Placebo effect in the treatment of duodenal ulcer

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Aims To assess whether frequency of placebo administration is associated with duodenal ulcer healing.

Methods A systematic literature review of randomized clinical trials was undertaken. 79 of 80 trials that met the inclusion criteria. The pooled 4 week placebo healing rate of all duodenal ulcer trials that employed a four times a day regimen was compared with the rate obtained from trials with a twice a day regimen.

Results The pooled 4 week healing rate of the 51 trials with a four times a day regimen was 44.2% (805 of 1821 patients) compared with 36.2% (545 of 1504 patients) in the 28 trials with a twice a day regimen (difference, 8.0% [equal effects model]; 95% confidence interval, 4.6% to 11.3%). Depending on the statistical analysis, the rate difference ranged from 6.0% (multivariable random effects model) to 8.0% (equal effects model). A number of sensitivity analyses showed comparable differences between the two regimens. Most of these sensitivity analyses were not significant, probably because a number of trials were excluded resulting in a loss of power.

Conclusions We found a relation between frequency of placebo administration and healing of duodenal ulcer. We realize that the comparison was based on nonrandomized data. However, we speculate that the difference between regimens was induced by the difference in frequency of placebo administration. A better knowledge of various placebo effects is required in order to make clinically relevant assessments of treatment effects derived from placebo-controlled trials.

Keywords: duodenal ulcer, placebo effect

Introduction

The term placebo has been defined as 'any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without *specific* activity for the condition being treated' [1]. According to this definition, the placebo effect is 'the psychological or psychophysiological effect produced by placebos'. A common method in the evaluation of placebo effects is to equate the results in the placebo group of a clinical trial to the placebo effect [2, 3]. However, the natural course of disease, regression towards the mean, measurement bias, and (unidentified) parallel interventions, may also play a role in the response in the placebo arm of a clinical trial [2].

Before *Helicobacter pylori* eradication became standard treatment, other medical therapies for duodenal ulcers were available from the late 1970s, when the H₂-receptor antagonist cimetidine was introduced [4, 5]. Since then, various drugs with different mechanisms of action have been tested in a large number of randomized clinical trials [6]. The dosage regimens of the drugs changed over the years, starting with a four times a day regimen in the early trials of the H₂-receptor antagonists, through a twice daily regimen, ending in a once daily regimen in the later trials of the H₂-receptor antagonists and proton pump inhibitors. Many trials have directly compared active drugs, but there are also numerous placebo controlled trials. Of the placebo controlled trials, by far the most have evaluated a four times a day or a twice a day administration.

Several authors have commented that randomized controlled trials in duodenal ulcer have given substantially different placebo healing rates [7–9]. It has not been postulated that in duodenal ulcers the frequency of

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placebo administration might influence the healing process. By means of a systematic review we aimed to examine the influence of frequency of placebo administration on duodenal ulcer healing. Therefore we calculated the pooled ulcer healing rate of the placebo arms of all randomized clinical trials with a four times a day regimen and compared this with the pooled placebo healing rate in trials with a twice a day regimen.

Methods

Published trials were located by various strategies, including extensive computer searches of Medline (1966–97), Embase (1974–97), and the Cochrane Library (1997, issue 4), checking reference lists of articles and text books, manufacturers of ulcer medication, and correspondence with gastroenterologists. Criteria for inclusion of the trials in this systematic review were (a) randomization, (b) double-blind methodology, (c) only uncomplicated ulcers (complication defined as bleeding, stenosis or recent perforation), (d) ulcers assessed by endoscopy at baseline and at the end of treatment, (e) healed ulcer as endpoint, (f) placebo administration four times a day (with each meal and at bedtime) or twice a day (in the morning and at bedtime), (g) placebo group taking tablets or capsules (not liquid preparations), (h) 4 week healing rate reported and (i) presentation as full paper, not as abstract. There was no language restriction. If it was not possible to separate duodenal from gastric ulcer in the case of mixed ulcers or if duodenal ulcers and prepyloric ulcers were reported together and the percentage of prepyloric ulcers was greater than 30%, the trial was excluded. In case of multiple publications of the same trial, the earliest full publication determined the year of publication, but the information from all publications was used. As most of the trials reported 4 week healing rates, we excluded trials that did not report 4 week healing rates. Trials assessing the efficacy of any of the following drugs were not included in the review: proton pump inhibitors because the expected benefit from the experimental treatment is not in the same range as the other drugs, possibly resulting in different expectations of both patients and physicians; colloidal bismuth subcitrate because it has mainly been evaluated as liquid preparations; pirenzepine because it has mainly been evaluated using a three times a day regimen.

