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Long-Term Treatment of Chronic Chagasic Cardioneuropathy With a Mixture of Gangliosides: Effect on Evolution of Circulating AntiGM1 Antibodies

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Abstract

Chagas disease involves a cardiac impairment, being the first alterations of autonomic disorders which affect heart rate and blood pressure control. At this stage, diminished heart rate responses to atropine and propranolol are observed. Prior studies have shown that short term ganglioside treatment improves the responses to these agents, but there is no information about the long term effect of gangliosides and the evolution of antiGM1 titers.

The effects of long term treatment with gangliosides on autonomic tests in patients with chagasic cardiodisautonomy and the evolution of antiGM1 titers were studied in 90 patients (57 men, 33 women, aged 25–60 years) with positive serology for Chagas disease and electrocardiogram showing sinusal bradycardia and incomplete right branch block, without cardiomegaly, with autonomic alterations by postural and Valsalva's tests. All patients were submitted to a test that consisted of intravenous injection of atropine 0.04 mg/kg followed 3 min later by intravenous injection of propranolol 0.2 mg/kg. During these tests heart rate and blood pressure were recorded continuously. Subsequently, 30 patients were treated with 100 mg/day of a mixture of gangliosides by intramuscular injection during 15 days in a row, followed by 40 mg/day during another 75 days. Another 30 patients received continuous treatment for 12 months. The remaining 30 patients were controls. The antiGM1 antibody circulating titers were determined before the treatment, at the third and 12th month.

Seventy-four patients completed the study. Before treatment, the heart rate increased, though slightly, after the injection of atropine. After 3 months of ganglioside treatment a statistically significant increase in the response to atropine was recorded. In the controls at 12 months, the response to atropine remained increased without differences between the patients treated for 3 and 12 months. The control patients did not show any modification of the heart rate response during 12 months. Both ganglioside-treated groups showed an increase in the response to propranolol. The antiGM1 titer distribution was similar in both healthy subjects and chagasic patients. None of the patients had positive antiGM1 titers in basal conditions nor significant modifications after the ganglioside treatment.

Chagasic cardioneuropathy was not associated in this study with high antiGM1 antibody titers. Chagasic patients showed a diminished heart rate response to atropine as well as to propranolol. Ganglioside treatment determined an increased heart rate response, particularly after atropine. Increased heart rate response was maintained until 1 year, without differences between the patients treated for 3 and 12 months. No changes in the antiGM1 titers were observed during the ganglioside treatment.

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Key Words

■**Cardiomyopathies, other (Chagas disease)**
■**Autonomic nervous system (cardioneuropathy)**
■**Arrhythmias (sinus bradycardia)** ■**Drug therapy (gangliosides, antiGM1 antibodies)**

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INTRODUCTION

Chagas disease involves a severe cardiac impairment. No sooner is the acute stage overcome than most of the patients enter a latent phase in which there are no clinical signs or symptoms related to *Trypanosoma cruzi* infection[1,2]. Most of the patients progress to the chronic phase of Chagas disease[2] which is manifested by cardiovascular, digestive and autonomic nervous system disorders[3]. The most important cardiovascular signs and symptoms are hypotension, orthostatism, dizziness, palpitations, different kinds and severity of arrhythmia and congestive cardiac disease[4]. Some of these cardiovascular signs and symptoms are the result of the autonomic nervous system dysfunction[4], as the changes in heart rate and blood pressure control the first alterations in this sense[4]. These initial alterations of the autonomic nervous system can be studied using autonomous and pharmacologic tests in which the heart rate and blood pressure changes are recorded before and after the acute intravenous administration of a parasympatholytic (atropine) and a beta-blocker (propranolol). The response to these agents in chagasic patients with cardioneuropathy decreases considerably[4].

Prior studies have shown that short term treatment with a mixture of gangliosides enhances the response to the above-mentioned agents[5,6]. However, there is no information about the duration of this effect once the administration of gangliosides is suspended, nor about the results of a long term administration of these agents, nor about the clinical significance of these modifications. If beneficial effects maintained over time are confirmed, gangliosides could be considered for prevention (or, at least, for the postponement) of some of the cardiac alterations determined by Chagas disease.

