CARNITINE SUPPLEMENTATION IN DIPHTHERIA

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ABSTRACT

We studied the effect of carnitine supplementation in patients with diphtheria. Six hundred and twenty five children of diphtheria received either DL-carnitine (100 mg/kg/day in two divided doses orally for four days), or no carnitine, in addition to the routine treatment for diphtheria. The patients receiving carnitine (n=327) and controls (n=298) were matched for age, sex, duration of symptoms, grade of toxemia and immunization status. Patients receiving carnitine showed a significant reduction in incidence of myocarditis as compared to controls ($p=0.001$). Cases with myocarditis receiving carnitine therapy showed a significant reduction in mortality as compared to controls ($p<0.001$). In view of a significant decline in incidence and mortality of myocarditis in cases of diphtheria, we recommended that all cases with diphtheria should receive carnitine supplementation.

Key words: *Diphtheria, Myocarditis,Carnitine.*

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Diphtheria remains a serious public health problem in places where primary immunization is not available. Carnitine depletion(1) and fatty acid accumulation are observed chiefly in the myocardial cells(2,3) as a consequence of ribosomal damage(4) and reduction in the number of the membrane carriers for carnitine transport(5). The reduction in incidence of myocarditis and consequent mortality in carnitine-treated, diphtheric animals(6), and the increase of L-carnitine and uptake by more than 50% by cultured heart cells(7) suggest its importance as a therapeutic agent.

The first clinical attempt to observe the effect of orally administered carnitine in diphtheria patients was reported from Rio de Janeiro(8). We now report on a large scale analysis involving 625 patients of diphtheria treated with oral DL-carnitine.

Material and Methods

This study was carried out in 625 children with diphtheria diagnosed by clinical (immunization status, onset of symptoms, toxemia grade) and bacteriological criteria (*Table I*). Informed consent was obtained from the parents at admission. The distribution of patients was as follows: 339 children in the metropolitan area of Rio de Janeiro. 186 at Recife and 100 at Maceio, the latter two cities being set in the Northeast coast of Brasil. All collected data were sent to Rio de Janeiro for laboratory processing. The Rio de Janeiro survey lasted 30 months. The Racife and Maceio observations took about 12 months.

Patients were assigned to the control or the carnitine groups according to the week which had an odd or an even number when counted from the beginning of the study. Children admitted in the odd numbered weeks were assigned to the control group

TABLE I— *Clinical Characteristics of Control and Carnitine Groups**

Clinical Features	Control group		Carnitine group	
	No.	%	No.	%
No.	298		327	
Age (yr)				
0-4	165	(55.4)	206	(63.0)
5-9	93	(31.2)	92	(28.1)
>10	40	(13.4)	29	(8.9)
Sex				
Male	157	(52.7)	174	(53.2)
Female	141	(47.3)	153	(46.8)
Color				
White	143	(48.0)	166	(50.8)
Mullato	126	(42.3)	131	(40.0)
Negro	29	(9.7)	30	(9.2)
Immunization				
Novaccinated	196	(65.8)	194	(59.3)
Incompletely Vaccinated	67	(22.5)	97	(29.7)
Vaccinated**	35	(11.7)	36	(11.0)
Onset of symptoms(days)				
<3	136	(45.6)	148	(45.3)
5-6	126	(42.3)	131	(40.0)
>7	36	(12.1)	48	(14.7)
Severe toxemia	93	(31.0)	105	(32.1)

* Difference of proportions not significant.
** Three primary doses and one booster dose.

and those admitted in the even numbered weeks were included in the carnitine group. The control group (n=298) was provided with routine therapy (antitoxin, penicillin and routine care). The carnitine group (n=327) received the same therapy but were supplemented with 10% DL-carnitine syrup, 100 mg/kg per day in two divided doses for four days from the date of hospitalization. Racemic carnitine was purchased from Ajinomoto, Brasil.

Patients who died before 48 hours of hospitalization were excluded from the comparative analysis, since it was not possible to submit them to the routine for diagnosis of myocarditis. The majority of such children died due to obstruction of upper airways. Patients were followed with repeated clinical, electro-cardiographical, radiological and when possible (Rio de Janeiro and Maceio) with enzymatic determinations. Myocarditis was diagnosed when one or more of the criteria mentioned in *Table II* were positive.

In addition, 60 patients with diphtheria in Rio de Janeiro were randomly divided

between the racemic and L-forms to compare the efficacy. The L-form of carnitine was given by Sigma-Tau, Italy. Syrup of both forms (concentration of 10 g/dl) was made by the pharmacy service of Hospital Universitario, UFRJ.

Statistical analysis was based on the difference of proportions for single samples(9).

Results

As shown in *Table III* the overall incidence of myocarditis was significantly reduced ($p<0.01$) in the carnitine treated group. The observed reduction was 15.8% in Rio de Janeiro ($p=0.00256$), 6.6% at Recife ($p>0.05$) and 5.1% at Maceio ($p>0.05$).

