Lactitol or Lactulose in the Treatment of Chronic Hepatic Encephalopathy: Results of a Meta-analysis

PIERRE BLANC,[1] JEAN-PIERRE DAURES,[2] JEAN-MICHEL ROUILLON,[1] PASCALE PERAY,[2] ROBERT PIERRUGUES,[1] DOMINIQUE LARREY,[1] FRANÇOIS GREMY[2] AND HENRI MICHEL[1]

[1]*Service des Maladies de l'Appareil Digestif, Hôpital Saint-Eloi,* [2]*Département d'Information médicale, Hôpital Lapeyronie, 34059 Montpellier, France*

Lactitol (β-galactosido-sorbitol) has been recently compared with lactulose for the treatment of chronic hepatic encephalopathy in a few studies, each comprising a small number of patients. The results are controversial. We studied the efficiency and tolerance of both compounds by using a meta-analysis on the basis of published controlled trials. Our study only included controlled or randomized trials comprising cirrhotic patients with chronic hepatic encephalopathy. Analyzed parameters were the portosystemic encephalopathy index of Conn after treatment, the percentage of improved patients and the percentage of patients who had ill effects related to the treatment (flatulence, diarrhea). Bibliographical screening revealed five studies comparing the effects of lactitol and lactulose in chronic hepatic encephalopathy. Four crossover studies were done that included 48 patients and one parallel study that included 29 patients. The duration of the treatment ranged from 3 to 6 mo. All studies found a similar efficiency with both drugs. However, they exhibited some discrepancies in the relative frequency of adverse reactions (flatulence). Meta-analysis showed no statistical differences in the portosystemic encephalopathy index after lactitol or lactulose treatment. The percentage of improved patients after lactitol or lactulose was similar. In contrast, the analysis revealed a higher frequency ($p < 0.01$) of flatulence in patients treated with lactulose compared with those treated with lactitol. In conclusion, this meta-analysis shows no statistical difference between therapeutic effects of lactitol and lactulose, but it does show a higher frequency of flatulence with lactulose. This suggests that lactitol should be preferred to lactulose for the treatment of chronic hepatic encephalopathy. (HEPATOLOGY 1992; 15:222-228.)

Chronic hepatic encephalopathy (HE) is a disabling complication of cirrhosis raising difficult therapeutic questions. Lactulose (β-galactosido-fructose), introduced by Bircher et al. (1) in 1966, has become the reference treatment (2). However, lactulose is often badly tolerated, mainly because of its overly sweet taste and adverse digestive reactions such as nausea, flatulence and diarrhea (2).

In 1982 a new synthetic disaccharide—lactitol (β-galactosido-sorbitol)—similar to lactulose was suggested for the treatment of chronic HE (3). Five controlled clinical investigations have compared the therapeutic effect of both disaccharides, but each trial included only a small number of patients (4-8). None of the experiments showed a difference in efficacy between the two treatments, but some trials reported a better tolerance for lactitol. However, the small sample size and the weak statistical power of such trials make their conclusions uncertain and open to discussion.

Chronic HE is a disturbance of low prevalence making it difficult to undertake a clinical trial with a large number of patients (9). Under these conditions the statistical method of meta-analysis, which combines the findings from different studies, appears to be an appropriate method of investigation (10).

MATERIAL AND METHODS

Source of Articles and Publications

We obtained the list of published articles or summaries by consulting the MEDLINE data base. We then verified and completed the list through an exhaustive study of the references quoted in each article. A recent publication (11) provides a list identical to the one we obtained, with the exception of a study by Riggio et al. (4), which was published later on and had only appeared as a summary at the time of our analysis. Complementary information for this study was provided by the authors.

Variables Taken into Consideration for Meta-analysis

The parameters were chosen according to the recommendations made by Chalmers et al. (12-14), Poynard (15) and Gerbarg and Horwitz (16), and they relate to the following variables.

Variables Describing the Study Population. Included in the variables describing the study population are the country where the study took place, sex distribution and mean age of patients, number of centers, starting date, type of study (stratified or not), diagnostic means, cause and severity of cirrhosis (serum bilirubin and albumin, prothrombin time),

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Address reprint requests to: P. Blanc, Service des Maladies de l'Appareil Digestif, Hôpital Saint-Eloi, 34059 Montpellier Cédex, France.

