Acute exacerbation of pain in irritable bowel syndrome: efficacy of phloroglucinol/trimethylphloroglucinol. A randomized, double-blind, placebo-controlled study.

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Acute exacerbation of pain in irritable bowel syndrome: efficacy of phloroglucinol/trimethylphloroglucinol (P/TMP). A randomised, double-blind, placebo-controlled study.

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Abbreviations:

IBS   Irritable Bowel Syndrome
GPs   General Practitioners
VAS   Visual analog scale
P   Phloroglucinol
TMP   Trimethylphloroglucinol

Abstract

Background: Abdominal pain is the predominant symptom in IBS patients. Phloroglucinol (P) and its methylated derivative (TMP) are antispasmodic agents acting on smooth muscle. **Aim**: To evaluate the efficacy of P/TMP on pain intensity during an acute exacerbation of pain of IBS over a one-week period treatment. **Methods**: IBS Rome II patients seeking medical advice for an acute exacerbation of abdominal pain were randomised to P/TMP (62.2mg P + 80mg TMP) 2 pills tid or placebo for 7 days. Patients were included if they had a pain with a minimal intensity of 40 on a 100 mm visual analog scale, and if pain occurred at least 2 days during the week previous inclusion. **Results**: 307 patients were included by 78 GPs. The intent to treat population included 300 patients, aged of 46.9±14.8 years (73% female). The relative decrease of pain intensity at day 7 was 57.8±31.7% vs. 46.3±34.7% (Δ=11.5±3.8%, [$CI_{95\%}$: 4.0 ; 19.1], p=0.0029) and the percentage of patients with at least a 50% decrease of pain intensity was 62.3% vs. 47.0% (Δ=15.3±5.7%, [$CI_{95\%}$: 4.1 ; 26.5], p=0.0078) in P/TMP and placebo groups respectively. **Conclusions**: A one-week P/TMP treatment significantly reduces pain intensity in IBS patients consulting their GPs for pain exacerbation.

Introduction

Irritable bowel syndrome (IBS) is a chronic and frequent condition characterized by abdominal discomfort or pain associated with defecation and/or changes in bowel habit (diarrhea, constipation or alternating of both), more evident during acute pain episodes [1]. These symptoms fluctuate over time, typically with exacerbations associated with life stress events. During exacerbations, patient's expectation is a fast and significant improvement of abdominal pain, the main factor affecting health-related quality of life [2].

The most recent theories regarding the pathogenesis of IBS have emphasized the role of visceral hypersensitivity as the source of pain [3]. Nevertheless, an increased or disorganized motor activity in the small bowel and/or the colon remains relevant to the generation of abdominal pain or discomfort. Manometric studies have shown that patients with diarrhea-predominant IBS have more jejunal contractions during phase II of the migrating motor complex and postprandial than healthy subjects. In addition, there is a relationship between the occurrence of pain episodes and the onset of clusters of jejunal motor activity [4-7]. ~~Kellow et al. have identified the coincidence of painful cramps with the passage of high amplitude pressure waves through the ileocecal region [7].~~ Pain episodes have been also related to altered colonic phasic contractions and some studies have provided evidence of increased responsiveness of the IBS colon, both to the effects of eating and to stress [8]. ~~Moreover, while the normal colon is quiescent during sleep, sleep is often altered in IBS, with more periods of arousal and the colon is consequently more active [9].~~ It must be also pointed out that visceral pain and altered gut motility may depend upon altered motility reflexes resulting from increased sensitivity of the digestive tract [9]. Taken together, all these data provide rationale for the usefulness of antispasmodic agents in the short-term treatment of acute painful episodes.

Phloroglucinol (P) and its methylated derivative (TMP) are both antispasmodic agents acting on smooth muscle and devoted to treat abdominal pain. Based on glycerol-induced visceral

pain model, animal studies suggested that P/TMP may modulate the release of prostaglandins and/or other inflammatory mediators such as nitric oxide (Bueno L et al, unpublished data). In IBS patients, P has been shown to reduce glycerol-induced abdominal pain and to inhibit colonic phasic contractions without affecting colonic tone [10]. P/TMP is also characterized by a rapid and potent spasmolytic activity, suggesting that it may have some efficacy to relieve pain particularly during acute pain episodes.

