

## **Ciguatera fish poisoning**

### **A double-blind randomized trial of mannitol therapy**

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*Study treatment (mannitol and normal saline) was provided by Baxter New Zealand at no cost to the hospital.*

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## **Abstract—**

### ***Background:***

**Ciguatera poisoning (CP) is worldwide the most common fish-borne illness and one of the most common forms of nonbacterial food poisoning. IV mannitol is considered the treatment of choice for CP but has not been evaluated in a double-blind randomized trial.**

### ***Methods:***

**A prospective clinical study of 50 patients with CP on Rarotonga, Cook Islands, was conducted to better define the neurologic picture of CP and to study the effect of mannitol or normal saline under double-blind randomized conditions over a 24-hour period.**

### ***Results:***

**The neurologic presentation of CP was that of a predominantly sensory, length-dependent polyneuropathy, with preferential small-fiber involvement. Motor paresis, cranial nerve dysfunction, and CNS abnormalities were absent but for a rare mild transitory cerebellar syndrome. At 24 hours, 96% of mannitol-treated patients and 92% of normal saline-treated patients had some improvement of symptoms ( $p = 1.0$ ), whereas 12% and 24% of patients in each group were asymptomatic ( $p = 0.46$ ). By 24 hours, the prevalence of the various polyneuropathic symptoms and signs was reduced roughly by half in both groups. Discomfort or pain along the vein used for infusion was more frequent in the mannitol group (84%) than in the normal saline group (36%) ( $p = 0.0015$ ).**

### ***Conclusion:***

**Mannitol was not superior to normal saline in relieving symptoms and signs of CP at 24 hours in this study population but had more side effects. These results do not support single-dose mannitol as standard treatment for CP.**

## **Introduction**

Ciguatera fish poisoning (CP), the most common food-borne illness related to fish consumption, is a worldwide health concern, being endemic throughout the India-Pacific and Caribbean regions, <sup>[1] [2] [3] [4] [5]</sup> but has also been reported from more northern portions of the United States. <sup>[6] [7]</sup> Ciguatoxin, produced by the dinoflagellate *Gambierdiscus toxicus*, which is associated with algae and dead corals, is concentrated and passed up the fish food chain to the human eating the fish. Ciguatoxin induces a prolonged opening of voltage-gated sodium channels in nerves and, to a lesser degree, in muscle tissue. <sup>[1] [8]</sup> CP-related neuropathy thus belongs to the category of axonal channelopathies. <sup>[9]</sup> The clinical symptoms of CP fall broadly into four categories: gastrointestinal, neuropathic, cardiovascular, and a diffuse pain syndrome; the particular polyneuropathic feature of “cold reversal” (cold stimuli being felt as painful and hot) is considered to be almost pathognomonic. <sup>[1] [2] [3] [4]</sup> Most studies on CP focus on describing the symptomatology of CP, <sup>[5] [6] [10] [11] [12] [13] [14] [15] [16] [17] [18]</sup> whereas the objective neurologic examination of a larger series of patients with CP has been less well documented. <sup>[19] [20] [21]</sup>

Since the publication of an uncontrolled study in 1988, reporting the reversal of symptoms of acute CP by IV mannitol, <sup>[15]</sup> mannitol has gained acceptance as treatment of choice in CP, <sup>[1] [2] [3] [4] [22]</sup> supported by single case reports and several studies. <sup>[10] [11] [12] [13] [14] [15] [18] [19] [20]</sup> However, all these studies were either uncontrolled <sup>[10] [12] [13] [14] [15] [19] [20] [23]</sup> or randomized but not double-blinded, <sup>[11]</sup> and

the role of mannitol in the treatment of CP has yet to be established in a double-blind randomized trial. We therefore conducted a prospective clinical study of 50 patients with CP to better define the neurologic picture of ciguatera poisoning and to study the effect of mannitol under double-blind randomized conditions.

## **Materials and methods.**

### *Protocol.*

This was a single-center randomized double-blind investigation with a 24-hour study–observation period, conducted on Rarotonga, Cook Islands, between August 1998 and October 1999.

### *Inclusion criteria.*

Inclusion criteria were 1) consumption of local reef fish, followed within 30 minutes to 48 hours by 2) gastrointestinal symptoms (diarrhea, vomiting, or abdominal cramping and 3) neuropathic symptoms (one of the following: acral or perioral paraesthesia, dysesthesia, numbness, reversal of cold/warm sensation), 4) written informed consent to participate in the study by the patient, and 5) absence of any exclusion criteria.

