

Acidifying Enemas (Lactitol and Lactose) vs. Nonacidifying Enemas (Tap Water) to Treat Acute Portal-Systemic Encephalopathy: A Double-Blind, Randomized Clinical Trial

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A double-blind, controlled trial to study the efficacy of acidifying enemas of lactitol, a new galactoside-sorbitol disaccharide, and lactose vs. nonacidifying tap-water enemas was performed in 45 episodes of acute portal-systemic encephalopathy. At the time of randomization, all patients had encephalopathy of at least Grade 2+ severity, delay in the performance of number connection tests and hyperammonemia. A sequential analysis was performed which revealed after the inclusion of the first 20 patients, a significant failure of the nonacidifying enemas as compared to the lactitol enemas ($p < 0.004$). The tap-water enema group was, therefore, suspended but the rest of the study continued after rerandomization for lactose and lactitol groups. A favorable response to treatment was obtained in 19 (86%) of the patients receiving lactitol enemas and in 14 (78%) of those receiving lactose enemas. A similar significant improvement in portal-systemic encephalopathy parameters and index was observed after both treatments. Both types of acidifying enemas induced a significant pH decrease in stool ($p < 0.05$). These data suggest that acidifying agents like lactose and lactitol are effective and superior to tap-water enemas for the treatment of acute nitrogenous portal-systemic encephalopathy.

The beneficial effect of the disaccharides lactulose and lactose in the management of patients with chronic and acute portal-systemic encephalopathy (PSE) has already been shown in double-blind, controlled clinical trials (1-3). In these trials, treatment response was in the range of 80 to 90%. Other treatments, like nonabsorbable antibiotics, are less commonly preferred to treat PSE because of their association with serious side effects.

It is believed that acidification and diarrhea induced by the presence of disaccharide maldigestion cause a decrease in the production of toxins and also reduce the intestinal time available for both the production and absorption of potential nitrogenous toxins. Acidification of the large bowel by lowering stool pH has been demonstrated after oral administration or rectal instillation of both lactulose and lactose and, recently, after the administration of the new disaccharide lactitol (4, 5).

Lactitol is a β -galactoside sorbitol-derived from lactose. It is not absorbed in the small intestine but is metabolized by colonic flora, which produces acid metabolites after its digestion. In recent trials (5-7), lactitol seems to be effective orally for the treatment of patients with PSE.

In patients with acute PSE and ileus or in those with severe impairment of consciousness, the rectal route for the administration of disaccharides is preferred. Gut cleansing has also been proposed as treatment of PSE; however, the efficacy of cleansing with nonacidifying effect, i.e., tap-water enemas, has not been subjected to controlled trials in patients with acute PSE (8).

Therefore, we thought that acidifying enemas should be compared in a randomized, double-blind, controlled fashion vs. tap-water enemas as a control treatment in which the cleansing factor is obtained, but no colonic acidification is achieved.

PATIENTS AND METHODS

Study Design

The method of group sequential design was used in this trial (9), where three therapeutic interventions were tested in patients with acute PSE, namely water, lactose and lactitol enemas. This design was selected because it permits the early elimination of any treatment which is substantially inferior to others. If any of the three interventions would achieve a substantially worse, i.e., a <0.50 response rate (considering an expected response of >0.9), it would be immediately eliminated and the randomization schedule adjusted to the new sample size requirements.

Eligibility Criteria

To participate in the trial, patients had to satisfy the following conditions: development within 24 hr of an acute episode of PSE, characterized by encephalopathy of at least Grade 2+ severity (3) plus two of the following abnormalities—(i) arterial ammonia levels above $120 \mu\text{g}\%$ ($n \leq 90 \mu\text{g}\%$); (ii) abnormal slow waves in the electroencephalogram, and (iii) protracted performance of a number connection test (NCT) of at least double the normal time ($n < 30$ sec) or inability to perform the test due to mental confusion or coma. PSE could be precipitated by nitrogenous substances (dietary proteins, use of diuretics) or idiopathic (endogenous) factors.

Patients were excluded if they: (i) required or had received systemic or rectal antibiotics; (ii) presented with active gas-

Received August 8, 1986; accepted February 19, 1987.
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trointestinal bleeding; (iii) presented with anorectal disease; (iv) had a history of previous neurological disease other than PSE, or (v) the relatives refused to sign a consent form.