The aim of this randomised, double-blinded, placebo-controlled study was to test the efficacy of P-TMP in the treatment of an acute exacerbation of pain in IBS patients seen in a primary care practice.

Materials and Methods

Design

This one-week randomised, multicenter, double-blinded, placebo-controlled trial was carried out by general practitioners (GPs) in France according to the recommendations for the Treatment of IBS [11-13]. Consecutive patients were recruited between December 2004 and July 2005.

The protocol was approved by the Saint-Louis hospital ethic committee according to the French bioethical law. Written informed consent was obtained from all patients before enrolment into the study.

Patients

Eligible patients were male and female patients 18 to 75 years old who had IBS diagnosed using the Rome II criteria [1] and who consulted their GPs for an exacerbation of abdominal pain (pain requiring a fast relief by an adapted treatment). Patients were required to have a

pain intensity score between 40 and 80 mm on a 0-100 mm Visual Analog Scale (VAS) at the time of inclusion, and to report pain which occurred at least two days, consecutive or not, during the week previous inclusion.

Patients were not included if they had a COVI Anxiety Scale score greater than 7. The COVI Anxiety Scale has 3 items answered by the clinician, with a global score ranging from 0 to 12. The COVI Scale is used for describing the intensity of anxiety [14]. A COVI score over 7 indicates a pathological anxiety. Patients were not included if the duration of IBS was greater than 10 years, or if they had a significant gastrointestinal disorder other than IBS, or an unstable medical disorder. Patients were also not included if they have had P/TMP in the month prior to the study. A stable antidepressant or anxiolytic treatment was allowed if started at least respectively one month or two weeks before inclusion.

Treatments

Patients were randomised to receive for one week either P/TMP (62.2 mg phloroglucinol + 80 mg TMP) 2 pills tid daily (Spasfon®; Cephalon, France) or an identical placebo. Patients were allowed to take twice daily 2 additional pills in case of insufficient pain relief. Neither the patients nor the study investigators were aware of the treatment assigned. A stable concomitant antispasmodic agent was allowed if started more than one week before inclusion.

Data collection

Patients had 2 visits at baseline and day 7. Medical history and current medication were recorded at baseline. Pain intensity was recorded by the patient at baseline and day 7 during the visit with the investigator, and during the one-week treatment on a daily diary, using a VAS ranging from 0 to 100 (maximal pain). Pain relief was daily assessed using a five point scale (Likert scale: 0=none, 1=slight, 2=moderate, 3=a lot, 4=complete). Study medication accountability was also recorded daily by the patient. Adverse events were recorded at day 7

by the investigator.

Endpoints

The primary efficacy endpoint was the relative decrease of pain intensity (PI) recorded by patients between baseline and day 7 [$(PI_7-PI_{Baseline})/ PI_{Baseline}$]. Secondary endpoints included the daily pain intensity and daily pain relief recorded by the patients on a diary, the number of responders (patients having at least a 50% decrease of pain intensity from baseline), the number of patients requiring an additional intake of pills, the total number of pills consumed, and adverse events.

Statistical analysis

Assuming that there would be a 30% decrease of pain intensity in the placebo group between baseline and day 7, we calculated that 302 patients were needed to detect a crude difference of 15% for this primary endpoint between placebo and P/TMP, with a power of 90% at the α=0.05 significance level. Consequently, 340 patients were needed to allow for a 10% dropout rate.

The analysis of efficacy was performed according to the intent-to-treat principle. All patients enrolled, having taken at least one dose of study medication, and having at least one efficacy assessment of the primary endpoint, were included in efficacy analysis. Analysis of safety was conducted by including all patients who had received at least one dose of study medication.

Categorical variables were described using frequencies and percentages and their distributions were compared between treatment groups, using the chi-square test or Fisher exact test. Continuous variables were summarized using mean and standard deviation. Their distributions were compared between treatment groups using Wilcoxon test. The variation of pain intensity between baseline and day 7 (the primary endpoint) was compared between the

two groups using an analysis of variance. The explicative covariate was the treatment group. A patient was defined as responder if he/she had a decrease of at least 50% of his/her pain intensity at day 7 compared to baseline. The rate of responders was compared between the placebo and the P/TMP groups using a Chi-square test.

