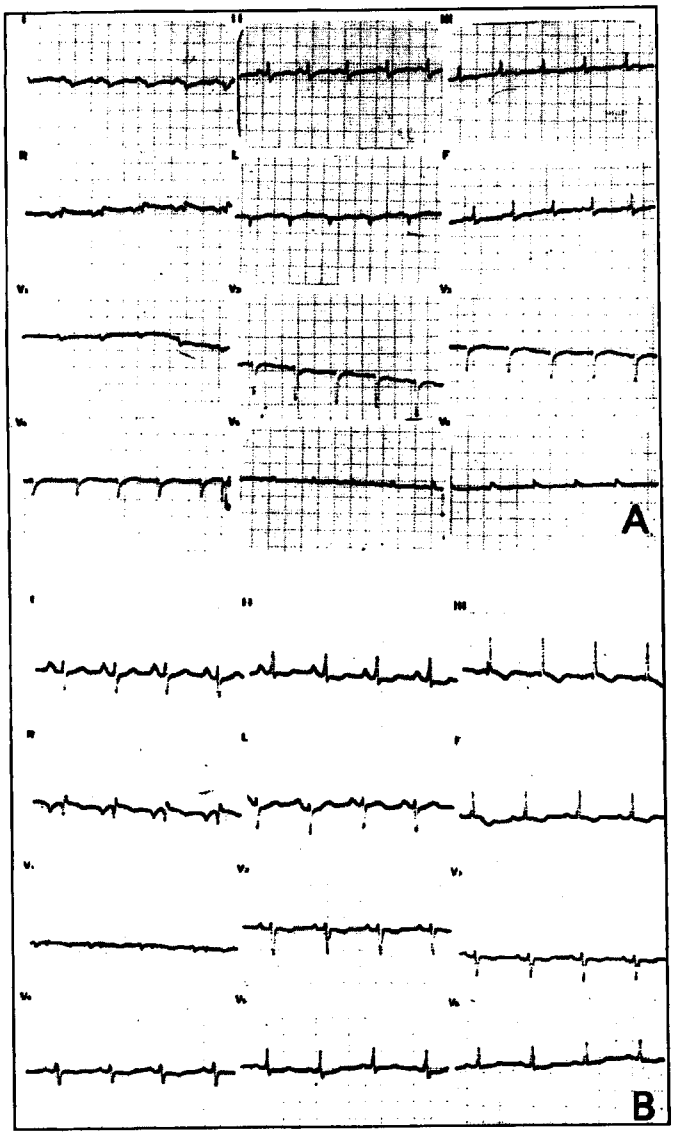

Fig. 2. Patient No. 12. Electrocardiogram before (A) and after (B) l-carnitine treatment for three months. A: observe low voltage P, QRS and T waves in all leads and ST-T segment alterations. B: observe voltage normalization. Discrete ST-T segment alterations are still observed. This figure is reproduced from the volume «Role of L-carnitine in cardiomyopathies in infancy» presented in the World Congress of Pediatric Cardiology and Cardiac Surgery, Paris, June 21-25, 1993, with the kind autorization of Dr. J. P. Bonnefont of the Hopital Necker enfants-malades of Paris, and Sigma Tau of Rome.

Patient No. 15 also showed electrocardiographic evidence of myocardial damage (prolonged QTc, ST-T and T waves abnormalities) and enzyme levels alterations (CK-MB: 24 U). Because of these abnormalities adriamycin treatment was discontinued.

Protected group

Between January 1987 and July 1995, 108 patients received l-carnitine according to the following protocol:

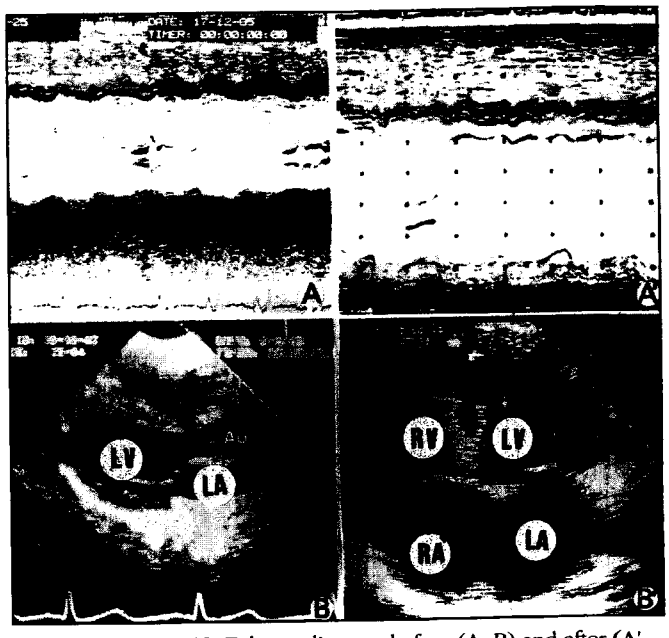

Fig. 3. Patient No. 12. Echocardiogram before (A, B) and after (A', B') l-carnitine treatment for three months. A: M-mode recording of left ventricular cavity showing important dilatation and mitral valve posterior displacement. B: bidimensional longitudinal axis, parasternal projection showing marked left ventricle dilatation. A': type B paroxistic movement of interventricular septum, even though ventricular function shows an improvement. B': apical chambers projection, showing left ventricular cavity dilatation. LA: left atrium, LV: left ventricle, Ao: aorta, RA: right atrium, RV: right ventricle. This figure is reproduced from the volume «Role of L-carnitine in cardiomyopathies in infancy» presented in the World Congress of Pediatric Cardiology and Cardiac Surgery, Paris, June 21-25, 1993, with the kind autorization of Dr. J. P. Bonnefont of the Hopital Necker enfants-malades of Paris, and Sigma Tau of Rome.

1) 1-2 g l-carnitine in 150 ml of 5% glucose was administered intravenously on the same day as ADM; and 175 mg/kg/day l-carnitine was administered PO, divided in three doses, during the entire ADM treatment period and up to a year after finishing chemotherapy. Forty two patients received l-carnitine during the last three years of the study.
2) The following evaluations were performed before, during and after ADM treatment: clinical tests, X-ray, EKG, echocardiography, glutamic-oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), creatine phosphokinase (CPK) and a creatine kinase isoenzyme (CK-MB) levels. Clinical evaluation and EKG were performed every other day during patient hospitalization. Emphasis was put on clinical findings, heart rate, cardiac rhythm, ST-T segment and T wave morphology on EKG. Enzyme changes, specially CK-MB and echocardiographic parameters of ventricular function and motion were also taken into account. Data obtained were analyzed by a computerized method, using a Statgraphics program.

RESULTS

Non-protected group

Three patients showed minor electrocardiographic changes: flattened T waves in left precordial leads

without other EKG alterations. These patients had also the lowest hemoglobin (Hb) and hematocrit (Ht) levels in this group (5.5 - 6.5 g % Hb and 15-19 Ht, respectively).