Relevant data for the evaluation were extracted from text, tables, and figures of the publications. In many trials the ulcer healing rate was computed by dividing the number of patients with a healed ulcer by the total number of evaluable and compliant patients. Our analyses are based on these reported healing rates. Differences in healing rates between placebo regimens were assessed by equal, fixed, and random effects models [10]. The equal

and fixed effects models assume all trials to be similar in that they share the same underlying healing rate, observed differences between healing rates are thus considered to be only due to chance. In the equal effects model, for each treatment regimen the pooled healing rate is computed as follows: the total number of healed patients divided by the total number of patients, this means that an *n*-weighted mean healing rate is computed. In the fixed and random effects analyses the logit of the healing rate is modelled. In the fixed effects model each study is weighted by the inverse of its sampling variance. Adjusting for differences between trials was employed in a multivariable fixed effects analysis using linear regression analysis with trial characteristics as independent variables and the logit of the healing rate as dependent variable [11]. For univariate random effects analysis the model as proposed by DerSimonian & Laird was used [12]. Random effects models incorporate potential heterogeneity of the healing rate among different studies by assuming that each study estimates a unique healing rate. A multivariable random effects analysis was carried out using a mixed linear model with study as random factor and all others as fixed factors. In the multivariable analyses, for trials with missing data, a dummy variable was added to the model and the overall mean substituted as observed value. Homogeneity of observed healing rates was assessed using chi-square tests of independence [10]. Differences between treatment regimens are presented as means with 95% confidence intervals (CI). Unless specified, all analyses are based on the multivariable random effects model.

Results

Eighty trials met the inclusion criteria. One trial was excluded because only patients were included who were refractory to histamine H₂-receptor blocker therapy [13]. This left 79 trials, reported in 78 publications, for our review (appendix). Fifty-one studies employed a four times a day regimen, 28 employed a twice a day regimen. Trials with twice a day regimens were more often carried out in the United States (Table 1); patient characteristics showed some differences between the two placebo regimens (Table 2).

In the four times a day regimen, 805 of 1821 patients (44.2%) were healed after 4 weeks of placebo treatment, while in the group that took a placebo twice a day 545 of 1504 patients (36.2%) were healed (difference, 8.0% [equal effects model]; 95% CI 4.6%, 11.3%). Table 3 shows equal, fixed, and random effect estimates of the difference in healing rate between the two dosage regimens. The multivariable fixed effect model, adjusted for differences between trials with regard to geographical area of study (United States *vs* all other regions), experimental drug (H₂-receptor antagonist *vs* all other

Table 1 Characteristics of studies included in the systematic review of four times a day *vs* twice a day placebo administration in duodenal ulcer healing.

Study characteristic	Four times a day regimen		Twice a day regimen	
	Studies (n = 51)	Patients (n = 1821)	Studies (n = 28)	Patients (n = 1504)
<i>Antacids allowed?</i>				
Yes	45 (88%)	1599 (88%)	25 (89%)	1413 (94%)
No	3 (6%)	141 (8%)	1 (4%)	49 (3%)
Unknown	3 (6%)	81 (4%)	2 (7%)	42 (3%)
<i>Comparator drug*</i>				
H ₂ -receptor antagonist	35 (68%)	883 (49%)	21 (75%)	1120 (74%)
(Synthetic) prostaglandin E ₁	5 (10%)	310 (17%)	2 (7%)	140 (9%)
(Synthetic) prostaglandin E ₂	5 (10%)	368 (20%)	3 (11%)	130 (9%)
Sucralfate	6 (12%)	260 (14%)	2 (7%)	114 (8%)
<i>Geographical area</i>				
US	5 (10%)	267 (15%)	12 (43%)	967 (64%)
Europe	26 (51%)	954 (52%)	9 (32%)	344 (23%)
Other	20 (39%)	600 (33%)	7 (25%)	193 (13%)
<i>Year of publication</i>				
1977–79	21 (41%)	578 (32%)	0 (0%)	0 (0%)
1980–84	21 (41%)	656 (36%)	14 (50%)	444 (29%)
1985–89	7 (14%)	396 (22%)	14 (50%)	1060 (71%)
1990–94	2 (4%)	191 (10%)	0 (0%)	0 (0%)

*One trial compared both an H₂-receptor antagonist and sucralfate against placebo and is categorized under H₂-receptor antagonists.