The daily pain assessment was analyzed using a repeated-measure variance analysis to search for a treatment effect and a time effect. Area under the curve calculated from the daily VAS values, reflecting pain intensity over the 7-day treatment period were compared between the two groups using Wilcoxon test. The effect of the treatment was considered persistent when a patient became and remained responder until day 7 (i.e. at least 50% of pain intensity decrease from one daily assessment compared to baseline).

In case of missing value for the primary endpoint, the last value recorded in the patient daily diary was used, if it was recorded after day 5. In case of missing value for the values recorded daily in the patient diary, the precedent or the following value was used if the number of missing values was not greater than 2.

Multivariate logistic regression analysis, adjusted on treatment, using likelihood ratio test, was used to look for factors measured at baseline which were independently predictive of response. Variables proposed for this analysis were age, sex, pain frequency, trigger factors (meal, anxiety, gynecologic event, gastroenteritis), pain at baseline duration of symptoms, COVI scale score and additional pills intake. Results were expressed as Odds Ratio (OR) with a 95% confident interval (CI).

Results

Characteristics of the patients

Three hundred and seven patients were included; 155 patients were randomly assigned to

receive P/TMP and 152 patients to receive placebo (Figure 1). Three patients did not receive the treatment and were dropped out of all analyses. Four other patients were dropped out of the intent to treat analysis of efficacy.

Consequently, 300 treated patients were included in the intent to treat analysis. Their mean age was 46.9 ± 14.8 years, and 73% were women. All patients fulfilled IBS Rome II criteria. All of them had a history of abdominal pain or discomfort, and at least 2 among the 3 following criteria: abnormal stool frequency (89% of patients), abnormal stool consistency (82%), and symptom relief by exoneration (86%). The abdominal pain intensity recorded on VAS at baseline was 61.9 ± 8.7 mm. The mean duration of IBS symptoms was 3.8 ± 2.8 years. A majority of patients had several other symptoms commonly associated with IBS such as bloating (Table 1). Seventy seven patients (25.7%) were treated with antispasmodic agents. Comparability of the two treatment groups was confirmed for all socio-demographic and clinical baseline characteristics, particularly pain intensity, illness duration and diagnostic criteria (Table 1).

Efficacy

All endpoints showed a greater decrease of abdominal pain severity in patients treated with P/TMP.

The relative decrease of pain intensity between baseline and day 7 (primary endpoint) was 57.8 ± 31.7% in the P/TMP group versus 46.3 ± 34.7% in the placebo group, with a difference of 11.5 ± 3.8% [CI$_{95\%}$: 4.0 ; 19.1], p=0.0029 (Table 2). The rate of responders was significantly greater in patients treated with P/TMP, than in patients treated with placebo, respectively 62.3% versus 47.0%, with a difference of 15.3 ± 5.7% [CI$_{95\%}$: 4.1 ; 26.5], p=0.0078 (Table 2 Figure 2).

The decrease of daily pain intensity was higher in the P/TMP group than in the placebo group starting from day 1, the difference being significant at day 4 (p=0.007), day 5

(p=0.013), and day 7 (p=0.030) (Figure 2 3). The repeated-measure variance analysis carried out in 289 evaluable patients confirmed these results showing a significant treatment effect (p=0.015) and time effect (p<0.0001), without time-treatment interaction. Finally, area under the curve from the daily VAS values, reflecting pain intensity over the 7-day treatment period was also smaller in the P/TMP group than in the placebo group: respectively 211 ± 98 versus 239 ± 107 mm.day, p=0.017. A higher percent of patients had a persistent treatment effect (i.e. patients having at least a 50% decrease of pain intensity at one daily assessment compared to baseline, and remaining daily such responders until day 7): 47.3% in the P/TMP group versus 33.3 % in the placebo group, with a difference of 14.0 ± 5.7% [$CI_{95\%}$: 2.7 ; 25.2], p=0.015.

The daily pain relief assessment was in favour of P/TMP compared to placebo, the difference being significant from day 3 to day 7 (repeated-measure variance analysis) (Figure 3 4).

Searching for factors associated with pain relief at day 7 the multivariate logistic regression analysis showed that P/TMP treatment (OR: 2.0; 95% CI: 1.2-3.4; p=0.005), and pain triggered by meals (OR: 1.9; 95% CI: 1.2-3.3; p=0.013) increased the likelihood of a good response.