A total of 37 cirrhotic patients fulfilled the aforementioned criteria in 45 instances. Six cases were included two times and one case was studied three times during different episodes of precoma.

Enemas

Eligible patients were randomly assigned to receive either: (i) 20% lactose enemas (Lactose USP, Drogueria Cosmopolitana SA, Mexico City, Mexico); (ii) 20% lactitol enemas (Lactitol, Laboratories Zyma SA, Nyon, Switzerland), or (iii) tap-water enemas, at a dose of 1 liter t.i.d. Duration of the enema administration was variable and response-dependent (see "Therapeutic Response").

To maintain the double-blind status of the study, enemas were bottled in dark brown containers which made difficult the recognition of the content. They all were prepared with distilled water. The mean pH (\pm S.D.) was 5.9 ± 0.9 for the tap-water enemas, 5.6 ± 0.7 for the lactose enemas and 5.5 ± 0.2 for the lactitol enemas. Tap-water enemas were significantly less acid than were the lactose and lactitol ones ($p < 0.01$).

Nurses caring for the patients were instructed to shake the enemas vigorously before their administration. They were informed of the necessity to maintain the study "blind" for both patients and doctors. If they realized the differences in the appearance of the content of the bottles at the time of the rectal administration, they were asked to make no comments to the patients and doctors involved in the PSE assessment.

Tap-water enemas were administered in only five patients; occurrence of a high rate of PSE deteriorations and deaths made discontinuation of this group mandatory (see "Results"). Lactose enemas were administered in 18 instances and lactitol enemas in 22 instances. All patients were studied in the Emergency Room and in the Intensive Care Unit of the Instituto Nacional de la Nutricion "Salvador Zubirán," Mexico City, under the close supervision of Dr. Uribe.

PSE Parameters

Mental State. As described by Conn et al. (2), mental state was graded from alertness to deep coma (0 to 4+).

NCT. This test (10) is the time in seconds required for a patient to connect 25 circled numbers. To avoid the learning effect, four different versions of the NCT were used.

Versions of the NCT designated A, B, C and D were given to 40 control individuals with a similar educational level as the patients. The exhibited control score for Version A ranged from 11 to 25 sec (mean = 19 sec). For Version B, the range was from 11 to 27 sec (mean = 19 sec). For Version C, the range was from 10 to 31 sec (mean = 21 sec). For Version D, the range was from 12 to 26 sec (mean = 20 sec). As the NCT is the time expressed in seconds required to connect 25 numbers, it was arbitrarily graded as follows: Grade 0 = <30 sec; Grade 1+ = 31 to 60 sec; Grade 2+ = 61 to 100 sec; Grade 3+ = 101 to 200 sec, and Grade 4+ = >200 sec or patient unable to perform the test.

Asterixis. Presence of asterixis was graded as follows: Grade 0 = no flapping motion; Grade 1+ = rare (5 flaps per min); Grade 2+ = occasional irregular flaps (6 to 10 flaps per min); Grade 3+ = frequent flaps (11 to 20 flaps per min) and Grade 4+ = almost continuous flapping motions or patient in coma and unable to maintain wrist dorsiflexion.

Electroencephalograms. These were taken by a model Van Gogh E PB B that uses standard 10 to 20 electrode placements (Ahrenal Co, The Netherlands). Electroencephalograms were read blindly and graded by one of us (G. G. R.),

who was unaware of the kind of medication given to the patients. Tracings were assessed semiquantitatively on a 0 to 4+ scale: Grade 0 = normal α -rhythm; Grade 1+ = 7 to 8 cycles per sec or θ -activity; Grade 2+ = 5 to 6 cycles per sec; Grade 4+ = 3 to 4.5 cycles per sec, and Grade 4+ = <3 cycles per sec or δ -rhythm.

Blood Ammonia Concentration. Fasting arterial blood ammonia levels were measured (11) by using a Beckman microtiterator (Model 153, Beckman Instruments, Fullerton, Calif.). It was arbitrarily graded as follows: Grade 0 = $\leq 90 \mu\text{g}\%$; Grade 1+ = 91 to 120 $\mu\text{g}\%$; Grade 2+ = 121 to 150 $\mu\text{g}\%$; Grade 3+ = 151 to 180 $\mu\text{g}\%$, and Grade 4+ = >180 $\mu\text{g}\%$ (normal = 60 to 90 μg per 100 ml).