Table 2 Characteristics of patients with duodenal ulcer included in the placebo groups of the trials of duodenal ulcer healing, by treatment regimen.

	Four times a day regimen (51 studies, 1821 patients)				Twice a day regimen (28 studies, 1504 patients)			
	Number of studies with data	Number of patients	Weighted mean	Range	Number of studies with data	Number of patients	Weighted mean	Range
Male (%)	38	1436	80.4	44–100	19	1166	71.8	55–100
Age (years)	33	1196	42.3	27–58	19	1146	45.4	35–52
Smokers (%)	16	722	61.1	33–79	17	1124	57.5	44–84
Length of history (years)	19	544	9.1	2.1–14.9	10	412	7.1	4.2–14.0
Ulcer diameter (mm)	6	362	7.9	6.2–9.3	6	388	8.4	5.8–8.9

Table 3 Differences in healing rate between groups with four times (51 trials, 1821 patients) and twice a day placebo administration (28 trials, 1504 patients) in randomized clinical trials of duodenal ulcer.

Statistical method	Univariate Difference in healing rate (%)	95% Confidence interval	Multivariable Difference in healing rate (%)	95% Confidence interval
Equal effects	8.0	4.6,11.3	—	—
Fixed effects	7.1	4.2,9.9	7.4	3.3,11.3
Random effects	7.0	0.9,13.4	6.0	0.3,12.7

drugs), antacids allowed (yes *vs* no/unknown), gender, age, and smoking, yielded a 7.4% difference (95% CI 3.3%, 11.3%). Estimating variation between study outcomes, revealed significant heterogeneity for both placebo regimens ($P < 0.001$), so random effects analyses were also performed. The univariate random effects model

gave a 7.0% difference (95% CI 0.9%, 13.4%). Incorporating the same set of trial and patient characteristics as in the fixed effects analysis, the multivariable random effects model yielded a 6.0% difference (95% CI 0.3%, 12.7%) in healing rates.

Limiting the analysis to studies that were carried out

in the United States a 10.7% difference was observed (95% CI -3.2% , 20.5%). Excluding trials that were published before 1980 did not change the difference between treatment regimens (6.4%; 95% CI -2.3% , 15.5%). Within the subgroup of studies that evaluated an H₂-receptor antagonist against placebo, a 3.0% difference was found (95% CI -1.1% , 8.6%). Both treatment regimens had 11 studies with more than 50 patients in the placebo group. In these larger trials the difference was 5.3% (95% CI -7.0% , 14.2%).

Discussion

The results of our review suggest a relation between frequency of placebo administration and healing of duodenal ulcer. Depending on the method of statistical analysis, the difference in mean pooled 4 week healing rates ranges from 6% to 8%, the higher healing rate observed in trials with a four times a day regimen. What might have caused the difference in healing rates between the two groups?

First, the pooled healing rates of the two treatment regimens were obtained from different trials, so it is possible that the two groups were not comparable. Patients in the trials with a four times a day regimen were slightly more often male, were somewhat younger, and were more often smokers. Male gender, younger age, and smoking have been associated with lower healing rates [6], so adjusting for these baseline characteristics would have resulted in a larger rather than smaller healing rate difference. Half of the patients in trials with a four times a day regimen originally came from trials that evaluated an H₂-receptor antagonist, whereas in trials with a twice a day regimen 75% of patients came from trials that evaluated an H₂-receptor antagonist. When the analysis was restricted to trials with an H₂-receptor antagonist as the experimental drug, the difference was 3%. This means that adjusting for type of comparator drug in the multivariable analysis decreased the difference. The result was that the multivariable analyses which included gender, age, smoking, and type of comparator drug, yielded differences that were comparable with the univariate analyses. Moreover, the observed difference between regimens could be due to residual confounding. Although we adjusted for a number of possible confounders, we can not rule out that in this nonrandomized comparison the observed difference was caused by some unrecognized confounding factor or factors.