A subgroup analysis was performed among the 77 patients who had a concomitant antispasmodic agent at baseline. A trend in favour of the P/TMP group was still observed, although differences of pain intensity decrease between baseline and day 7 did not reach the significance level: 47.0 ± 31.3% (P/TMP) vs. 34.2 ± 31.6% (placebo), p=0.078.

Per-protocol analyses showed similar differences (Figure 2).

No significant difference was observed regarding the number of pills taken per day (5.7 ± 1.3 versus 5.9 ± 1.4, p = 0.24, respectively in P/TMP and placebo groups), the proportion of patients who took additional pills (67% versus 64%, p = 0.716), and the number of additional

pills through the 7-day period (respectively 3.0 ± 6.1 versus 3.9 ± 8.0, p=0.371).

Safety

Frequency and severity of adverse events (AE) were not different between the two treatment groups. The percentage of patients who had at least one AE was 9% (14 patients / 23 events) in the P/TMP group and 7% (10 patients / 11 events) in the placebo group (p=0.53). No AE was considered as serious to stop the treatment. Only two AE were considered possibly related to the treatment: aggravated constipation, flatulence and abdominal pain in one patient (P/TMP), and nausea in one patient (placebo).

Discussion

The study aimed to test the efficacy of P/TMP as a symptomatic treatment for the relief of abdominal pain intensity during an acute exacerbation of IBS over a one-week period of treatment. Our objective differs of previously published trials devoted to IBS, in which the primary endpoint was the possible modification on the medium term of the natural history of IBS by a treatment given daily for at least four weeks in order to decrease not only the intensity but also the frequency of abdominal pain episodes. Indeed, IBS is a chronic syndrome characterized by recurrent abdominal pain episodes. Therefore, short term clinical trials, lasting only few days are considered of limited clinical relevance to conclude that the treatment is effective to improve IBS [15] and one to three months is the recommended trial duration to achieve a good compromise between the time needed to assess efficacy and the time to reach the recession of a placebo effect [11]. IBS is characterized during its cyclic evolution by abdominal pain/discomfort exacerbations lasting for less than a week [16, 17]. It was also suggested that antispasmodics are better used on an as-needed basis for pain, distension or bloating exacerbation [18]. A design of treatment trials committee recently recommended innovative trial design to evaluate short-course treatment after symptom

recurrence [19].

During such exacerbations, IBS patients seek medical advice to receive a treatment able to provide a quick and significant improvement of abdominal pain. This study was carried out to assess if P/TMP, an antispasmodic agent, was able to provide such a fast significant relief. To achieve this goal, the symptomatic efficacy of P/TMP was compared to that of placebo over a one-week period of treatment with study conditions as closed as possible to real-life management of IBS patients in a primary care practice. To our knowledge, this is the first study with such a design, focusing on the relief of exacerbation of painful symptoms.

Several meta-analysis or reviews have already reviewed the symptomatic efficacy of antispasmodics in IBS [20-22]. These trials are characterized by a low methodological quality and the heterogeneity of the populations recruited in these trials, leading to contradictory conclusions [23]. Antispasmodic efficacy to improve abdominal pain in IBS remains a matter of debate. To avoid these methodological criticisms, our study was designed in accordance with the "Points to consider" on the evaluation of drugs for the treatment of IBS and followed the recommended criteria for methodological good quality [11-13]. Our study was designed a randomised, double-blinded, placebo-controlled parallel trial and patients were enrolled both if they fulfilled Rome II IBS criteria [1] and if they suffered from an exacerbation of their abdominal pain when entering into the trial. The primary endpoint was abdominal pain intensity reduction using a well-established scale. Obviously, in this condition the patient is the best expert to judge the relief of his/her symptoms [12, 24].

The definition of responder was based on a 50% reduction in pain intensity [11]. Moreover, a sufficient sample size calculated on a priori hypotheses, the low number of patients lost to follow-up (1% of treated patients) and the comparability of the two treatment groups for all baseline characteristics were also important points to consider for the quality of this trial.