Many hypothesis have been suggested to explain the effect of gangliosides on chagasic cardiopathy, based on the following physiopathological considerations:

1) The infective form of *Trypanosome cruzi* is capable of destroying the sialic acid on the surface of epithelial cells in the myocardium and blood vessels by the effect of a parasitary neuraminidase[7].
2) The neuraminidase activity is raised up to 20-fold when the parasite changes from the non-infective form, suggesting that this enzyme is an important virulent factor in Chagas disease[7].
3) The gangliosides are natural glycosphingolipids highly concentrated in membranes, particularly in neurons and in the cardiac conduction system, which possess a bipolar lipidic-oligosaccharide structure with a lateral chain of one or more sialic acids[8]. A physiopathological interpretation of the effect of *Trypanosome cruzi* suggests that the parasite neuraminidase would alter the endogenous ganglioside structure[5,9].
4) Another possible interpretation would be an eventual production of antibodies, particularly antigangliosides, related to the infection. This effect could be similar to that recorded with other agents which share common epitopes with gangliosides, so the immunological response to the infection might lead to the production of antiganglioside antibodies. Other possible immunological mechanisms have been proposed[5,10,11]. This hypothesis has not been studied yet.

Another aspect to take into consideration is the long term security of gangliosides. Some years ago the administration of gangliosides was associated with the appearance of Guillain-Barré syndrome[12]. This association was based on a few reported cases and the observation of antiGM1 antibodies in some of the cases[12]. It was also found that Guillain-Barré syndrome was preceded, in many cases, by infection with some bacteria (the most frequently associated, *Campylobacter jejuni*) with common epitopes with GM1, so that the antiGM1 antibodies were, in fact, a response to a particular case of immunologic mimicry, a fact later observed in other studies[12,13]. It was also proved that the healthy population presents antiGM1 antibodies or anti-other gangliosides, in the absence of any previous recorded treatment and/or disease, with a variable incidence, in some cases high.

In spite of what was said before, there is no prospective information about the incidence nor the evolution of antiganglioside antibodies in Chagas disease nor about the evolution of antiGM1 antibodies titers before the administration of gangliosides, their evolution with the chronic administration of these preparations and after the discontinuation of administration of the same.

Based on the above, the following study was programmed with these objectives:

a) To study the distribution of antiGM1 antibodies titers in a chronic chagasic population in comparison with a normal population.

b) To confirm the effect of ganglioside treatment upon the alterations of the heart rate control mechanism observed in chagasic patients.
c) To study the evolution of this effect over short (3 months) or long (12 months) periods of treatment with a mixture of gangliosides.
d) To study the effect of ganglioside treatment upon the evolution of the antiGM1 antibodies titer.

MATERIAL AND METHODS

Ninety patients (57 men, 33 women, aged between 20 and 60 years) were incorporated into the study, after giving informed and signed consent, with positive serology for Chagas disease (enzyme-linked immunosorbent assay) and electrocardiogram showing sinusal bradycardia and incomplete right branch block without cardiomegaly. Thus, the inclusion criteria comprised chronic class II chagasic patients with dysautonomopathy and the exclusion criteria comprised chronic chagasic patients of other classes and other pathologies, situations or treatments that might occasion alterations of the autonomic nervous system (*i.e.* alcoholism, diabetes, drugs), myocardiopathies of another nature, pregnancy and lactation. There were also 30 clinically healthy subjects incorporated into the study (18 men and 12 women), without any record of chagasic serology or history of diarrhoea in the period prior to the study (age 27−40 years) ; these subjects were incorporated only to determine the antiGM1 antibody titers.

Prior to the beginning of the study the protocol was submitted to the approval of the Independent Ethics Committee of the First Chair of Pharmacology, Faculty of Medicine, University of Buenos Aires.

In basal conditions, all the patients underwent postural and Valsalva's tests[4] to confirm the existence of an autonomic alteration in the heart rate regulation mechanism determined by Chagas disease. Once the incorporation was decided, blood was withdrawn from each patient to perform general biochemical studies and to determine the circulating antiGM1 antibody (immunoglobulin M) titers (blood was obtained also from the healthy subjects). Each sample was allowed to coagulate, serum was extracted and frozen immediately at −20 °C until determination by a previously reported method[14]. Titers below 1: 3,200 were considered negative, 1: 3,200 were considered uncertain and titers of 1: 6,400 and more were considered positive.