PSE Index. This index was calculated as described by Conn et al (2). In it, mental state gradings are multiplied by a factor of 3, and the gradings of the NCT, asterixis, electroencephalographic tracings and blood ammonia levels are multiplied by a factor of 1. The total of these weighted scores, or PSE sum, is divided then by the maximal possible PSE sum to give the PSE index.

Fecal pH

Stools were collected immediately and their pH determined by pH paper (Phydriion, Micro Essential Laboratory, Brooklyn, NY). This approach has been shown to be reliable, particularly below 6.0 (12). The number of stools was also recorded.

Values for each group are referred to as the stool pH obtained before and after the administration of enemas.

Diet and Drugs

During the study, 29 patients initially received 5 to 10% dextrose infusions (in some cases supplemented with KCl). Improvement of 1 grade of mental state was accompanied by an increment of 20 gm protein (per day) to reach a maximum of 60 gm per day.

Therapeutic Response

A therapeutic success was defined as: (i) sustained improvement of one grade in mental state during ≤ 48 hr or (ii) improvement of more than two grades in mental state.

A therapeutic failure was defined as: (i) no change in mental state after 48 hr of therapy; (ii) sustained deterioration of one grade in mental state during 48 hr; (iii) deterioration of two grades in mental state, or (iv) death in coma in spite of treatment. The occurrence of a therapeutic failure [(i) through (iii)] was followed by an immediate suspension of the study intervention and institution of conventional therapy.

Sample Size

Assuming a 0.90 response rate (3) in each of the three groups and considering a difference of 0.40 as clinically significant, a one-sided α of 0.01 (each group would be compared against each of the other two groups three times during the trial; overall $\alpha = 0.05$) and a β of 0.20, with a sample size of 23 patients per group, were calculated. If any of the interventions were eliminated during the study, at least 18 patients per group would be needed to detect the same difference (one-sided $\alpha = 0.03$ and $\beta = 0.20$).

Analysis

A group sequential analysis of responses was planned to be performed at about every 20 patients entered in the trial, by means of the Fisher's exact test (significance level of 0.01). Differences in PSE parameters at the entrance to the study were tested by means of the χ^2 statistic.

Ethics

The protocol of this study was approved by the Committee for Human Studies of the Instituto Nacional de la Nutrición "Salvador Zubirán," Mexico City. Patients or their closest relatives (if severe mental state deterioration was present) were informed of the nature, purpose and hazards of this study. Then, informed consent was obtained.

The inclusion of the tap-water group was accepted by the Committee for Human Studies and conditioned on a close monitoring of outcomes (sequential analysis), which would lead to cessation of any of the study groups in which substantially poor responses were observed.

RESULTS

Analysis of the First 20 Patients

The analysis of the first 20 patients who entered the trial disclosed a highly significant difference between the lactitol and tap-water enema groups; response rates were 100 and 20%, respectively ($p = 0.0037$) (Table 1). Also, 3 of the 4 deaths which occurred at this first stage took place in the water enema group. Deaths occurred in patients in deep coma and were attributed to liver failure in two of them (both from the tap-water group) and to massive gastrointestinal bleeding in the other two (one patient from the tap-water group and one from the lactose group). Discontinuation of the tap-water group was, therefore, a consequence of both statistical and ethical considerations. The trial continued with the remaining groups, i.e., lactose vs. lactitol, previous readjustment of the randomization schedule.

At the time of the first analysis, all three groups were comparable in terms of basal protein intake, mental state, NCT, asterixis, ammonia levels and PSE index (Table 2).

Response to Disaccharide Enemas

Patients in the two disaccharide groups were similar in demographic characteristics, in the type and duration

TABLE 1. Therapeutic response during the trial

Response	First 20 patients		
	Tap-water group (n = 5) ^a	Lactose group (n = 5) ^a	Lactitol group (n = 10) ^a
Success ^b	1	3	10
Failure	4	2	0
Deaths	3	1	0

Response	Lactose vs. lactitol (after rerandomization)	
	Lactose group (n = 18)	Lactitol group (n = 22)
Success ^c	14	19
Failure	4	3
Deaths	1	0

^a At the time of first analysis (first 20 patients).