When analyzing the results of a trial, one needs to consider not only the statistical

significance of the results but also the clinical relevance of the study. This must be assessed in considering the effect of the treatment on the primary endpoint, i.e. the reduction of pain intensity. We have shown a greater reduction of abdominal pain intensity in patients treated with P/TMP with a relative reduction of pain intensity between baseline and day 7 of 57.8 ± 31.7% in P/TMP group. In the placebo group, the reduction was significantly lower, 46.3 ± 34.7% (p=0.0029). This led to a difference of 11.5 ± 3.8% [$CI_{95\%}$: 4.0 ; 19.1] between the two treatment groups while at least a 10% difference is usually considered as clinically relevant [11, 25]. Moreover, consistent results were obtained for all secondary endpoints, therefore contributing to the robustness of the conclusions. Per-protocol analysis showed also similar level of differences between treatment groups.

The placebo effect is known to be maximal during the first four weeks of treatment and reflects to a large part the spontaneous improvement of symptoms [11, 26]. Despite the high placebo response observed in this study, similar to that observed in previous published studies [27], P/TMP was still able to be significantly superior over placebo on all primary and secondary endpoints, e.g. by a 15.3 ± 5.7% [$CI_{95\%}$: 4.1 ; 26.5] difference in rate of responders, which in turn, results in a number needed to treat of 6.5. This number is much closed to the NNT of 6 reported by a recent Cochrane systematic review of antispasmodic agents in IBS [29]. Comparatively, a NNT value of 4 has been reported for acetaminophen in a similar chronic condition, i.e. osteoarthritis [30].

We have pointed out that the effect of P/TMP occurs within the first few days of treatment as a more significant improvement was already observed in the P/TMP group after the third day according to the daily diary filled by the patients. But, P/TMP had also an efficacy which is maintained since the daily improvement was persistent until the 7th day in the P/TMP versus placebo group. Indeed, more patients who achieved at least a 50% of decrease of pain intensity remained responders until day 7, when treated with P/TMP rather than with placebo, respectively 47.3% versus 33.3% (p=0.015).

Patients were included according to the strict Rome II criteria, which are conservative and underestimate the number of patients having functional intestinal disorders in general practice, e.g. when using Manning or Rome I criteria [28]. On the other hand, patients included in this study were likely to have a diagnosis of IBS and their characteristics at baseline were very similar to that reported in previous French epidemiological studies [28, 29].

In this trial, to be as closed as possible of the usual conditions in primary care, patients previously treated with other antispasmodics before exacerbation of their abdominal pain were included when the daily dose of antispasmodics was stable prior to the inclusion. This choice might have altered our ability to show a significant difference between P/TMP treatment and placebo. This was not the case and a subgroup analysis carried out on the 77 patients receiving concomitant treatment even showed the superiority of P/TMP over placebo with about the same level of difference than that observed on the whole population (although not reaching the significance, p=0.078, probably due to the small sample size).

In conclusion, this placebo-controlled trial demonstrated that P/TMP is effective to provide a fast and significant relief of abdominal pain, during an acute exacerbation of pain, in IBS patients fulfilling Rome II criteria. Our results confirm that antispasmodics can be used on an as-needed basis. Although the population included in this study corresponds to the majority of IBS patients managed in primary care, results may not be applicable to long standing sufferers and patients having a high level of anxiety. Further studies are warranted to demonstrate the sustained efficacy of repeated on-demand treatment during long-term disease management.

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Table 1. Demographic characteristics and symptoms of IBS patients at baseline

	P/TMP n = 151	Placebo n = 149	p
Age (yr)*	47 ± 15	47 ± 14	NS
Gender (female)**	109 (72)	109 (73)	NS
Duration of IBS Symptoms (yr)*	3.7 ± 2.8	3.6 ± 2.4	NS
Bowel habit and other symptoms commonly associated with IBS**			
- **Constipation**	75 (50)	70 (47)	NS
- **Diarrhea**	58 (38)	56 (38)	NS
- **Bloating**	146 (97)	142 (95)	NS
- **Gas**	140 (93)	130 (87)	NS
Frequency of pain episodes**			
Daily	42 (28)	51 (34)	
1 to 3 times / week	61 (40)	60 (40)	NS
Several per month	40 (27)	28 (19)	
Monthly	8 (5)	10 (7)	
Pain intensity (Visual Analog Scale)*	62.0 ± 9.0	61.8 ± 8.5	NS
COVI Anxiety scale score* (min-max : 0-12)	3.4 ± 1.6	3.5 ± 1.7	NS
Number of patients with concomitant antispasmodic agent prior to inclusion	39	38	NS