Then each patient was submitted to a pharmacological test which involved an intravenous injection of atropine 0.04 mg/kg followed 3 min later by an injection of propranolol 0.2 mg/kg[4]. During this period the patients were permanently controlled, determining heart rate and blood pressure by continuous recording. The assessment was based on the heart rate record obtained 1 min after the respective injections.

From this point on, 30 patients (control group) continued without treatment with gangliosides. Another 30 patients were treated with 100 mg/day intramuscular injection of a mixture of gangliosides (Sinaxial 100) for 15 days followed by 40 mg/day intramuscular injection (Sinaxial 40) for another 75 days ("short" treatment group). The remaining 30 patients received gangliosides (100 mg/day the first 15 days and then 40 mg/ day) for 12 months (with intervals of 15 days after every 90 days of treatment) ("long" treatment group). The patients were controlled on a monthly basis. At months 3 and 12 general biochemical analysis were determined, as well as the respective heart rate responses to the combined atropine-propranolol test. At each point of time, blood samples were taken for the determination of antiGM1 antibodies.

The assessment of the results comprised the following steps:
1) Evolution of heart rate response to atropine and propranolol at the distinct control moments (*t*-test for paired samples to analyse the responses to atropine and propranolol at each control moment and *t*-test for unpaired samples to compare the results between the controls and between each of the treatment groups).
2) AntiGM1 antibody titer in the healthy population and in the chagasic population.
3) Evolution of the antiGM1 antibody titer in the treatment groups.

RESULTS

Sixteen patients left the study, mainly between the second and third month. **Table 1** shows the causes of drop outs. Two patients from the control group left for economical and/or unknown reasons. Eight patients from the 12-month treated group left for reasons unrelated to the treatment, except for one patient who left because of intense headaches.

Table 1 Causes of withdrawal from study

Cause	3 months group (n=30)	12 months group (n=30)	Control group: without treatment (n=30)
Number of drop outs/incorporated initially	6/30	8/30	2/30
Refusal to continue with the injections	3	3	0
Financial problems	2	2	0
Headache	1	1	0
Unknown	0	2	2

Table 2 Clinical features of patients

	3 months group (n=24)	12 months group (n=22)	Control group (n=28)
Age (yr)	48.1±7.0	46.2±6.2	48.1±6.4
Sex (male/female)	14/10	12/10	15/13
Weight (kg)			
Male	68.1±5.0	69.8±4.2	68.0±4.8
Female	52.3±4.2	51.4±6.0	52.0±5.0
Body mass index			
Male	24.1±2.0	25.0±2.0	24.0±2.8
Female	21.2±1.8	20.8±1.8	21.2±2.0

Values are mean±SD.

Six patients from the 3-month treated group left the study, one because of headaches.

The final assessment was performed in 74 patients. The demographic characteristics are shown in **Table 2**. There were no significant differences observed between the 3 groups concerning age, sex distribution, weight and body mass index (BMI).

Fig. 1 shows the results of the atropine test in the 3 groups and the different controls (mean ± SEM). The response to atropine determined before the ganglioside treatment was a moderate increase in heart rate of less than 10 beats /min. This response to atropine increased significantly after 3 months of treatment with gangliosides. In the group treated for 3 months, the atropine response at month 12 (that is, 9 months after discontinuing the treatment) remained significantly enhanced, without statistically significant differences with the one recorded at the third month. In the patients treated for 12 months, the response at month 12 was also significantly bigger compared to the basal value but was not different from the one observed in the group treated for 3 months. The control group did not show any modification to the atropine response in comparison with the basal value.

Table 3 shows the qualitative assessment of the treatment. A clinically significant response was observed (that is, a difference of ≥ 10 beats/min) in only 5 patients (21%) whereas at the third month of treatment a clinically significant response was observed in all 24 patients (100%); at month 12, 17 patients (71%) still presented clinically significant responses to atropine.

Similar results were observed in the group treated for 12 months, although this group of patients showed a bigger percentage of clinically significant responses before the treatment. The control group did not show increases in the number of clinically significant responses; on the contrary, the percentage of positive responses at month 12 dwindled.