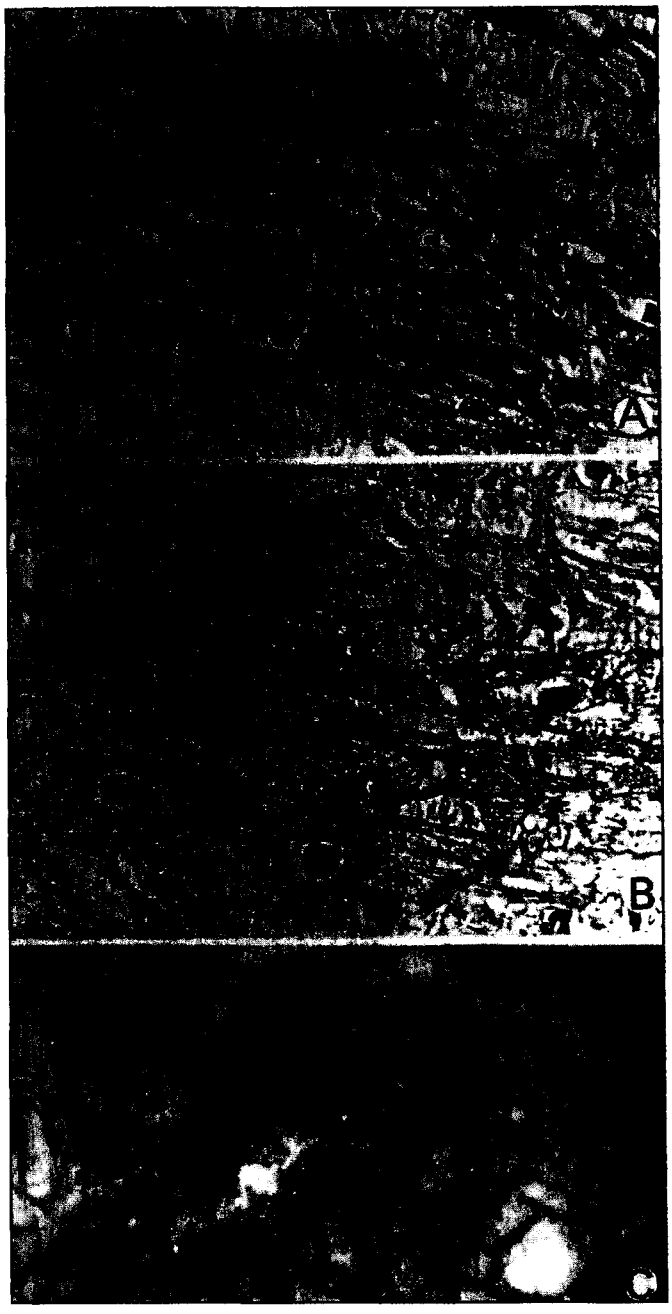

Fig. 4. Patient No. 12. Endomyocardial biopsy. Light (A,B) and electron microscopy (C). A: myocardial fibrils distortion. Swelling and interstitial fibrosis are present (Col. H-E x 100). B: Cell degeneration, myofibrils dissolution and marked nuclear changes. Swelling and interstitial fibrosis are observed (Col. H-E x 480). C: Mitochondrial swelling and cristae distortion are evident. Bar = 0.16 m (x 90.000). (Courtesy of Dr. Claudia Suárez, Cardiovascular Pathology, Institute of Pathology, Universidad Central de Venezuela).

Patient No. 12 did not improve with conventional anticongestive treatment during one month. Then, l-carnitine was started intravenously for three days (1 g every 8 hours) and 175 mg/kg/day per os, divided in three doses, for three years. A steady improvement was observed, and after three months of l-carnitine treatment the patient was in CHF I, NYHA. There were no complaints about the treatment; an improvement on X-ray alterations (fig. 1B), and normalization of P; QRS, T voltage and ST-T segments alterations in the EKG were observed (fig. 2B). Echocardiogram showed a marked improvement of ventricular function and motion: EF 57% and ShF 29% after l-carnitine treatment (fig. 3B and B').

Protected group

In this group, none of the patients showed any sign of ADM induced myocardial toxicity. Three patients presented mild electrocardiographic alterations. Laboratory data showed a mild increase in GOT before and after treatment (above 60 U) in 3 patients; they also showed a moderate increase in lactic dehydrogenase (LDH), CK and CK-MB, but these values were within normal limits both before and after treatment (fig. 5). Echocardiography disclosed 43% of average value in shortening fraction before treatment and 41% at the end of treatment (fig.6) The ejection fraction was between 63% average value before to a 65% after treatment (fig.7).

DISCUSSION

Prolonged use of ADM in the treatment of some tumors may pose some danger for the patient; so, it must be limited because of cardiotoxicity, as shown in two patients of the non-protected group. Myocardial toxicity is dose-dependent and it is cumulative between 440 and

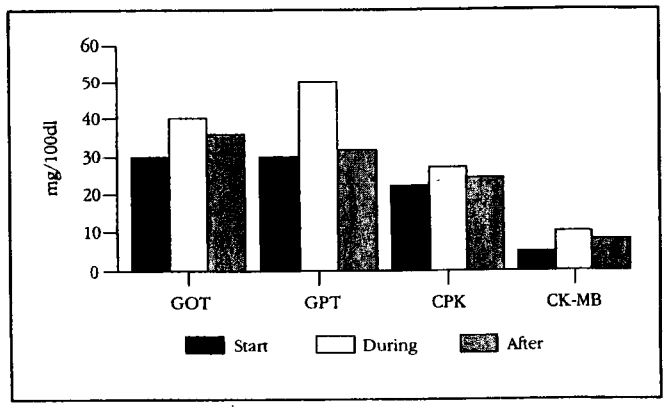

Fig. 5. Protected group with l-carnitine. Levels of glutamic-oxaloacetic transaminase (GOT), pyruvic transaminase (PT), creatine phosphokinase (CPK) and creatine kinase isoenzyme (CK-MB) at the beginning, during and after discontinuing chemotherapy. No significative changes in enzyme serum levels, particularly CK-MB, were observed.