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existence of spontaneous or surgically induced porta-caval shunt, severity of HE assessed with the Porto-Systemic Encephalopathy Index or PSE Index by Conn et al. (9), type of treatment (lactitol or lactulose), dosage and duration, number of patients included in each treatment group, number of patients improved or deceased in each group, duration of follow-up and patient's consent.

Variables Assessing the Study Quality. Variables used in assessing the study quality were precision of inclusion and noninclusion criteria, number of eligible patients not included into the study, number of patients excluded and lost to follow-up, precision of reasons for exclusion, randomization method (double-blind, single-blind or open design), blinding of inclusion assessor (i.e., the physician who decides on inclusion is not the same one who later treats), calculation of number of patients needed, assessment of the study's statistical power, control of comparability of treatment groups, subgroup analysis, statistical adjustment, type of statistical tests applied and statistical significance of results.

In practice, the methodological quality of each trial was quantified according to a grid defined by Poynard based on 13 items and a power correction. The methodological score had a range of −2 to 26 points.

Control for Potential Bias: Trial Selection

Considering that meta-analysis aims at aggregating and simultaneously assessing data from different investigations, a minimal degree of comparability between trials is required. As for a clinical trial, the protocol for a meta-analysis requires a definition of inclusion and exclusion criteria to be applied to each trial.

Criteria of Eligibility Applied to the Trials. The trials selected for meta-analysis met the following criteria: (a) the patients suffered from chronic HE (defined by clinical status, psychomotor tests and electroencephalographic tracings), requiring restriction of protein intake and long-term treatment; (b) the studies had to be randomized or controlled and published; (c) the patients had been treated orally with lactitol or lactulose if the study design had parallel treatment groups or sequentially with lactitol and lactulose (or *vice versa*) if the study had been performed in crossover fashion; (d) the treatment modalities were required to be comparable in terms of dosage and duration (3 to 6 mo).

Criteria of Ineligibility Applied to the Trials. Excluded from the meta-analysis were all the studies that were either not controlled, had not been published or had appeared only as summaries or letters not permitting a through assessment of the methodology and trials that did not compare lactitol with lactulose in the treatment of chronic HE.

Accordingly, for the meta-analysis we excluded 7 of the 12 studies published on the therapeutic effect of lactitol in HE: a study without a control group (3), a study comparing lactitol with lactose (17), a study in which lactitol and lactulose were administered by enema (18), and three studies in acute (19-21) or in subclinical HE (22). Finally, we excluded an investigation by Morgan et al. quoted by Conn and Bircher (11) because it was an open unpublished study for which the information was fragmentary.

Comparison of Efficacy and Tolerance to Lactitol and Lactulose

The efficacy of each treatment was assessed after (a) the PSE Index as defined by Conn et al. (9) and measured at the end of treatment; (b) the percentage of patients who improved after lactitol or lactulose administration.

The tolerance for each treatment was evaluated by the number of patients complaining of flatulence or diarrhea.

Statistical Methods of Analysis

To better define the results several methods have been applied, with an estimation of the size of the effect and of its variance. The results were obtained using the following methods:

Method No. 1. According to Der Simonian and Laird (23), Method No. 1 consists of assessing at fixed points in time the percentage of patients who improved or had complained of flatulence or diarrhea in each treatment group, thus obtaining an estimate of the size of the effect.

Method No. 2. According to Mantel-Haenszel, the method developed by Peto (24), Method No. 2 describes a modification of the Mantel-Haenszel test (i.e., a method that does not take into account a correction factor controlling for a possible heterogeneity when calculating the final confidence interval). However, such heterogeneity can be assessed separately.

Method No. 3. According to Hedges and Olkin (25), Method No. 3 describes an aleatory method that takes a possible heterogeneity into account and expresses the effect of treatment against a weighted average of the ratios of deviations to the quantity $V = \sqrt{p\,(1 - p)}$, where p is the average percentage of events in each trial.

Regardless of the method applied, CI represents the 95% confidence interval of the estimated value. The method according to Der Simonian and Laird is mostly equivalent (by simulation) to that of Peto in the absence of heterogeneity (26); however, the method of Der Simonian offers the advantage of taking into account a possible heterogeneity and of comparing rates, thus answering the clinical query.