*Mean ± SD; ** n (%)*

Visual analog scale of pain intensity ranging from 0 to 100 (maximal pain)

Table 2. Abdominal pain intensity at baseline and day 7 (Recording at the visits with the GPs) in the intent to treat population

Pain intensity (Visual Analog Scale)	P/TMP*	Placebo*	Δ**	p
ITT population (n=300)	n = 151	n = 149		
Day 0 (mm)	62.0 ± 9.0	61.8 ± 8.5		0.918
Day 7 (mm)	25.9 ± 20.0	33.8 ± 23.2		0.004
Absolute reduction (mm) (Day 7 – Day 0)	36.1 ± 21.0	28.1 ± 21.7	8.0 ± 2.5 [3.1 ; 12.9]	0.001
Relative reduction (%) ((Day 7 – Day 0)/Day 0)	57.8 ± 31.7	46.3 ± 34.7	11.5 ± 3.8 [4.0 ; 19.1]	0.0029
Responders (%) ***	62.3%	47.0%	15.3%	0.011

*n, Mean ± SD; visual analog scale of pain intensity ranging from 0 to 100 (maximal pain)

** Difference between groups: mean ($CI_{95\%}$)

*** A responder was defined as having a decrease of at least 50% of pain intensity on the visual analog scale between the assessments of baseline and day 7

Figure 1. Flow chart of patients randomised in the trial.

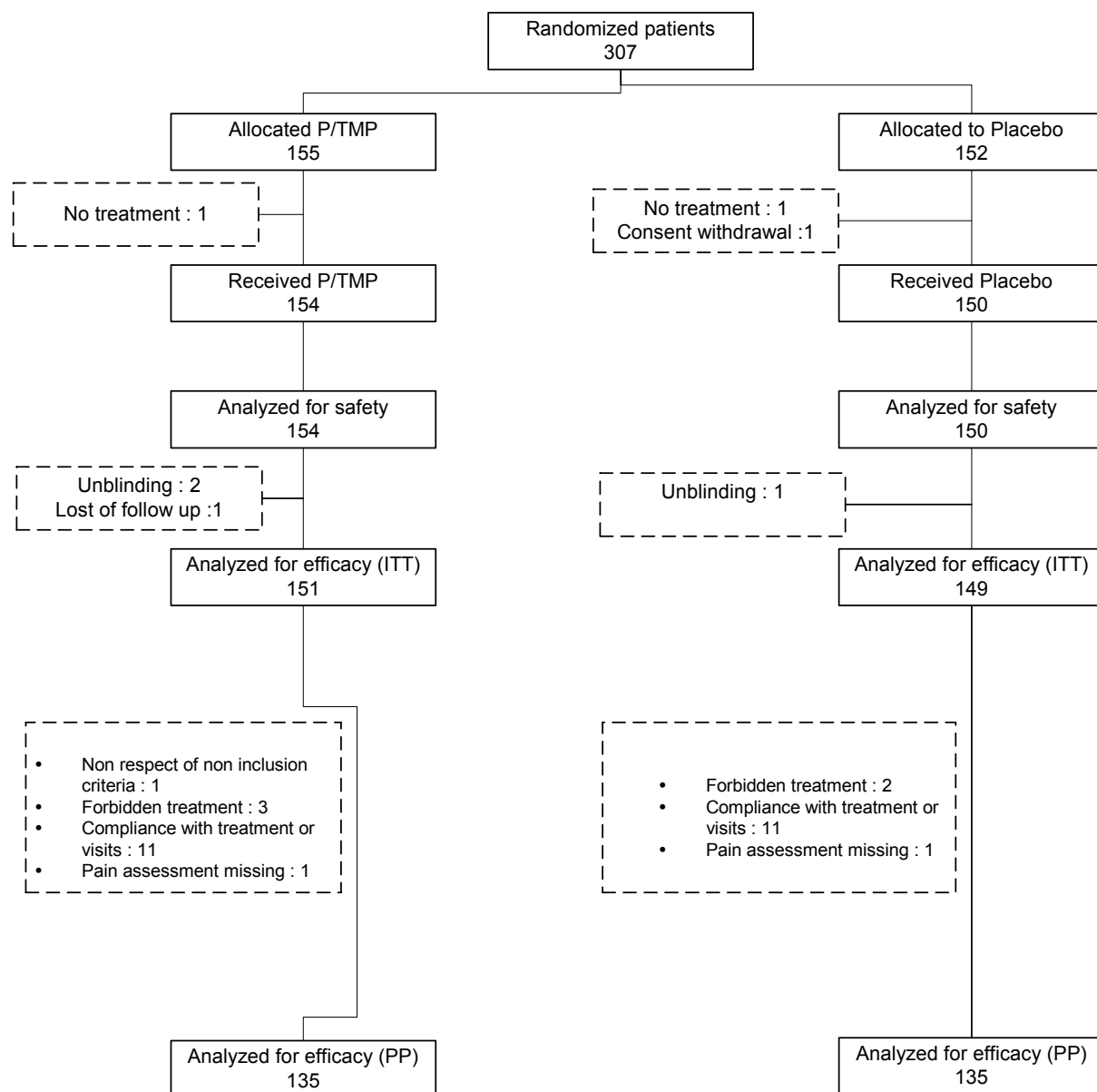Figure 2. Evolution of the daily assessment of pain intensity (diary)