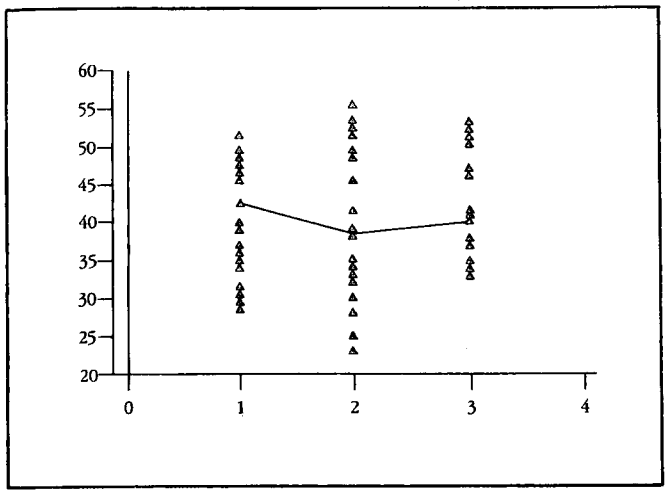

Fig. 6. Protected group with l-carnitine. Shortening fraction (ShF) for patients in the protected group: before (1), during (2) and after (3) ADM treatment. Observe average values (continuous line) among normal limits.

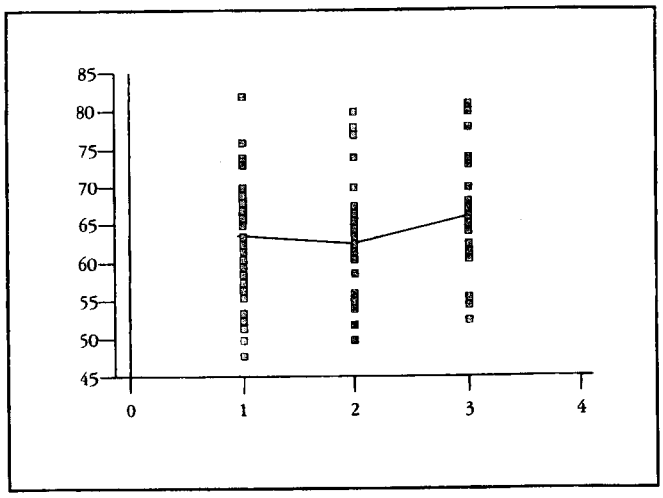

Fig. 7. Protected group with l-carnitine. Ejection fraction (EF) : before (1), during (2) and after (3) ADM treatment. Average values (continuous line) were within normal limits.

550 mg/m²/BSA in adults[6,7,24]. This has also been reported in children[7,24]. Risk factors also are important. Besides a high cumulative dose, risk factors include: previous mediastinal irradiation, myocardiopathy or congenital heart diseases, anemia, fever, infections, tumor infiltrations, excessive liquid retention, concurrent cyclophosphamide treatment in children with Wilms' tumor. *Acute* toxicity some times can occur after initial dose or during treatment. Manifestations are generally mild, transient and reversible. *Chronic* toxicity occurs after the first month from chemotherapy discontinuation, appearing as a severe and generally irreversible CHF, with 60% mortality among all cases. Nevertheless, this classification[22,27] may not always be accurate, since patient No. 12 showed cardiotoxicity within the first month of chemotherapy as an «acute» CHF (sudden onset). Probably, terms such as «early» and «late» toxicity[12] would be more precise, and so it would be «very late toxicity» referring to myocardial toxicity cases appearing at any time after the first year of finishing cancer chemotherapy. Manifestations of toxicity and its severity, presents a wide range from one case to another: from subclinical manifestations (EKG, echocardiographic or enzyme alterations) to severe CHF, which may appear during or after chemotherapy.