^b Lactose vs. lactitol, $p = 0.095$; lactose vs. water, $p = 0.26$; lactitol vs. water, $p = 0.0037$.

^c Lactose vs. lactitol, $p = 0.38$.

of cirrhosis, in the clinical and biochemical manifestations of cirrhosis, cause of acute PSE episodes and PSE parameters (Table 2). Duration of therapy and protein ingestion were also comparable between both lactose and lactitol groups (Table 3), but were quite different when compared with the tap-water group, where the poor responses and early deaths necessitated early stopping of enema administration and a sustained low protein intake.

At the end of the study, a total of 18 and 22 patients were allocated to the lactose and lactitol enema groups, respectively. There were 14 therapeutic successes in the former and 19 in the latter. The differences between response rates (0.78 vs. 0.86) did not reach statistical significance ($p = 0.383$) (Table 1).

PSE Parameters (Figures 1 and 2)

Mental State. Fourteen (78%) of the 18 patients receiving lactose enemas improved at least one grade of mental state; among them, seven improved two grades. Nineteen (86%) of the 22 patients receiving lactitol enemas improved at least one grade of mental state; among them, 10 patients improved two grades.

TABLE 2. Basal PSE parameters in the studied groups

PSE parameter	First 20 patients		
	Tap-water enemas (n = 5) ^a	Lactose enemas (n = 5) ^a	Lactitol enemas (n = 10) ^a
Mental state (grades)	2.8 ± 0.8	2.2 ± 0.4	2.2 ± 0.4
NCT (sec)	196 ± 20	123 ± 66	190 ± 66
Asterixis (grades)	4.0 ± 0.0	3.6 ± 0.5	2.9 ± 0.8
EEG ^b (grades)	4.0 ± 0.0	2.4 ± 0.8	3.1 ± 0.6
Blood ammonia (μg%)	151 ± 35	158 ± 48	236 ± 130
PSE index	0.81 ± 0.10	0.62 ± 0.09	0.66 ± 0.09

PSE parameter	Lactose vs. lactitol (after rerandomization)		
	Tap-water enemas	Lactose enemas (n = 18)	Lactitol enemas (n = 22)
Mental state (grades)	—	2.3 ± 0.6	2.2 ± 1.2
NCT (sec)	—	170 ± 58	157 ± 57
Asterixis (grades)	—	2.9 ± 1.3	3.1 ± 1.3
EEG (grades)	—	2.4 ± 0.9	2.5 ± 1.2
Blood ammonia (μg%)	—	174 ± 55	217 ± 119
Pse index	—	0.66 ± 0.15	0.65 ± 0.15

^a At the time of first analysis (first 20 patients).

^b EEG = electroencephalogram.

TABLE 3. Characteristics of the studied groups during therapy

Characteristic	Tap-water enemas (n = 5)	Lactose enemas (n = 18)	Lactitol enemas (n = 22)
Stool pH before enemas	6.1 ± 0.6	6.2 ± 0.7	6.3 ± 0.9
Stool pH after enemas	6.2 ± 0.6	5.5 ± 0.5 ^a	5.6 ± 0.3 ^a
Protein intake (gm/day)	16 ± 4	26 ± 6	24 ± 8
Duration of therapy (days)	2.6 ± 0.9	3.5 ± 1.2	3.7 ± 1.2

^a Before vs. after enemas, $p < 0.05$.

There were no differences in the daily improvement of mental state among the two groups of patients receiving disaccharide enemas.

Figure 2 shows the mean improvement in mental state after lactose or lactitol enemas. The basal mean grading of mental state, which was similar in the two groups (2.3 ± 0.6 in the lactose group and 2.2 ± 1.2 in the lactitol group), improved significantly ($p < 0.05$) after either treatment (1.0 ± 1.2 and 0.8 ± 0.6 , respectively).

NCT. After lactose enemas, the NCT showed improvement but did not reach statistical significance (from 170 ± 58 to 154 ± 60 sec, not statistically significant). After lactitol enemas, there was a significant improvement in the NCT (from 157 ± 57 to 114 ± 58 sec, $p < 0.05$). In both groups, a wide range in the performance time of the NCT was observed.