### *Exclusion criteria.*

Exclusion criteria were any one of the following: 1) age below 16 years, 2) pregnancy, 3) body temperature above 38°C, and 4) decompensated heart failure or evidence for acute myocardial ischemia.

### *Treatment.*

Patients fulfilling the inclusion criteria were hospitalized for at least 24 hours. A masked bag bearing a number between 1 and 50 and containing either the treatment solution (500 mL of 20% mannitol solution) or the control solution (500 mL of 0.9% normal saline) was taken blindly from a container that contained the 50 bags. Each patient was thus provided with a number between 1 and 50. Both patient and the medical personnel were blind as to which type of solution (mannitol or normal saline) was infused rapidly IV ([table 1](#)) immediately after baseline evaluation by the neurologist (see below). Masking of the treatment had been achieved prior to starting the study by wrapping the mannitol or normal saline solution bags with uniform brown paper. The wrapped bags were then shuffled in big container and thereafter labeled by a third person, the pharmacist, who was blind as to their contents, with numbers 1 to 50. After labeling, the pharmacist reopened the bags for identifying which solution (mannitol or normal saline) was in each labeled bag (study code), and the bags were closed again. The pharmacist wrote the study

code in two sealed letters, which were opened only after completion of the study. After infusion, the empty, wrapped study bags of each patient were kept in a separate place for double check of the study code once the trial had been completed.

<b>Table 1. Clinical, biochemical, and treatment characteristics of the study sample</b>		
<b>Characteristics</b>	<b>Mannitol, n = 25</b>	<b>Normal saline, n = 25</b>
Age, mean (SD), y	39.8 (14.8)	37.4 (12.1)
Sex, male/female	17/8	10/15
Diabetes mellitus, n (%)	3 (12)	1 (4)
Alcohol abuse, n (%)	3 (12)	2 (8)
Heart rate at baseline, mean (SD), beats/min	68 (15)	69 (11)
Bradycardia, <sup>‡</sup> <60 beats/min, n (%)	5 (20)	3 (12)
Blood pressure at baseline, mean (SD), mm Hg		
Systolic	118 (18)	120 (16)
Diastolic	74 (12)	79 (12)
Hypotension, <100/55 mm Hg, n (%)	1 (4)	1 (4)
Hypertension, <sup>‡</sup> >145/90 mm Hg, n (%)	4 (16)	2 (8)
Selected pathologic laboratory results, n (%)		
Blood sedimentation rate, elevation	6 (24)	4 (16)
Leukocytosis	4 (16)	6 (24)
Amylase, elevation	3 (12)	3 (12)
Creatinine kinase, elevation	0	1 (4)
Creatinine, elevation	1 (4)	2 (8)
Latency, fish consumption → onset of first symptoms, h median (range/interquartile range)	6.5 (1–36/4–11)	6.0 (1–36/3–17)
Latency, first symptoms → onset of study treatment, h median (range/interquartile range)	19 (4.5–672/9–69)	40 (3–576/11–77)
Patients treated within 24 h of symptoms onset, n (%)	13 (52)	11 (44)
Patients treated within 12 h of symptoms onset, n (%)	10 (40)	8 (32)
Duration of treatment infusion, mean (SD), min	24 (8)	21 (7)

All *p* values were >0.05 from  $\chi^2$  test, Wilcoxon rank sum test, or Student's *t*-test, as appropriate.

\* Bradycardia was mild (50–59 beats/min), except in one patient of each group, where bradycardia was moderate (40–49 beats/min); there were no patients with tachycardia.

† Hypertension was always mild (below 170/105 mm Hg).

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### *Evaluations.*

Questioning with the 5-point symptom severity scale (see Primary endpoints below) was performed just before study treatment was initiated (= baseline) and 1, 3, and 24 hours after onset of treatment. The time of onset of symptoms was established by interviewing the patient during hospitalization. Clinical examination and laboratory studies (see below) were performed before treatment onset and at 24 hours. Questioning and clinical examination were undertaken by one neurologist. Tendon stretch reflexes were graded (0 = absent, 1 = weak, 2 = normally active, 3 = brisk, 4 = clonus or extension of the reflexogenic zone). Vibration sensation was assessed by the semiquantitative method. Blood pressure and heart rate were monitored upon admission, at baseline, every 10 minutes during treatment infusion, and at least 1, 3, 6, 12, and 24 hours after onset of the randomized treatment. An EKG and chest radiograph were performed during the first 12 hours of hospitalization. Study treatment was begun immediately after clinical examination and after blood samples had been taken. If systolic arterial blood pressure was below 100 mm Hg, 0.9% normal saline was infused prior to the study treatment until systolic blood pressure stabilized at or above 100 mm Hg. In case of symptomatic bradycardia associated with arterial hypotension or with orthostatic dizziness, IV atropine sulfate was administered prior to the randomized treatment. If either atropine or saline had to be given upon admission and prior to the administration of the study treatment, the symptom score was obtained just prior to initiation of the study treatment (baseline). At 24 hours, subjective treatment satisfaction was assessed by asking the patients if they thought that the treatment given and its effect on the symptoms were excellent, good, moderate, or poor. Side effects data of the treatment were collected during infusion of the study treatment as spontaneously reported by the patient and thereafter by interviewing the patient. If possible, patients were re-examined in the outpatient clinic or contacted by phone at 7 days after onset of treatment.