The mean (± SE) daily VAS pain values in each group are presented. The difference between groups is statistically significant at days 4, 5 and 7.

Figure 3. Evolution of the daily assessment of pain relief (diary)

Percentage of patients who answered "a lot" or "complete" pain relief on a 5-point Likert Scale (for clarity, the data have been pooled: "a lot" and "complete relief" have been represented).
The difference between groups is statistically significant from 3rd day until the 7th day (p values shown on the graph.
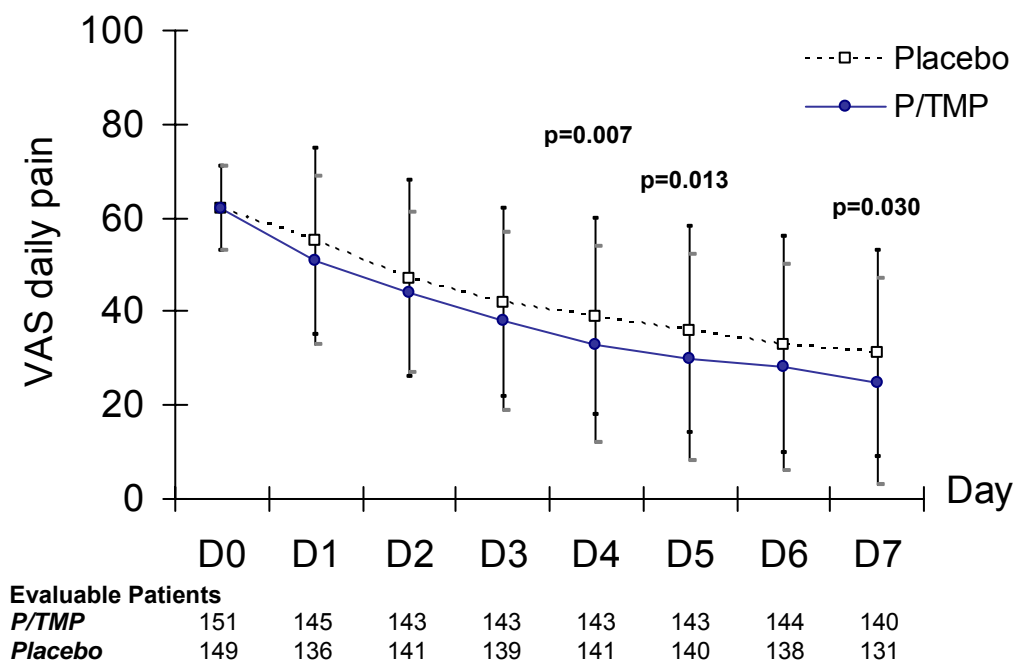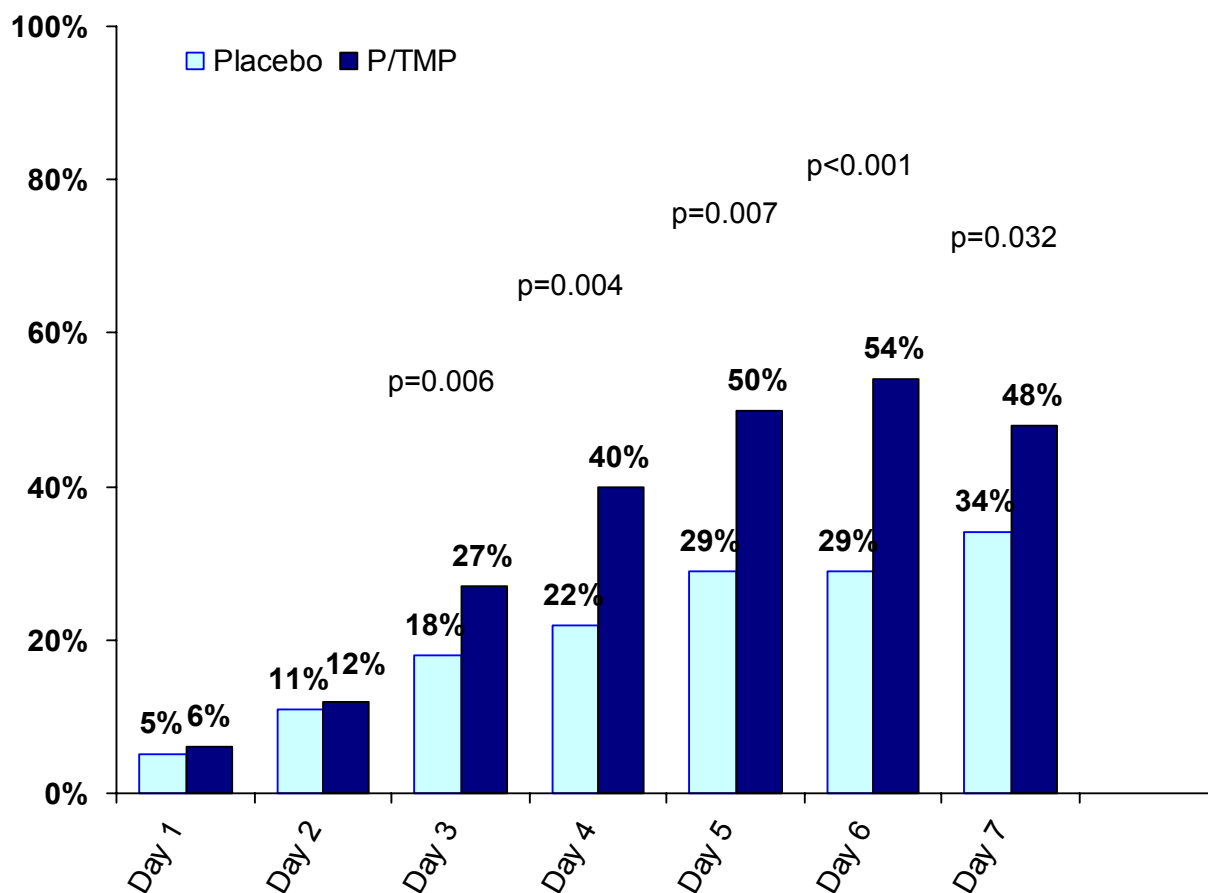
Figure 1. Flow chart of patients randomized in the trial.

Figure 2. Evolution of the daily assessment of pain intensity (diary)

Evaluable Patients	D0	D1	D2	D3	D4	D5	D6	D7
P/TMP	151	145	143	143	143	143	144	140
Placebo	149	136	141	139	141	140	138	131

The mean (± SD) daily VAS pain values in each group are presented. The difference between groups is statistically significant at days 4, 5 and 7.

Figure 3. Evolution of the daily assessment of pain relief (diary)

Percentage of patients who answered "a lot" or "complete" pain relief on a 5-point Likert Scale (for clarity, the data have been pooled: "a lot" and "complete relief" have been represented).

The difference between groups is statistically significant from 3rd day until the 7th day (p values shown on the graph.