Asterixis. The grade of asterixis improved from 2.9 ± 1.3 and 3.1 ± 1.3 to 1.6 ± 1.5 and 1.7 ± 1.4 grades after both lactose and lactitol enemas, respectively ($p < 0.05$). Asterixis disappeared in five patients treated with lactose enemas and in six patients treated with lactitol enemas.

Electroencephalograms. Significant improvements in electroencephalographic tracings were observed

after both treatments, i.e., from 2.4 ± 0.9 and 2.5 ± 1.2 to 1.5 ± 0.6 and 1.6 ± 1.3 grades in the lactose and lactitol groups, respectively ($p < 0.05$). In four cases of each group, enemas restored the electroencephalographic features to normal patterns (α -rhythm = Grade 0).

Blood Ammonia Concentration. The mean value of blood ammonia levels showed a trend (not statistically significant) to improve after both lactose (from 174 ± 55 to 146 ± 52 $\mu\text{g}\%$) and lactitol (from 217 ± 119 to 170 ± 73 $\mu\text{g}\%$) enemas. There was a wide range of variation in blood ammonia values after either treatment.

PSE Index. After the administration of lactose enemas, the PSE index improved significantly from 0.66 ± 0.15 to 0.38 ± 0.18 ($p < 0.01$). The same phenomenon occurred in the group treated with lactitol enemas, where the PSE index decreased from 0.65 ± 0.15 to 0.49 ± 0.18 ($p < 0.01$).

Fecal pH

Stool pH decreased in most patients receiving disaccharide enemas. These changes achieved statistical significance in both lactose and lactitol enema groups ($p < 0.05$) (Table 3).

The number of stools per day at the beginning and at the end of the study increased from 1.7 ± 0.8 to 3.0 ± 0.0 , from 1.8 ± 0.7 to 2.7 ± 0.7 and from 2.0 ± 0.8 to 2.8 ± 0.6 in the tap-water, lactose and lactitol enema groups, respectively. Differences among groups were not statistically significant.

Chemistries and Clinical Features

No striking changes in liver function tests, white blood cell, red blood cell, prothrombin time and clinical features (hepatomegaly, jaundice, ascites, etc.) were observed during the study.

Side Effects

During lactose therapy, three patients experienced adverse effects. In one case, serum sodium dropped from 140 to 120 mEq per liter after 72 hr of lactose enema administration. In spite of a significant improvement in

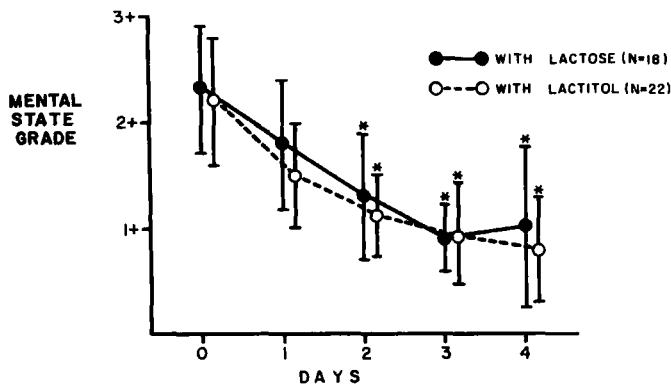


FIG. 1. Mean (\pm S.D.) of daily mental state gradings during disaccharide treatment. The asterisk indicates $p < 0.05$ in comparisons against basal values.