Fig. 2 shows the results (mean ± SEM) of the propranolol tests. The group treated during 3 months showed a small heart rate decrease and, after the treatment with gangliosides, an increase in the bradycardic response that did not reach any statistical significance. At month 12 the response to propranolol was similar to the basal one. In the group treated for 12 months, propranolol did not cause a mean bradycardizing response in basal con-

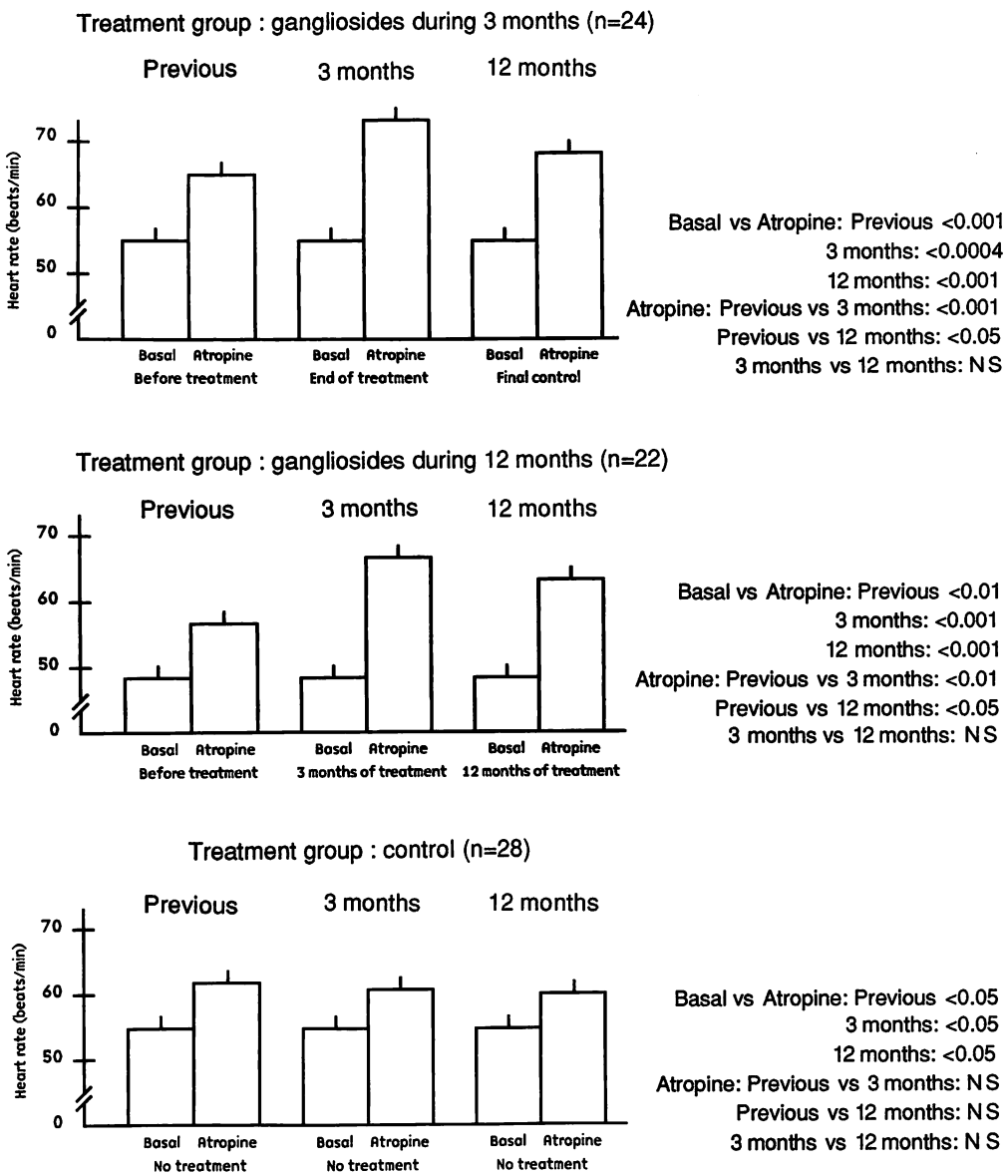

Fig. 1 Heart rate before and after intravenous injection of atropine 0.04 mg/kg in basal conditions and after 3 and 12 months in groups treated with gangliosides for 3 or 12 months and in a control group

The levels of significance (p value) pre- and post-atropine (Basal vs Atropine) and between responses to atropine in the distinct controls (Atropine) are shown.