Since an early diagnosis of ADM-induced cardiotoxicity is difficult, several methods have been devised[7] in order to decide on the convenience to discontinue ADM treatment. Some of the methods have proven to be useful; for example:

1) Electrocardiogram: is an useful tool, specially for diagnosing tachyarrythmia, extrasystole, ST-T wave alterations, all of them suggestive of electrolyte and ischaemic disturbances. Other findings are increased P-R and decreased QTc intervals. EKG changes must be evaluated according to Hb and Ht values, because a severe anemia may cause a misinterpretation of the clinical situation, as it has occurred with some of our leukemic patients. EKG is important in the evaluation of myocardial toxicity[12]. Prolongation of QTc and ventricular arrhythmia are an ominous sign; with QTc values > 0.46, CHF is present[28]. Electrocardiographic signs of late toxicity –QRS complex prolongation and AV conduction alterations– are obvious and related to CHF. These changes are neither specific nor predictive of CHF. A low QRS voltage is not exclusively related to ADM induced myocardiopathy and it can also be found in associate pericarditis, massive pleural effusion, neoplasic infiltration of myocardium, chest wall edema. Tachycardia may appear in fever, anemia, concurrent infections and tumor infiltration of myocardium. It can also be found in ADM treated children, even 7 years after discontinuation of chemotherapy[2]. A 24 hours Holter is useful when arrhythmia is suspected to be a delayed effect of chemotherapy. Patients in the Protected Group showed no EKG changes. It is important to correlate this with alterations in other parameters such as enzyme and echocardiographic changes, for an early detection of ADM induced myocardial toxicity.

2) Enzymes: The most sensitive enzyme assay, according to some authors[11], is the CK-MB determination. It also is the most specific and it shows early changes in cases of ADM induced myocardial toxicity[11]. Patients in the protected group did not show significative changes in CK-MB serum levels (fig. 5). Other enzymes such as GOT, GPT and CPK, are less specific but may be useful in monitoring patients with myocardial toxicity.

3) Echocardiography: This is a very useful method for detection of cardiotoxicity as it is a simple, non-invasive and inexpensive one. It also allows an easy observation of changes in ventricular function. Compared to that

observed in adults, it is an easier method to run and interpret in children, due to technical reasons. The most important measurements are: a) Left ventricular dimensions and posterior wall thickness; the latter becomes an early echocardiographic sign of myocardial toxicity as a decrease is observed in comparative studies; b) Shortening fraction (ShF); c) Ejection fraction (EF). It has been shown that detection of myocardial dysfunction and the consequent discontinuation of chemotherapy prevent cardiomyopathy development and reduces the risk of CHF in children[29-31]. No echocardiographic abnormalities were found in patients in the protected group (fig. 6 and 7).

Some other investigations for early detection of ADM toxicity such as stress test[32], radionuclide angiocardiography[33-35], and endomyocardial biopsy[7,8,36-38], have been performed. However, these methods are limited as a routine myocardial toxicity control in children, specially if they are younger than 6 years old. Actually, severely sick children are unable to fully cooperate when they have anemia and fever. Furthermore, some of these methods are of high cost and invasive nature, and have limited availability. Some of these evaluations, such as radionuclide angiocardiography, should be carried out in patients with clinical and laboratory values suggestive of cardiotoxicity. To our knowledge, the remarkable improvement of patient No. 12 (non-protected group) after l-carnitine treatment (figs. 1-3) is the first case, at least in children, who has recovered from a severe toxic ADM induced cardiomyopathy. Recently, Boon et al.[39] reported similar success in a child with severe ADM-myocardiotoxicity, who improved after ibopamine and l-carnitine treatment. These and those findings in the protected group show the efficacy of l-carnitine in the treatment of ADM induced myocardial toxicity, and supports its use in the prevention of toxicity in children with different type of tumors treated with daunurobicin derivatives. Protective effect of l-carnitine during ADM therapy may be related to free fatty acids transport from cytoplasm to the mitochondrial matrix of myocardial cells, thus reducing ADM damaging action. On the other hand, l-carnitine decreases acetylCoA/CoA ratio, facilitating oxidative use of glucose; it restores ATP production[40], prevents dangerous accumulation of calcium[40], limits free radicals production[41], and has a protective effect against ADM induced arrythmia[40]. Recently, in our Laboratory, Strauss et al.[42] demonstrated enhancement of cell-protecting mechanism based on an induction of skock protein produced by l-carnitine which probably accounts for a reduced severity of very late ADM-myocardiotoxicity. Preliminary experiments with chick embryo[143] suggest that experimental disturbances induced by ADM are similar to those observed in human endomyocardial biopsies, as in our case. Myocardial protection with l-carnitine in patients treated with ADM is promising. Since this is the first trial in children, further experimental research and clinical investigations with larger number of pediatric patients are warranted, in order to understand the role of l-carnitine as a myocardium protective agent in patients subjected to cancer chemotherapy.

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