### *Laboratory investigations.*

Laboratory investigations included full blood count and differential count, urea, creatinine, sodium, potassium, amylase,  $\gamma$ -glutamyltransferase, aspartate aminotransferase, creatinine kinase, and random blood sugar. Patients with dysuria had a urine sample checked for cells, protein, glucose, and bacteria.

### *Additional medication.*

During the 24-hour study period, the following medications were allowed on a “as-requested” basis: paracetamol (500-mg tablets), promethazine (10-mg tablets), and scopolamine butylbromide (10-mg tablets). Patients were informed that they could have medications against pain, pruritus, and abdominal cramps, if needed. Patients with symptomatic bradycardia received

IV atropine sulfate, whereas symptomatic hypotensive patients received additional normal saline, as judged by the doctor, once the study treatment had been given. No additional medication was given at the same time as the randomized treatment.

The protocol allowed the administration of 500 mL of open-label 20% mannitol solution to patients who remained symptomatic after 24 hours (i.e., after completion of the study observation period) in order not to preclude patients from a potential benefit of this treatment.

### *Primary endpoints.*

Primary endpoints of the study were 1) the evolution of the following 13 subjective symptoms, as judged by the patients using a 5-point symptom severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable), at baseline and at 24 hours after onset of the randomized treatment, with additional scores being taken at 1 and 3 hours after treatment onset; and 2) the evolution of the neurologic status at baseline and at 24 hours.

The 13 symptoms featuring in the symptom scoring scale (modified after Lange <sup>[24]</sup>) were 1) gastrointestinal symptoms (nausea and vomiting, diarrhea, abdominal cramping), 2) neuropathic symptoms in a perioral and/or acral distribution (numbness, paraesthesia and/or dysesthesia, cold allodynia/reversal of cold–warm sensation), 3) diffuse pain syndromes (myalgia, arthralgia, headache), 4) other symptoms (pruritus, dizziness, asthenia/general weakness, dysuria). For evaluating the evolution of the symptom score, we not only used the score sum per individual patient (maximal possible total score is 52, minimal score is 0) but also established four disease severity groups: asymptomatic (score = 0), mildly symptomatic (only symptoms rated as 0 or 1 [mild]), moderately symptomatic (belonging neither to mildly nor to severely symptomatic), and severely symptomatic (at least three different symptoms scored 3 [severe] or at least one symptom scored 4 [unbearable]).

### *Secondary endpoints.*

Secondary endpoints were 1) the need for additional medication during the first 24 hours (paracetamol, scopolamine butylbromide, promethazine, normal saline, atropine); 2) the frequency of poor responders, defined as at least one of the following (the need for hospitalization longer than 24 hours because of persistent, severe symptoms, the administration of open-label mannitol treatment at 24 hours (see above) because of persistent severe symptoms, rehospitalization within 7 days because of persistent and/or recurrent symptoms without re-exposure to fish); and 3) subjective treatment satisfaction (as defined above).

### *Statistical methods.*

Proportions were compared by the  $\chi^2$  test with Yates corrections for small numbers. Summary data are expressed as the mean (with SD) or median (with interquartile range) and values compared by the *t*-test or Wilcoxon rank sum test, as appropriate.

## Results.

Participant flow is summarized in the [figure](#). Baseline and treatment characteristics did not differ significantly in the two groups, except for a gender imbalance, which was not significant ( $\chi^2 = 2.899$ ,  $p = 0.089$ , with Yates correction) (see [table 1](#)).

Figure. Trial profile.