Values are mean ± SEM.

Table 3 Qualitative assessment of response to atropine

	Treatment group: gangliosides for 3 mo (n=24)			Treatment group: gangliosides for 12 mo (n=22)			Control group: without treatment (n=28)		
	Previous	3 mo	12 mo	Previous	3 mo	12 mo	Previous	3 mo	12 mo
Response (beats/min)									
≥10	5(21)	24(100)	17(71)	9(41)	18(82)	12(54)	7(25)	7(25)	4(14)
1–10	17(71)	0	7(29)	13(59)	4(18)	10(46)	19(68)	19(68)	19(68)
Without changes	2(8)	0	0	0	0	0	2(7)	2(7)	5(18)

( ) : %. mo=months.

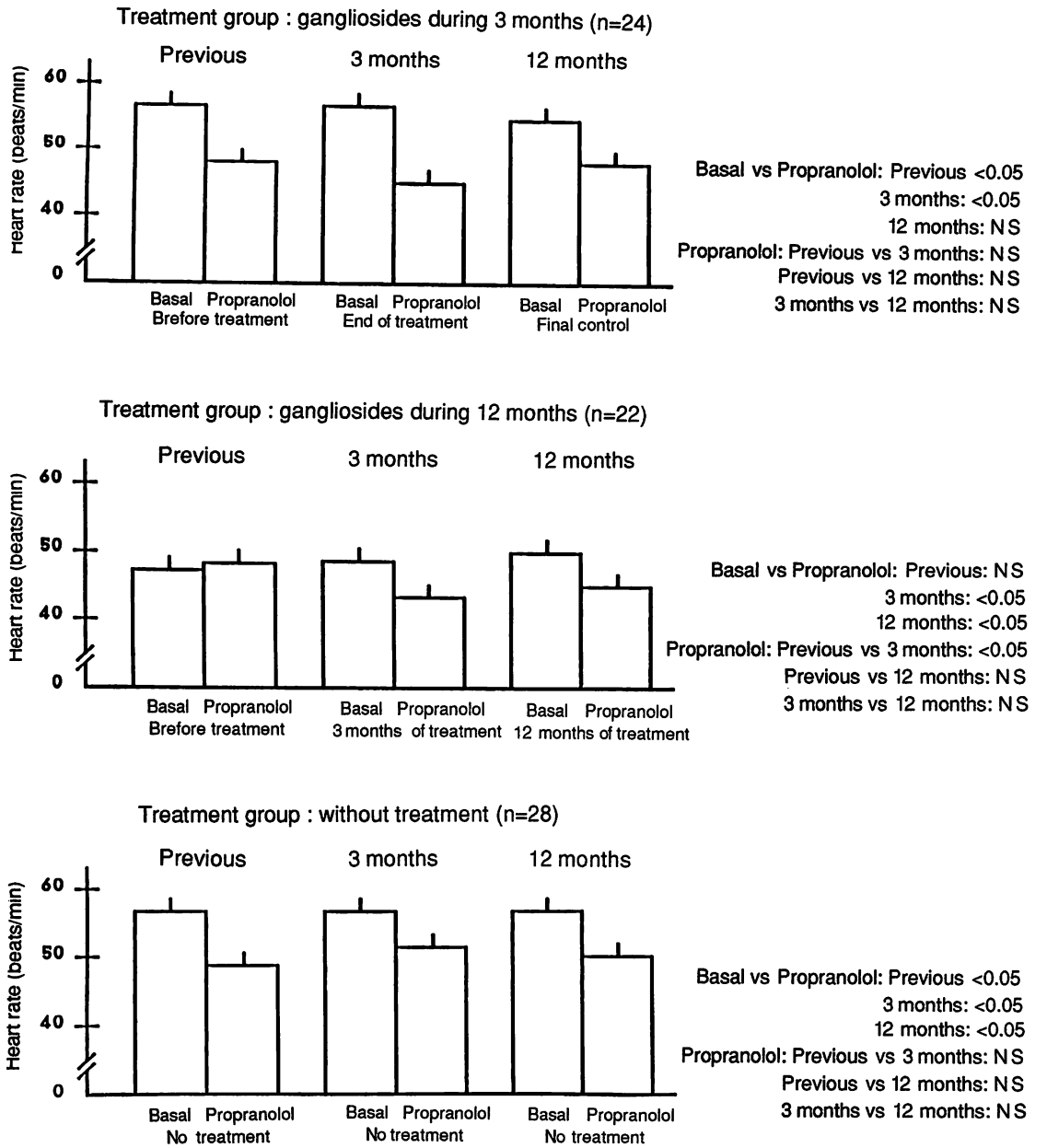

Fig. 2 Heart rate before and after intravenous injection of propranolol 0.2 mg/kg in basal conditions and after 3 and 12 months in groups treated with gangliosides for 3 or 12 months and in a control group