RESULTS

Characteristics of Trials Selected for the Analysis

Five controlled trials were considered (4-8), four of which were randomized and one controlled; four trials (4-7) had a crossover design for a total of 46 patients, and one study (8) had two parallel groups of treatment for a total of 29 patients. None of the four crossover trials had a washout period between the two treatments, and only two trials (5, 6) took a sequence effect into account.

In three studies (5-7) lactitol and lactulose were administered for 3 mo. In two other trials (4, 8) each medication was administered for 6 mo, but the PSE Index was assessed at 3 mo also. Only one of these two studies (8) reported the percentage of patients who had improved at 3 and 6 mo. The investigations by Riggio et al. in 1988 (4) and by Heredia et al. (7) failed to report the rates of improvement. The PSE Index was either reported fully or could be calculated for all five studies. In meta-analysis, to standardize the duration of treatment, the PSE Index and the rates of improvement have been assessed at a fixed point in time (3 mo after inclusion).

Tolerance to lactitol and lactulose was assessed at the end of treatment by the presence of diarrhea or flatulence. The percentage of patients who experienced diarrhea was reported in four studies (4-7). The proportion of patients reporting flatulence was indicated in four trials (4-8), whereas the remaining trial by Heredia et al. (7) reported digestive tract disturbances such as

TABLE 1. Characteristics of trials

Authors and year (Ref.)	Country	Inclusion criteria	Exclusion criteria	Diagnostic tools for HE	Lactitol Dose[a] (gm/day)	Lactitol Duration (mo)
Riggio et al. 1990 (4)	Italy	Cirrhosis (biopsy) Portosystemic shunt Surgically induced Chronic HE Protein restriction Long-term lactulose	Active cirrhosis Renal failure Abstinence from alcohol not observed	Clinical examination Psychomotor tests EEG Blood ammonia	36.3 ± 5	6
Lanthier and Morgan 1985 (5)	United Kingdom	Cirrhosis (biopsy) Portosystemic shunt Chronic HE Protein restriction Long-term lactulose ± Bromocriptine	Interruption of abstinence from alcohol	Clinical examination Psychomotor tests EEG Blood ammonia	64	3
Morgan et al. 1987 (6)	United Kingdom	Cirrhosis (biopsy) Surgical or spontaneous Portosytemic shunt Chronic HE Protein restriction Long-term lactulose ± Bromocriptine	Active cirrhosis Viral hepatitis B Hepatorenal syndrome Interruption of abstinence from alcohol	Clinical examination Psychomotor tests EEG Blood ammonia	31.9 ± 11.2	3
Heredia et al. 1988 (7)	Spain	Cirrhosis (biopsy) Portosystemic shunt Chronic HE Protein restriction	Hepatorenal syndrome Hepatocarcinoma Interruption of abstinence from alcohol	Clinical examination Psychomotor tests EEG Blood ammonia	35.6 ± 17.5	3
Riggio et al. 1989 (8)	Italy	Cirrhosis (biopsy) Surgical Portosystemic shunt Chronic HE Protein restriction Long-term lactulose	Lack of compliance Interruption of abstinence from alcohol	Clinical examination Psychomotor tests EEG Blood ammonia	36 ± 7	6

[a]Mean ± S.D.

"abdominal discomfort," which can be considered similar to flatulence. Morgan, Hawley and Stambuk (6) described dose-dependent and dose-independent instances of flatulence and diarrhea; for our calculations we took into account the total number of flatulence and diarrhea reports, whether they were dose-dependent or not.

Methodological Evaluation of the Trials

The variables taken into account for each investigation are listed in Tables 1, 2 and 3.

Cirrhosis was mainly due to alcohol abuse in two trials (5, 7) and was described as "cryptogenic" in more than half of the patients included in the studies of Morgan, Hawley and Stambuk (6) and Riggio et al. (8) (Table 2). Patients in the study by Heredia et al. (7) exhibited a more severe cirrhosis than that seen in the four other trials (4-8) (Table 2). In the five studies, all patients had spontaneous or surgical portacaval shunts; the proportion of surgical shunts was 30% in one study (6), 40% in another (5) and 100% in the three remaining studies (4, 7, 8).

The study by Lanthier and Morgan (5) had a mediocre methodological score of 4 out of 26 according to the evaluation grid of Poynard (15) because the study had an open, unblinded and unrandomized design. The remaining four studies (4, 6-8) had a satisfactory and comparable methodological level with scores varying between 16 and 18. In none of the five studies did the methodological paragraph mention the calculated number of patients required for demonstrating a potential statistical difference.