*Baseline parameters.*

*Initial symptoms.*

The most frequent initial symptoms, occurring within 1 to 40 hours (median 6 hours), reported in the total study sample ( $n = 50$ ) were diarrhea ( $n = 27$ ), abdominal cramping/abdominal pain ( $n = 23$ ), asthenia and hypersensitivity to cold ( $n = 21$  each), paresthesia ( $n = 17$ ), nausea ( $n = 16$ ), dizziness ( $n = 15$ ), numbness ( $n = 14$ ), myalgia and headache ( $n = 12$  each), arthralgia and pruritus ( $n = 11$  each), and dysuria ( $n = 3$ ). Often several symptoms were reported to have appeared simultaneously. The number of symptomatic patients with respect to any of the 13 symptoms at baseline was not statistically different between the two groups ([table 2](#)), nor was severity of symptoms with respect to median individual symptom score sum and frequency of patients falling within the different disease severity groups (mildly, moderately, and severely symptomatic) ([table 3](#)). One patient reported a metallic taste in the mouth.

<b>Table 2. Evolution of symptoms during 24-hour observation period</b>				
<b>Symptom</b>	<b>Mannitol,<sup>‡</sup> n = 25</b>	<b>Normal saline,<sup>‡</sup> n = 25</b>	<b>p Value<sup>‡</sup></b>	<b>Total study sample,<sup>§</sup> n = 50</b>
Nausea	6/5/5/2	7/5/5/3	1.00	13 (26)/5 (10)
Diarrhea <sup>‡</sup>	13 /5 <sup>‡</sup>	12 /5 <sup>‡</sup>	1.00	25 (50)/10 (20)
Abdominal pain	13 /9/7/3	13 /7/6/4	1.00	26 (52)/7 (14)
Numbness	20 /15/13/8	18 /17/13/7	1.00	38 (76)/15 (30)

<b>Table 2. Evolution of symptoms during 24-hour observation period</b>				
<b>Symptom</b>	<b>Mannitol,<sup>‡</sup> n = 25</b>	<b>Normal saline,<sup>‡</sup> n = 25</b>	<b>p Value<sup>‡</sup></b>	<b>Total study sample,<sup>§</sup>n = 50</b>
Paresthesia/dysesthesia	16 /12/12/7	20 /12/15/7	1.00	36 (72)/14 (28)
Cold allodynia	23 /15/14/12	24 /18/18/13	1.00	47 (94)/25 (50)
Myalgia	15 /11/10/6	13 /10/5/4	0.72	28 (56)/10 (20)
Arthralgia	16 /12/8/6	15 /12/11/5	1.00	31 (62)/11 (22)
Headache	11 /8/9/6	14 /7/6/7	1.00	25 (50)/13 (26)
Pruritus	11 /5/3/7	10 /6/8/7	1.00	21 (42)/14 (28)
Dizziness	17 /12/11/5	14 /9/9/6	1.00	31 (62)/11 (22)
Asthenia/weakness	21 /19/17/13	19 /15/10/8	0.25	40 (80)/21 (42)
Dysuria	6/3/2/2	7/5/3/1	1.00	13 (26)/3 (6)

$T = 0$  designates the onset of study treatment;  $T = 1$  h,  $T = 3$  h, and  $T = 24$  h designate 1 h, 3 h, and 24 h after the onset of study treatment. The  $p$  values from  $\chi^2$  test, comparing numbers at 24 h in the mannitol and saline groups.

\* Diarrhea at  $T = 0$  h/ $T = 24$  h.

† No. of symptomatic patients at  $T = 0$ / $T = 1$  h/ $T = 3$  h/ $T = 24$  h.

‡ Comparing numbers at 24 h.

§ No. (%) of symptomatic patients at  $T = 0$ / $T = 24$  h.

<b>Table 3. Twenty-four-hour evolution of ciguatera fish poisoning/treatment efficacy</b>			
<b>Outcome characteristics</b>	<b>Mannitol, n = 25</b>	<b>Normal saline, n = 25</b>	<b>p Value<sup>‡</sup></b>
Total symptom score sum per patient at $T = 0$ / $T = 1$ h/ $T = 3$ h/ $T = 24$ h, mean	14.2/8.7/6.8/4.5	14.0/8.3/7.1/4.4	0.77
Asymptomatic at $T = 0$ / $T = 24$ h, n (%)	0/3 (12)	0/6 (24)	0.46
Mildly symptomatic at $T = 0$ / $T = 24$ h, n (%)	0 /15 (60)	2 (8)/15 (60)	1.00
Severely symptomatic at $T = 0$ / $T = 24$ h, n (%)	5 (20)/1 (4)	9 (36)/1 (4)	1.00
Improvement of total score at $T = 24$ h, n (%)	24 (96)	23 (92)	1.00