The levels of significance (p value) pre-and post-propranolol (Basal vs Propranolol) and between the responses to propranolol in the distinct controls (Propranolol) are shown.

Values are mean ± SEM.

ditions, whereas after the third and 12th month of ganglioside treatment a clear decrease in heart rate was observed after the injection of propranolol. The control group did not show any difference regarding the response to propranolol at any time.

Table 4 shows the qualitative assessment of the responses to propranolol. In the group treated for 3 months, the test made before the treatment showed clinically significant responses in only 6 patients (25%) whereas the percentage rose to 46% of the patients after 3 months of treatment and decreased to 38% at month 12. The group treated with gangliosides for 12 months showed peculiar results. The rate of significant responses before treatment

Table 4 Qualitative assessment of response to propranolol

	Treatment group: gangliosides for 3 mo (n=24)			Treatment group: gangliosides for12 mo (n=22)			Control group: without treatment (n=28)		
	Previous	3 mo	12 mo	Previous	3 mo	12 mo	Previous	3 mo	12 mo
Response (beats/min)									
≥10	6(25)	11(46)	9(38)	0	1(5)	0	4(14)	3(11)	0
1–10	15(62)	11(46)	7(29)	7(32)	18(82)	10(45)	19(68)	19(68)	20(71)
Without changes	1(4)	1(4)	6(25)	7(32)	1(5)	5(23)	3(11)	5(18)	6(21)
Increased HR	2(8)	1(4)	2(8)	8(36)	2(9)	7(32)	2(7)	1(4)	2(7)

( ) : %
HR=heart rate. Other abbreviation as in Table 3.

was zero and remained this way until the final control; the percentage of moderate responses increased, after 3 months of treatment with gangliosides, from 32% to 82%, and decreased at month 12. This "long" treatment group also showed a high percentage (36%) of patients with paradoxical response (tachycardia instead of bradycardia) before the treatment. At the third month the paradoxical responses dropped to 9% but after 12 months of treatment rose again up to 32%. The patients of the control group showed impairment in the response to propranolol at the successive times.

Table 5 shows the results that correspond to the antiGM1 antibody (immunoglobulin M) titers in healthy subjects and in patients before and after ganglioside treatment. None of the patients showed a titer at any time that could be plainly considered positive nor any important antiGM1 antibody titer variation was recorded in the treated patients. The healthy controls showed an antiGM1 antibody titer distribution which was very similar to that of the patients; one healthy control showed a titer considered positive of 1: 6,400. The laboratory analyses performed, including haemogram, glycaemia, creatininaemia, uricaemia, urine, hepatogram, proteinogram and lipidogram, did not show anomalies at any stage.

DISCUSSION

In the first place the distribution of antiGM1 antibody titers must be considered before the treatment with gangliosides and in the healthy subjects. The absence of titers that might be considered plainly positive in the chagasic group of patients disagrees with an eventual generation of antiganglioside antibodies as a physiopathological mechanism of autonomic alteration. The levels of antiGM1 antibodies found in healthy subjects, in accordance with the previous concept, did not differ from the levels found in chagasic patients. On the other hand, the fact that a healthy individual had a level of antiGM1 antibodies that can be considered positive is in accord with the findings of other authors, who reported a variable incidence of positive titers in healthy subjects[12].