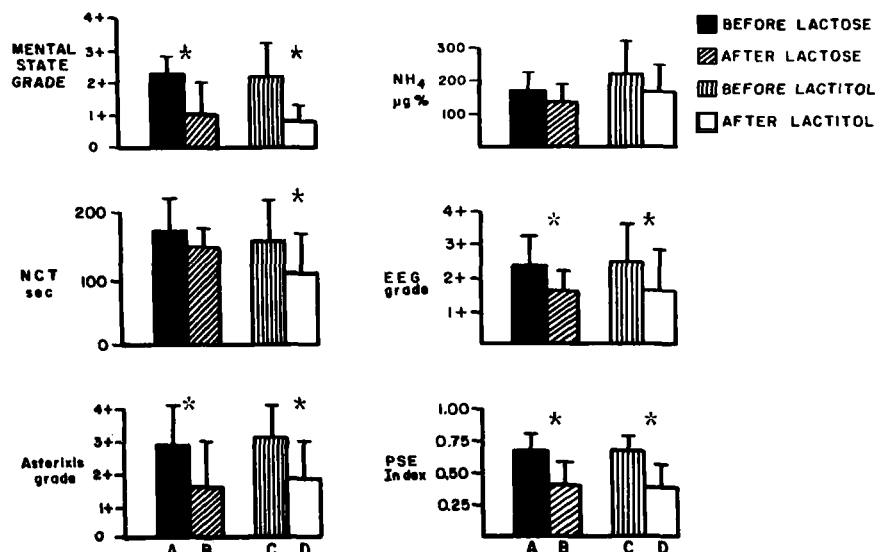


FIG. 2. PSE parameters before and after lactose and lactitol enemas. The asterisk indicates $p < 0.05$.

mental state (from Grade 3+ to Grade 1+), and because of the risk of electrolyte imbalance, the study of this patient was stopped, the code opened and oral neomycin instituted. Another case, a diabetic patient, experienced hyperglycemia (280 mg%) without improvement in PSE; these conditions made discontinuation of the experimental treatment mandatory. Finally, the third patient presented moderate rectal bleeding from a rectal fissure; although the bleeding did not modify the hematocrit, and since the patient already improved two grades of mental state (after 4 days of therapy), his study was considered concluded.

In regard to lactitol enemas, one patient complained of severe abdominal distention after application of lactitol enemas. This, however, was no reason to discontinue treatment.

DISCUSSION

Results of our double-blind, randomized study demonstrate the beneficial effect of both lactose and lactitol enemas, and the failure of nonacidifying gut cleansing in patients with acute PSE episodes. After the administration of both acidifying agents, significant improvements in most of the clinical and laboratory components of the PSE syndrome were observed.

Both sugars reduced stool pH, whereas tap-water enemas exerted no such effect. Similarities in the basal stool pH permitted postevacuation comparisons. It is likely that lactose and lactitol are rapidly degraded in the colon. Bond and Levitt (13) infused lactose into the cecum in a group of patients and observed the appearance of hydrogen gas in expired air within minutes; since sugar breakdown is very rapid, colonic acidification may occur soon after disaccharide enemas.

Improvement in PSE parameters may be explained by a combination of factors.

(i) Colonic acidification after administration of disaccharide enemas may reduce the diffusion of ammonia and other deleterious nitrogen substances from the colon to the systemic circulation. This may be a critical factor, since cleansing of the colon alone, as represented by the tap-water enemas, resulted in treatment failure in 4 of 5 patients. For severely ill subjects, this factor must be very important, while in some cases with mild chronic PSE, cleansing alone may be enough to maintain patient alertness (14).

(ii) As occurred with lactulose, the presence of a fermentable carbohydrate (like lactose and lactitol) may decrease blood ammonia as well as other nitrogenous metabolites by providing an energy source and thus spare the metabolism of exogenous aminated compounds with subsequent decrease in ammonia generation by colonic bacteria (4).

(iii) The hypertonicity of both lactose (364 mOsm per liter) and lactitol (310 mOsm per liter) enemas probably exert an osmotic effect in the catharsis.

Caution in patients with diabetes is advisable when administering lactose enemas because this disaccharide may be degraded to absorbable glucose and galactose and

cause hyperglycemia. In a preliminary, double-blind trial, we administered lactose and lactitol enemas to diabetic patients and observed hyperglycemia in 4 of the 5 who received lactose; this effect was not detected after lactitol enemas (15). Hyperglycemia was observed within 30 min after the disaccharide load, thus supporting the concept of rapid lactose breakdown and absorption.

As stated previously, lactitol demonstrated in this study its therapeutic benefit in acute PSE. This disaccharide will soon be marketed in some countries like ours, where lactulose is not available. In diabetic patients with PSE, the use of lactitol is more advisable than lactose. Also, in patients with chronic PSE and with no lactase deficiency, oral lactitol may be the treatment of choice.

For practical purposes, we have demonstrated in a double-blind, controlled fashion that acidifying enemas are superior to tap-water enemas in the treatment of acute PSE and that lactose and lactitol enemas are equally effective. In diabetic patients, however, lactitol is preferable.

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