<b>Table 3. Twenty-four-hour evolution of ciguatera fish poisoning/treatment efficacy</b>			
<b>Outcome characteristics</b>	<b>Mannitol, n = 25</b>	<b>Normal saline, n = 25</b>	<b>p Value<sup>‡</sup></b>
Worsening of total score at T = 24 h, n (%)	0	2 (8)	0.47
Poor responders, n (%)			
(a) Hospitalization over 24 h	4 (16)	5 (20)	1.00
(b) Readmission	2 (8)	1 (4)	1.00
(c) Open-label mannitol after 24 h	2 (8)	4 (16)	0.66
a + b, n (%)	6 (24)	6 (24)	1.00
a + b + c, n (%)	6 (24)	7 (28)	1.00
Treatment side effects, n (%)			
Burning/pain/discomfort along vein used for IV line	21 (84)	9 (36)	0.0015
Treatment satisfaction, n (%)			
Excellent	14 (56)	17 (68)	0.31 <sup>‡</sup>
Good	6 (24)	5 (20)	
Moderate or bad	2 (8)	3 (12)	
Not rated	3 (12)	0	

T = 0 designates the onset of study treatment; T = 1 h (3 h, 24 h) designates 1 hr (3 h, 24 h) after the onset of study treatment. “Asymptomatic” is defined as symptom score sum = 0; “mildly symptomatic” designates patients who had symptoms rated 0 or 1 only; “severely symptomatic” designates patients with at least three different symptoms scored 3 (severe) or at least one 4 (unbearable). All p values from  $\chi^2$  or t-test, comparing numbers or values at 24 h in the mannitol and saline groups.

\* Comparing numbers or values at 24 h.

†  $\chi^2 = 3.581, 3 df$ .

#### *Baseline clinical examination.*

Pathologic neurologic findings are summarized in [table 4](#). Paresthesia was experienced, in decreasing order of frequency, in an acral, facial, or throat/tongue distribution pattern, and no patient had paresthesia of the face, tongue, or throat without additional limb paresthesia. No patient had cranial nerve paresis, positive Romberg sign, or signs of pyramidal tract involvement. Although general asthenia was frequent, no patient had true motor paresis. No skin rash was observed in patients with pruritus. Bradycardia was present in five patients (20%) of the

mannitol group (M group) and in three patients (12%) of the normal saline group (NS group). At baseline, mild hypertension was present in four patients (16%) of the M group and in two patients (8%) of the NS group. One patient in each group had a systolic blood pressure at or above 100 mm Hg but a diastolic blood pressure below 55 mm Hg (see [table 1](#)). Two patients in each treatment group had severe symptomatic bradycardia or severe arterial hypotension upon admission, necessitating treatment with atropine or IV fluids or both prior to study treatment.

<b>Table 4. Neurologic status at baseline and at 24 hours</b>				
<b>Neurologic status, pathologic findings<sup>‡</sup></b>	<b>Mannitol, n = 25</b>	<b>Normal saline, n = 25</b>	<b>p Value<sup>†</sup></b>	<b>Total study sample, n = 50</b>
Achilles tendon areflexia	3 (12)/3 (12)	3 (12)/4 (16)	1.00	6 (12)/7 (14)
Patellar tendon areflexia	2 (8)/2 (8)	1 (4)/2 (8)	1.00	3 (6)/4 (8)
Triceps tendon areflexia	1 (4)/1 (4)	2 (8)/3 (12)	0.60	3 (6)/4 (8)
Biceps tendon areflexia	1 (4)/1 (4)	3 (12)/2 (8)	1.00	4 (8)/3 (6)
Light touch sensation <sup>‡§</sup>	7 (28)/4 (16)	11 (44)/4 (16)	1.00	18 (36)/8 (16)
Vibration sensation	13 (52)/6 (25)	13 (52)/9 (36)	0.54	26 (52)/15 (30)
Position sensation	1 (4)/0	0/0	1.00	1 (2)/0
Pinprick sensation	13 (52)/4 (16)	15 (60)/3 (12)	1.00	28 (56)/7 (14)
Temperature sensation <sup>¶</sup>	19 (76)/11 (44)	21 (84)/11 (44)	1.00	40 (80)/22 (44)
Cerebellar signs <sup>  </sup>	0	2 (8)/0	1.00	2 (4)/0

$T = 0$  designates the onset of study treatment and  $T = 24$  h designates 24 h after the onset of study treatment. All  $p$  values from  $\chi^2$  test, comparing numbers at 24 h in the mannitol and saline groups.

\*  $T = 0/T = 24$  h, n (%).

† Comparing numbers at 24 h.

‡ One patient of the mannitol group had marked mechanoallodynia, with light touch being perceived as painful.

§ In one patient in the normal saline group, sensory abnormalities were asymmetric, i.e., more pronounced on the left side.