Because of the unequal methodological level of these five studies, two meta-analyses have to be performed: one with all five studies and the other with only four of them (4, 6-8), excluding the trial by Lanthier and Morgan (5) because of its lesser methodological value.

Tables 4 to 7 summarize the data concerning the

Lactulose		
Dose[a] (gm/day)	Duration (mo)	Concomitant treatment
38.2 ± 19	6	Protein restriction (0.8-1.0 gm/kg/day)
29	3	Protein restriction (40-60 gm/day) ± Bromocriptine
21.9 ± 11.1	3	Protein restriction (40-50 gm/day) ± Bromocriptine
40.2 ± 19.6	3	Protein restriction (40-60 gm/day)
30 ± 16.6	6	Protein restriction (1 gm/kg/day)

following variables: PSE Index after treatment, improvement of clinical status, incidence of flatulence and incidence of diarrhea. For each trial, the tables also indicate the percentage of patients who improved, who reported flatulence or who reported diarrhea; the differences between such percentages; and the 95% confidence interval for these differences. All studies included a small number of patients.

Meta-analysis

Meta-analysis was performed on the following variables: PSE Index after treatment, the percentage of patients who improved on lactitol or lactulose, the percentage of patients with flatulence and the percentage of patients with diarrhea.

PSE Index After Treatment. None of the five studies reported a statistically significant difference for the PSE Index between the two treatments (Table 4). The meta-analysis did not show a statistically significant difference in PSE Index between the two treatment groups, lactitol and lactulose, whether the study by Lanthier and Morgan (5) was taken into account or not (Table 8). Being a quantitative variable, the PSE Index was analyzed statistically only by using Hedges's method.

Percentage of Patients Improved. No statistical difference was found between the rates of patients who improved after the two treatments (Table 5) in the three studies assessing this point (5, 6, 8). The meta-analysis showed no significant difference in the rates of patients who improved with lactitol and lactulose, whether the study by Lanthier and Morgan (5) was taken into account or not (Table 8). The heterogeneity tests performed with the methods of Peto and Hedges were not significant.

Percentage of Patients who Experienced Flatulence. Analysis of the whole group showed that 11 of 60 patients taking lactitol (18%) complained of flatulence as opposed to 26 of 61 (43%) patients taking lactulose. In three studies (4, 5, 8) flatulence was significantly more frequent with lactulose than with lactitol. For the two other studies, no significant difference was found (Table 6). This observation stressed the value of meta-analysis, which showed that flatulence was significantly more frequent with lactulose than with lactitol, whether the study by Lanthier and Morgan was taken into account or not (Table 8). The results were statistically significant for all methods (Hedges, Peto, Der Simonian).

Percentage of Patients who Experienced Diarrhea. The frequency of diarrhea was similar between patients taking lactitol and those taking lactulose in two studies (7, 8). Diarrhea was more frequent after lactulose therapy in two other trials (5, 6) (Table 7). In the meta-analysis including the study by Lanthier and Morgan (5), diarrhea was slightly more frequent with lactulose, without reaching a statistical significance ($p = 0.09$ for Der Simonian and $p = 0.07$ for Peto). Excluding the study by Lanthier and Morgan (5), the results were not statistically significant for all methods (Table 8). The heterogeneity tests performed with the methods of Peto and Hedges were not significant.

DISCUSSION

Lactitol has recently been introduced as the potential successor to lactulose for the treatment of chronic HE. To our knowledge, only five clinical trials have been published, comparing lactitol with lactulose in chronic HE (4-8). In fact, chronic HE is a rare condition: a multicenter investigation conducted by Conn in 1977 in seven American hospitals was only able to recruit 33 patients over 4 yr (9). That is why four of the five trials were conducted in crossover fashion, thus allowing an increase in the sample studied for each treatment. The inclusion criteria were comparable among the five studies. The lactitol and lactulose treatment groups were strictly comparable in all studies except one: Riggio et al. in 1989 (8), found patients in the lactitol group were significantly older, had significantly higher blood sugar levels and had more marked mental disturbances. The two disaccha-