The response prior to the treatment to intravenous injections of atropine and propranolol confirmed the findings of other authors in the sense of a diminished response to these agents in chagasic patients[4,6]. However, different responses to propranolol were observed before treatment in the group that afterwards received gangliosides for 3 months and in the group to be treated during 12 months. This fact could diminish the possibility of a comparison between times of treatment with gangliosides, at least referred to propranolol. The increased response to these agents observed after 3 months of treatment with the mixture of gangliosides also confirms previous findings in short periods[4,6]. The comparison between the basal responses at months 3 and 12 suggests that the amelioration of the response to atropine and propranolol is maintained throughout time. Nevertheless, the absence of significant differences between the group treated for 3 months and the group treated for 12 months is noteworthy, which suggests that such a long ganglioside administration would not be necessary for accomplishing a more or less sustained improvement in the response to autonomic stimuli. However, it remains to be elucidated what the long term clinical significance of ganglioside administration might be, in terms of incidence of complications in chagasics and/or life expectation. The presence of patients with paradoxical responses to pro-

Table 5 AntiGM1 (immunoglobulin M) antibody titers in healthy subjects and in chagasic patients

Controls	Titer	Treatment group			
		3 mo gangliosides (n=24)	12 mo gangliosides (n=22)	Control without treatment (n=28)	Healthy subjects (n=30)
Basal	1 : 400	1(4)	4(18)	3(11)	4(13)
	1 : 800	11(46)	8(36)	11(39)	13(43)
	1 : 1,600	7(29)	6(27)	8(29)	9(30)
	1 : 3,200	5(21)	4(18)	6(21)	3(10)
	1 : 6,400	0	0	0	1(3)
	No detectable	0	0	0	0
3 months	1 : 400	2(8)	4(18)	3(11)	
	1 : 800	9(38)	8(36)	12(43)	
	1 : 1,600	8(33)	3(14)	7(25)	
	1 : 3,200	2(8)	4(18)	6(21)	
	1 : 6,400	0	0	0	
	No detectable	3(13)	3(14)	0	
12 months	1 : 400	2(8)	4(18)	4(14)	
	1 : 800	12(50)	10(45)	11(39)	
	1 : 1,600	6(25)	4(18)	9(32)	
	1 : 3,200	4(17)	3(14)	4(14)	
	1 : 6,400	0	0	0	
	No detectable	0	1(5)	0	

( ) : %
Abbreviation as in Table 3.

pranolol that improved their situation after the administration of gangliosides is also noteworthy. Speculatively, it might be thought that the previously mentioned paradoxical responses might be related to the parasite differential effect upon the beta-1 and beta-2 receptors.

The improvement effect in the autonomic responses determined by gangliosides[4,6] has been attributed to their capacity for inducing nerve regeneration and also to the possibility of replacement of endogenous gangliosides with neuraminic groups altered by the parasites neuraminidase[7]. In this sense it is worth commenting that recent studies have shown that gangliosides are capable of regulating the apoptotic activity[15-17], by regulating the synthesis of sphingosine-1-phosphate by acting on Tka receptors and in this way, modulating the response to endogenous neurotrophins[15-17]. It is possible that this situation might compensate for the eventual proapoptotic action of the *Trypanosome cruzi*.

With regard to the evolution of the antiGM1 antibodies titer, there was no significant modification recorded in the treated patients nor in the control patients. This suggests that the prolonged administration of exogenous gangliosides seems to be safe in terms of inducing the formation of antiGM1 antibodies. This fact is in accordance with studies from other groups in other models and pathological circumstances, which postulate that the antigenic capacity of gangliosides would be very low[12]. With regard to the ganglioside administration safety, it is worth stressing the very low incidence of side effects and the absence of modification of the controlled biochemical parameters.

From the previous comments it can be concluded that:

1) The generation of antiGM1 antibodies does not seem to be related in this study to the physiopathology of chagasic cardiodysautonomopathy.
2) The administration of gangliosides improved effectively the response to atropine and, to a lesser extent, the response to propranolol in short as well as in long term treatment. These results can be interpreted as an improvement of the patients' chagasic cardiodysautonomopathy.
3) Since the results obtained with 3 and 12 months

of treatment did not seem to differ, particularly for the atropine test, it might be thought that 3-month courses ganglioside treatment could be enough. In this sense, the improvement after the course of 3 months seemed to persist at least until 9 months after discontinuing the treatment. However, the differences between groups in the response to propranolol in basal conditions precludes definitive confirmation of this idea. More clinical studies are indeed necessary.

4) The incidence of side effects suggests that the long-term ganglioside administration is safe. Particularly, the evolution of antiGM1 antibodies suggests that the prolonged administration of gangliosides do not induce an increase in the antibody titer, at least in the conditions of this study.

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