¶ Pathologic temperature sensation was always due to cold allodynia and cold hyperpathy.

|| Cerebellar signs were mild dysmetria of the upper limbs in one patient and saccadic ocular pursuit in the other patient.

### *Laboratory investigations.*

The two groups were similar regarding the results of laboratory investigations done before treatment and 24 hours after the onset of treatment (see [table 1](#)). The EKG in nine patients (five patients of the M group and four patients of the NS group) was abnormal, usually because of sinus bradycardia or signs of left ventricular strain in the presence of chronic hypertension. One patient of the NS group, possibly with pre-existing compensated but unrecognized chronic renal disease, developed acute renal failure and mild thrombocytopenia during the first 24 hours, ultimately necessitating transfer and hemodialysis at a tertiary care center.

### *Twenty-four hours after onset of treatment.*

At 24 hours after onset of treatment, the two groups were similar as to clinical and biochemical characteristics (see [table 1](#)) and neurologic status (see [table 4](#)).

### *Symptom score.*

The two groups did not differ in the frequency of the different symptoms at 24 hours (see [table 2](#)) or in the severity of symptoms with respect to mean individual symptom score sum and frequency of patients belonging to the different disease severity groups (asymptomatic, mildly, moderately, and severely symptomatic) (see [table 3](#)). Seven patients (28%) of the M group and 10 patients (40%) of the NS group had an excellent outcome at 24 hours, being minimally symptomatic or asymptomatic (defined as a total score of  $\leq 1$ ) ( $\chi^2 = 0.357, p = 0.55$ ).

The outcome at 24 hours in those patients treated within 24 hours of onset of symptoms was similar in the two groups: Of the 13 patients of the M group treated within 24 hours of symptom onset, the mean symptom score sum at the onset of treatment, 1 hour, and 24 hours after the onset of treatment was 14.9/7.7/4.9, while 1 patient was asymptomatic and 2 were minimally symptomatic at 24 hours. For the 11 patients in the NS group being treated within 24 hours after symptom onset, the mean symptom score sum was 18.5/10.5/7.1, with 4 patients being asymptomatic at 24 hours (comparing numbers of asymptomatic patients at 24 hours,  $p = 0.94, \chi^2$  test). Of the 12 patients of the M group treated after 24 hours from symptom onset, the mean symptom score sum at the onset of treatment, 1 hour, and 24 hours after the onset of treatment was 13.5/8.8/3.6, while 2 patients were asymptomatic and 3 were minimally symptomatic at 24 hours. For the 14 patients in the NS group being treated after 24 hours after symptom onset, the mean symptom score sum was 10.5/6.0/2.3, with 2 patients being asymptomatic and 4 patients being minimally symptomatic at 24 hours (comparing number of asymptomatic patients at 24 hours,  $p = 0.42, \chi^2$  test).

### *Clinical examinations.*

The neurologic status of the patients is listed in [table 4](#). At 24 hours, bradycardia was present in seven patients (30%) of the M group and in four patients (16%) of the NS group. Bradycardia was mild in five patients of the M group and in four patients of the NS group. Mild hypotension was observed in four patients (16%) of the M group and in one patient (4%) of the NS group.

#### *Secondary outcome points.*

The two groups did not differ with respect to additional medication needed. Eighteen patients in the M group asked for a total of 43 paracetamol tablets, 6 patients asked for a total of 8 promethazine tablets, 3 patients asked for a total of 4 scopolamine-butylbromide tablets, 3 patients needed IV atropinesulfate (total: 4.2 mg), whereas 5 patients needed additional IV hydration after having received the study treatment (total: 10,900 mL normal saline). In the NS group, 14 patients asked for a total of 42 paracetamol tablets, 8 patients asked for a total of 10 promethazine tablets, 4 patients asked for a total of 5 scopolamine-butylbromide tablets, 1 patient needed IV atropinesulfate (1.8 mg), whereas 4 patients needed additional IV hydration after having received the study treatment (total: 8,700 mL normal saline). ( $\chi^2$  test  $p$  values < 0.05 for all numbers.) There was no significant difference between the two study groups in the frequency of poor responders (see [table 3](#)).

None of the three patients who had to be readmitted had received open-label mannitol at 24 hours. Four of the six patients in the M group and five of the seven patients in the NS group, considered to be poor responders, were treated within 24 hours after symptom onset. Treatment satisfaction was similar in both groups (see [table 3](#)).

#### *Treatment side effects.*

Local discomfort or burning pain along the vein being used was more frequent in the M group (84%) than in the NS group (36%) ( $p = 0.0015$ ,  $\chi^2$  test) (see [table 3](#)).