TABLE 2. Patient characteristics

Authors and year (Ref.)	Age[a] (yr)	Sex ratio (M/F)	Cause of cirrhosis			Bilirubin[a] (μmol/L)	Prothrombin time[a] (sec. or % of normal)	Serum albumin[a] (gm/L)
			Alcoholic (%)	Viral (%)	Cryptogenic (%)			
Riggio et al. 1990 (4)	57 ± 6	9/3	n.i.[b]	n.i.[b]	n.i.[b]	27.2 ± 13.6	n.i.[b]	37 ± 7
Lanthier and Morgan 1985 (5)	54.4 ± 8.6	5/0	60	0	40	29.8 ± 19.5	16.6 ± 2.9 sec	33.8 ± 2.5
Morgan et al. 1987 (6)	57.3 ± 11.5	5/4	45	0	55	25.9 ± 12.8	16.2 ± 2.5 sec	37.7 ± 3.9
Heredia et al. 1988 (7)	54.5 ± 2.1	14/6	60	24	16	47.6 ± 16.3	65.7% ± 17.3%	32.9 ± 4.4
Riggio et al. 1989 (8)	54.4 ± 11.3	21/8	20	20	60	28.9 ± 14.6	74% ± 16%	37 ± 5.4

[a]mean ± S.D.
[b]n.i. = not indicated.

TABLE 3. Variables defining study quality

Authors and year (Ref.)	Study design	Randomization	Blinding	Calc[a] No.	No. patients analyzed lactitol/lactulose	No. excluded or lost to follow-up	Reason for exclusion	No. of deaths	Mo of evaluation
Riggio et al. 1990 (4)	Crossover	Yes	Single blind	No	12/12	2	Yes	1	3 + 6
Lanthier and Morgan 1985 (5)	Crossover	No	None	No	5/5	n.i.[b]	n.i.[b]	n.i.[b]	3
Morgan et al. 1987 (6)	Crossover	Yes	Double-blind	No	9/9	3	Yes	1	3
Heredia et al. 1988 (7)	Crossover	Yes	Double-blind	No	20/20	5	Yes	2	3
Riggio et al. 1989 (8)	Parallel	Yes	Single blind	No	14/15	2	Yes	0	3 + 6

[a]Calculated number of patients needed to achieve the study.
[b]n.i. = not indicated.

TABLE 4. PSE Index as assessed after 3 mo therapy

Authors and year (Ref.)	No. patients (lactitol/lactulose)	PSE index[a] after lactitol	PSE index[a] after lactulose
Riggio et al. 1990 (4)	12/12	0.30 (±0.05)	0.30 (±0.03)
Lanthier and Morgan 1985 (5)	5/5	0.133 (±0.09)	0.175 (±0.1)
Morgan et al. 1987 (6)	9/9	0.126 (±0.11)	0.12 (±0.08)
Heredia et al. 1988 (7)	20/20	0.29 (±0.19)	0.257 (±0.1)
Riggio et al. 1989 (8)	14/15	0.29 (±0.11)	0.20 (±0.11)

[a]Mean ± S.D.

rides were always administered in a dose leading to two soft stools per day.

The meta-analysis of the five trials shows a negligible difference in efficacy between the two sugars. With the exception of one study—Heredia et al. (7)—all investigators reported a lower incidence of gastrointestinal disturbances with lactitol.

The performance of a meta-analysis of controlled clinical investigations comparing lactitol with lactulose in chronic HE appears justified for two main reasons. The published results as such could wrongly lead to the conclusion of the absence of a therapeutic advantage of lactitol owing to study populations that were too small. Meta-analysis compensates for the difficulty of conducting a large therapeutic multicenter trial with a large number of patients because of the low prevalence of chronic HE. However, meta-analysis faces various difficulties caused mainly by the differences in method-

TABLE 5. Percentage of patients who improved after 3 mo of treatment

Authors and year (Ref.)	No. of patients taking lactitol/lactulose	% who improved on lactitol	% who improved on lactulose	Difference of percentages	Variance in difference	CI of difference[a]
Lanthier and Morgan 1985 (5)	5/5	80	60	20	0.08	−0.354; 0.754
Morgan et al. 1987 (6)	9/9	22	45	−23	0.047	−0.646; 0.201
Riggio et al. 1989 (8)	14/15	28	40	−12	0.028	−0.476; 0.176

[a]CI = 95% confidence interval of difference.