Second, the trials with a twice a day placebo administration were carried out from 1980 onwards, whereas trials with a four times a day administration were also conducted at the end of the 1970s. The analysis that excluded trials published up to 1980 found the same difference between regimens, although it was no longer

significant, probably because 21 trials were excluded resulting in a loss of power. The same results were obtained when we restricted the analysis to trials that were published from 1985 onwards. This eliminates time dependent influences on the healing rate such as inclusion of more treatment resistant patients in later trials. Furthermore, trials with a twice a day regimen were more frequently carried out in the United States. The analysis that included only trials from the United States showed a 10% difference which just failed to achieve statistical significance. However, this analysis was based on only 17 trials which reduces statistical power enormously. Hence we think that calendar time and geographical area are not a main source of confounding.

Third, in numerous trials the statistical analysis was based on the number of evaluable patients, while some trials also excluded patients from the analysis who did not comply with the treatment regimen. In theory, patients on a four times a day regimen are more likely to be noncompliant. So analysing healing rates of compliant and evaluable patients only, could have resulted in biased healing rate estimates. However, many reports did not specify the number of excluded patients because of noncompliance. Therefore we were not able to examine the impact of noncompliance on the healing rate. Using the total number of randomized patients in the denominator instead of the number of evaluable and compliant patients did not change the healing rate difference between the two placebo regimens.

Fourth, it would be possible that the physician who decides to include a patient in a trial, makes an assessment whether an individual patient will comply with a certain drug regimen. Therefore the group of patients in the trials with a four times a day regimen might be different from the patients in the twice a day trials. In a randomized trial to evaluate the efficacy of lipid-lowering drugs in the therapy of coronary heart disease, patients in the placebo arm of the trial who complied with the prescribed treatment regimen (took at least 80% of placebo capsules) had a lower 5-year mortality compared with the noncompliers [14]. We may hypothesize that in this trial, among other reasons, the frequency of placebo administration had some effect on mortality, or that patient compliance was related to other factors which are associated with mortality. Although we consider it unlikely, similar selection bias might have occurred in the trials that employed a four times a day regimen may explaining the difference between the placebo regimens.

Fifth, the difference in healing rates could be the result of the frequency of placebo administration. Patients on the more intense regimen might have felt they were receiving more treatment. This might have induced a psychophysiological response: decreased gastric acid production, increased prostaglandin synthesis, a psychoneuro-

immunological response against *Helicobacter pylori*, or a combination of these. Additionally, subjects on the four times a day regimen might have paid more attention to the composition and timing of meals.

Some trials have evaluated a once daily drug administration against placebo [15–19]. These trials originate mainly from the United States and were published in the late 1980s and 1990s. In one trial [15], a dose validation study of once daily cimetidine, the placebo regimen was four placebos at night. The healing rate in the placebo group was 45%. The healing rate in the remaining four trials ranged from 31% to 61%.

A number of small randomized controlled trials have evaluated the association between frequency of placebo administration and efficacy with inconsistent results [20–22]. In 1970, Rickels *et al.* [21] concluded that ‘... the dosage of the placebo may be a significant and determining factor in the placebo response, although this is not clearly determined.’ Since then, little research on this subject has been carried out, with the exception of a study by Ilnyckij *et al.* who recently demonstrated that the placebo response in ulcerative colitis is greater in trials with more frequent study visits [23]. We realize that it is not possible to test our findings in a randomized clinical trial. Blinding is not possible and it would be unethical since it is now generally accepted that duodenal and stomach ulcers are causally linked to *Helicobacter pylori* infection [24] and effective therapy is available. Therefore we feel that our approach to this question, although not perfect, is the best available option.

In this systematic review we have shown that there is a relation between frequency of placebo administration and duodenal ulcer healing. We realize that the comparison was based on nonrandomized data. Therefore we speculate that the difference between regimens was induced by the difference in placebo administration. Other factors such as reputation of the doctor, the patient’s attitude towards the expected benefit of the treatment, quality of the physician–patient communication, and perceptual characteristics of the treatment might also influence therapeutic outcomes. Although these factors are widely recognized in medicine, they have generally been regarded as random error in research. It is important to identify these factors in order to optimize clinical practice and improve the methodology of clinical research. We encourage researchers in other fields of medicine to look for comparable examples, either from combining results available in the literature or from new experimental studies.

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Appendix

Trials that employed a four times a day regimen

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