#### *Tardive symptoms (1 week after treatment).*

Eighteen patients of the M group (72%) and 22 patients (88%) of the NS group could be followed for 8 days. Seven patients of the M group (28% of the total M group, or 39% of those who could be followed) and seven patients of the NS group (28% of the total NS group, or 33% of those who could be followed) were asymptomatic 8 days after treatment onset ( $p = 0.89$ ,  $\chi^2$  test). One patient of the M group and two patients of the NS group were symptomatic at 8 days but had been asymptomatic at 24 hours.

## **Discussion.**

The frequency and spectrum of the various symptoms of CP in our study are similar to those reported in the literature (see [table 2](#)).<sup>[1][3][5][6][16][17][18]</sup> The most frequent initial symptoms were gastrointestinal (diarrhea and abdominal cramps), followed by cold allodynia. At baseline, the most frequent symptoms were those related to peripheral neuropathy, with cold allodynia being reported by 95% of all patients, while numbness, paresthesia, and general asthenia were each reported by about three quarters of the patients. Neurologic baseline examination (see [table 4](#)) revealed that in the majority of patients, neurologic symptoms were associated with objective signs of a polyneuropathy: Pathologic temperature sensation was present in approximately 80% of all patients, essentially in the form of cold allodynia/cold hyperpathia. About half of the patients had diminished vibration and pain sensation in a sock-and-glove distribution, that is, distally in the extremities. About a third had distally diminished sensation to light touch, whereas pathologic position sensation was observed in only one patient. The anatomic distribution of paresthesia suggests a length-dependent neuropathy, with proximal parts of the body, such as the face, being involved only in the presence of paresthesia in distal body parts (extremities). Tendon areflexia was seen in approximately 10% of patients, again with a length-dependent emphasis, and generalized areflexia was seen only once. Twenty-four hours after baseline examination, the frequency of each symptom was reduced roughly by half, independent of the treatment modality (see [table 2](#)). Improvement of neurologic signs paralleled improving symptoms, with approximately 50% reduction in the frequency of pathologic results of examination of sensory functions (see [table 4](#)). However, there was no recovery of areflexia within the 24-hour observation period. In three patients, Achilles tendon areflexia might have been due to pre-existing diabetic or alcoholic polyneuropathy. The frequency of neuropathic symptoms might be over-represented in our study and in the literature owing to a selection bias because the presence of neuropathic symptoms is usually included as a diagnostic criterion of CP.<sup>[1][2][3][15]</sup> The rare patient with CP and prominent bradycardia and hypotension, but without associated polyneuropathic symptoms, would have escaped our inclusion criteria. Our study suggests that the polyneuropathy of CP is a predominantly sensory, length-dependent neuropathy of mixed large- and small-fiber involvement, with prominent small-fiber dysfunction. Our patients, none of whom was paretic, revealed a predominance of pathologic temperature and pain sensation as compared with the rare occurrence of diminished position sensation and the relative low frequency of areflexia.

Pacific ciguatoxin (P-CTX-1) has been shown in experimental animal studies to result in prolonged opening of both tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) voltage-gated sodium channels.<sup>[25]</sup> TTX-R sodium channels are present in cutaneous sensitive nerve fibers but are virtually absent in motor nerve fibers.<sup>[26][27]</sup> Dorsal root ganglion neurons principally express TTX-S sodium channels,<sup>[28]</sup> whereas both TTX-R and TTX-S sodium channels are present in small dorsal ganglion neurons of unmyelinated nerve fibers and in trigeminal ganglion neurons.<sup>[29][30]</sup> It is possible that this anatomically more restricted expression of TTX-R sodium channels is related to the clinical predominance of small-fiber involvement and paucity of motor signs observed in our study. We did not observe frank paresis, cranial nerve dysfunction, or evidence of CNS dysfunction other than mild transitory cerebellar signs in two patients. This contrasts with several published reports describing a variety of central and peripheral motor dysfunction.<sup>[3][5][15][16][19][22][23]</sup> Although CP can be associated with a true motor paresis owing to an axonal motor polyneuropathy<sup>[23]</sup> and subclinical involvement of motor nerves has been documented electrophysiologically,<sup>[21]</sup> motor paresis and signs of CNS dysfunction