TABLE 6. Incidence of flatulence during treatment

Authors and year (Ref.)	No. patients taking lactitol/lactulose	Rate of flatulence on lactitol	Rate of flatulence on lactulose	Difference of rates	Variance in difference	CI of difference[a]
Riggio et al. 1990 (4)	12/12	0.16	0.58	−0.42	−0.026	−0.677; −0.0375
Lanthier and Morgan 1985 (5)	5/5	0	0.40	−0.40	0.048	−0.829; −0.0294
Morgan et al. 1987 (6)	9/9	0.70	1.0	−0.30	−0.024	−0.0253; −0.641
Heredia et al. 1988 (7)	20/20	0.15	0.10	−0.05	0.0109	−0.154; 0.254
Riggio et al. 1989 (8)	14/15	0	0.43	−0.43	0.016	−0.648; −0.152

[a]CI = 95% confidence interval of difference.

TABLE 7. Incidence of diarrhea during treatment

Authors and year (Ref.)	No. of patients taking lactitol/lactulose	Rate of diarrhea on lactitol	Rate of diarrhea on lactulose	Difference of rates	Variance in difference	CI of difference[a]
Lanthier and Morgan 1985 (5)	5/5	0	0.40	−0.40	0.048	−0.829; −0.0294
Morgan et al. 1987 (6)	9/9	0.45	0.90	−0.45	0.038	−0.829; −0.0603
Heredia et al. 1988 (7)	20/20	0.1	0.10	0	0.01	−0.186; 0.186
Riggio et al. 1989 (8)	14/15	0	0	0	0	0; 0

[a]CI = 95% confidence interval of difference.

TABLE 8. Results of the meta-analysis: calculation of the 95% confidence interval by three statistical methods for the variables PSE index, patients who improved, flatulence and diarrhea

	Hedges's method	Peto's method	Der Simonian's method
Including the study by Lanthier and Morgan (5)			
PSE Index after treatment	−0.12; 0.584	–	–
Patients who improved	−0.184; 0.936	0.312; 2.624	−0.344; 0.124
Flatulence	0.210; 0.934	1.878; 10.726	−0.475; −0.0547
Diarrhea	−0.222; 0.807	0.978; 12.10	−0.272; 0.081
Excluding the study by Lanthier and Morgan (5)			
PSE Index after treatment	−0.0695; 0.655	–	–
Patients who improved	−0.272; 0.749	0.670; 6.957	−0.435; 0.0814
Flatulence	0.226; 0.921	1.673; 10.354	−0.487; −0.00536
Diarrhea	−0.0788; 0.872	−0.682; 11.037	−0.446; 0.226

ology between the various trials. This requires standardization of the assessment parameters during the trials. The first (Lanthier and Morgan [5]) and the last trial (Riggio et al. [4]) in our meta-analysis are only 5 yr apart, an advantage in terms of study homogeneity and standardization of evaluation criteria. However, one study (Lanthier and Morgan [5]), appeared to be of lesser methodological quality, and this led us to perform two separate meta-analyses to detect and avoid possible inclusion bias in the statistical analysis. The outcome of the meta-analysis did not change whether that study was taken into account or not.

Despite the increase in statistical power provided by meta-analysis, the three methods applied, namely Der Simonian, Peto and Hedges, did not allow detection of any statistically significant difference in therapeutic efficacy between the lactitol and the lactulose treatment group. In contrast, digestive disorders, in particular flatulence, were significantly less frequent with lactitol than with lactulose. Diarrhea was also less frequent with

lactitol, the difference here indicating a trend toward significance. All three statistical methods applied (Der Simonian, Peto and Hedges) gave concordant results.

The mode of action of lactitol is comparable to that of lactulose (27): it is not absorbed and is metabolized only in the colon by the bacterial flora, which transforms it into acetic, butyric, propionic and lactic acid. The superior tolerance to lactitol could result from a better taste (less sweet than that of lactulose, which often causes nausea) and from an ease of use and simpler adaptation of dosage. Indeed, flatulence that is observed independently of the dose used for lactulose occurs only for doses greater than 40 gm/day with lactitol. Thus untoward abdominal effects are more predictable and easier to avoid with lactitol than with lactulose.

In conclusion, despite the increased statistical power provided by meta-analysis, no significant difference was detected between the therapeutic efficacy of lactitol and lactulose. Nevertheless, untoward digestive effects were significantly less frequent after lactitol administration. Thus lactitol should be preferred to lactulose. However, the ideal solution would be to undertake a large multicenter investigation that would allow us to confirm or refute the result of our meta-analysis.

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