If the specific causes of death were considered, the protective effect of dl-carnitine therapy was clearly evidenced (for Rio de Janeiro, $p=0.005$; for Recife, $p=0.009$; for Maceio, p is not significant due to small number of patients). There was a highly significant reduction in death caused by myocarditis when the 6 carnitine treated children were compared to the 25 of the control group ($p<0.001$). The

TABLE II—*Diagnostic Criteria for Myocarditis*

Clinical:	Tachycardia, muffled heart sounds, gallop rhythm, regurgitant systolic apical murmurs, heart failure, low output syndromes.
Radiological:	Significant increase in cardiothoracic index.
Electrocardiographic:	Arrythmias, conduction disturbances, QRS or ST-T changes.
Enzymatic:	At least two samples of blood collected per patient, the first at hospitalization and the second two weeks after the onset of symptoms. Creatinine kinase MB isoenzyne (EC 2.7.3.2.) measures by immunological method (Merck, No. 15808); indicative of myocardial damage when levels greater than 10 IU/L.

TABLE III— *Morbidity and Mortality in Carnitine Treated and Control Groups*

	Rio de Janeiro		Recife		Maceio		Total	
	Control group (n = 151)	Carnitine group (n = 188)	Control group (n =96)	Carnitine group (n = 90)	Control group (n = 51)	Carnitine group (n = 49)	Control group n = 298 (%)	Carnitine group n = 327 (%)
Myocarditis incidence	92	84**	16	9*	38	34*	146(49.0)	127(38.8)**
Myocarditis mortality	14	4**	7	0**	4	2*	25(8.4)	6(1.8)**

* Not significant; ** $p<0.01$.

majority of patients who died due to myocardial damage had severe conduction disturbances on the electrocardiogram, especially complete atrio-ventricular block or dissociation, irresponsive to pacemaker implantations. Other causes of death included sudden death secondary to ventricular fibrillation or cardiac arrest, respiratory failure (2 in the control group and 2 in the carnitine group), gastro-intestinal hemorrhage in 2, sepsis in 2, and dyselectrolytemia in one case in the carnitine group.

The clinical outcome was clearly influenced by immunization status: 28 out of the 31 cases who died from myocarditis had never received even one dose of vaccine, 2 were incompletely vaccinated and only one was fully immunized; the last three patients belonged to the control group. The incidence of myocarditis was not significantly reduced in the groups of fully immunized children.

Treatment with L-carnitine, given to 30 patients with diphtheria, did not improve the incidence or mortality of myocarditis as compared to those receiving racemic carnitine.

Discussion

The treated and control groups were comparable in terms of age, color, sex, time from onset of symptoms and grade of toxemia (*Table I*). However, the immunization status was significantly different between the patients in various cities. Patients at Recife and Maceio were more incompletely vaccinated than those of Rio de Janeiro ($p=0.02$ and 0.009, respectively). There was no difference in the incidence of completed immunization, between cases of diphtheria in the treated and control groups of the three cities. The occurrence of diphtheria despite complete immunization in 11% cases represents a failure of the vaccine. This may be ascribed to a lower immunogenicity of the vaccine. Keeping the vaccine in cold box may reduce the efficacy in extremely hot climates.

The reduced incidence of myocarditis at Recife can partly be due to underdiagnosis because of inability to perform enzymatic determinations. However, the reduction in incidence of myocarditis in patients treated with carnitine was similar at Recife and Maceio (*Table III*). The results are in accordance with those of a previous study at Rio de Janeiro(8), in which the difference of myocarditis between groups did not reach a significant level, possibly due to the relatively small number of patients ($n=132$). However, in the present study, the difference in incidence and mortality of myocarditis was significantly different in the 2 groups when data from all 3 cities was combined. More cases in the control groups died of conduction disturbances and cardiac failure as compared to those treated with carnitine.

No signs of intolerance or deleterious effect of carnitine were detected after careful clinical observation; mild to moderate diarrhea was seen in 6 patients. The possible side effects of DL-carnitine present in the racemic form were not seen(6). This is probably due to the short duration of supplementation of the racemic form. This is certainly a cost advantage for the underdeveloped countries as the DL-form is about 200 times cheaper than the L-form.

Our observations suggest that carnitine supplementation reduces cardiac morbidity in patients with diphtheria. This may not be detectable when the carnitine and control groups are small as was in the original study(8). In view of the reduced morbidity and mortality due to myocarditis, therapy

with carnitine should be recommended in all patients with diphtheria.

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NOTES AND NEWS

III JOINT CONVENTION OF NATIONAL NEONATOLOGY FORUM AND INDIAN SOCIETY OF PERINATOLOGY AND REPRODUCTIVE BIOLOGY

The Department of Pediatrics, K.G's Medical College, Lucknow is hosting III Joint Convention of National Neonatology Forum and Indian Society of Perinatology and Reproductive Biology on 27th and 28th February, 1993 (C.M.E. on 26th February, 1993). The last date for registration is 15th November, 1992.

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