might be over-reported in the literature. The vast majority of reported patients with CP have not been examined by a neurologist and sometimes not even by a doctor, <sup>[18]</sup> and clinical documentation of motor paresis and neurologic status in general is often incomplete. <sup>[10] [11] [12] [13] [14] [15] [16]</sup> Reviewing the literature, we suspect that severe general asthenia (which is frequent) is sometimes being reported as “motor paresis” or “motor incoordination” or that an alternative diagnosis should be considered in some patients allegedly experiencing CP. <sup>[19]</sup> Supporting the rarity of true motor paresis in CP is a study conducted by Australian neurologists who found the same pattern of neurologic dysfunction as in our study and no evidence of motor paresis or CNS dysfunction in 15 patients with CP. <sup>[21]</sup> Polymyositis has been rarely associated with CP. <sup>[31]</sup> Despite the frequent occurrence of myalgia in our series, this symptom was never accompanied by elevated creatinine kinase levels, except in one patient who initially had mild elevation of this enzyme.

Since being mentioned as treatment option in CP in 1988, <sup>[15]</sup> mannitol has been accepted as the treatment of choice in CP, supported by several single case reports, <sup>[18] [20]</sup> small nonrandomized studies, <sup>[10] [12] [13] [14] [17]</sup> and a randomized but not double-blind study. <sup>[11]</sup> Mannitol has been shown in in vitro animal experiments to reverse the prolonged opening of sodium channels <sup>[32]</sup> and to reduce the periaxonal edema of Schwann cells induced by ciguatoxin <sup>[32]</sup> and is therefore an appealing treatment candidate for CP. However, mannitol did not influence the signs of intoxication or the time to death in in vitro and in vivo assessment in mice. <sup>[33]</sup> Under double-blind randomized conditions, we found no evidence of mannitol being superior to the infusion of normal saline, which was associated with a similar degree of clinical improvement but with fewer side effects. Overall symptom score had improved at 24 hours in 24 patients (96%) and 23 patients (92%) of the M group and NS group, respectively. At 24 hours, 12% of patients in the M group and 24% of patients in the NS group were asymptomatic, 60% of patients in each group were mildly symptomatic at 24 hours, and one patient in each group was still severely symptomatic. The number of poor responders, as defined in our protocol, was similar in both groups, accounting for about a quarter of patients (see [table 4](#)). That the two groups did not differ in the need for additional medication or IV fluids shows that a similar degree of clinical improvement did not come at the expense of additional medication. Last, treatment satisfaction at 24 hours was similar in both treatment groups: Eighty percent of patients of the M group and 88% of the NS group considered treatment to be good or excellent (see [table 3](#)). Bradycardia did not respond to either study treatment, consistent with previous observations. <sup>[12]</sup> However, severe symptomatic bradycardia (with or without hypotension) always responded to IV atropine, which sometimes had to be given repeatedly. Our study protocol ensured that mannitol was given in an optimal dosage (i.e., at least 1 mg of mannitol/kg of body weight), which has been thought to be more effective than lower doses of mannitol, <sup>[10] [22]</sup> and at a rapid rate of infusion (see [table 1](#)) to obtain the maximal antiedema effect of mannitol, as suggested by others. <sup>[10] [22]</sup> The latter contributed without doubt to the significantly higher frequency of discomfort and pain along the injection site in the M group (see [table 3](#)). Some have suggested that mannitol might be more efficient when given early, that is, within 24 hours after onset of CP symptoms. <sup>[10]</sup> In our study population, the median duration of symptoms prior to treatment was longer than 24 hours. Comparison of those patients treated within 24 hours with those being treated after 24 hours, while too small a subgroup analysis to be conclusive, did not reveal a better outcome at 24 hours or a more rapid clearing of symptoms in the M group. Our study was not designed to investigate if a second dose of mannitol at 12 to 24 hours <sup>[22]</sup> might be superior to single-dose mannitol or to

normal saline infusion or if symptoms beyond 24 hours might be influenced by treatment modality. However, >70% of patients could be followed for at least 1 week, and the prevalence of asymptomatic patients at 1 week was similar (28% of each group). The significant clinical improvement at 1, 3, and 24 hours witnessed in our study probably reflects the natural evolution of CP. Given that improvement was also seen in patients who sought medical attention with a considerable delay after first symptoms, a beneficial diluting effect of the rapidly infused solution (mannitol or normal saline) on the toxin, rather than any putative specific action of mannitol, <sup>[32]</sup> may have contributed to the favorable evolution. We are not aware of any plausible mechanism (other than dilution of the toxin and restoration of a volume deficit) that could explain a potential therapeutic effect of normal saline in CP.

Gabapentin, with a known efficacy in neuropathic pain, <sup>[34]</sup> has recently been reported to improve polyneuropathic symptoms of CP in two patients, <sup>[35]</sup> but it is too expensive to be used in the majority of countries where CP is endemic.

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