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Effect of Information on Reported Adverse Events in a Placebo-Controlled Trial

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Abstract

Objective: Although placebo controls are a standard measure in clinical trials the mechanisms underlying placebo effects are still not fully understood. We hypothesised that information about the likelihood of receiving placebo might influence the perception of adverse effects in volunteers participating in a clinical trial.

Methods: Healthy subjects received either nifedipine 20mg or placebo in an adaptive two-stage crossover study. Sixty subjects were randomised to a group given either correct (50% chance) or misleading (100% chance) information about the likelihood of receiving the active drug. A sum of the severity scores from visual analogue scales over all individual adverse effects was defined as the primary endpoint.

Results: The analysis revealed no difference in the primary endpoint between the two groups. This lack of difference may in part be attributable to a conditioning effect as on the first study day higher symptom scores were reported by the participants than on the second study day. Furthermore, the day effect seemed to arise mainly when the first day treatment was the placebo. For the placebo the day effect was clearly significant ($p = 0.012$), with higher scores on the first day. A further explorative finding in patients given placebo was a tendency for higher scores in the group with the misleading information ($p = 0.08$). Nothing of that sort was found in the analysis for active treatment. The day effect collapsed and the factor information did not show any tendency of being a potential influence.

Conclusions: In the present study we did not find a statistically significant effect of misleading information on reported adverse events. The large treatment and day effects observed made it difficult to detect a potential small information effect. However, this study excluded a strong and relevant effect of information on the frequency and severity of reported adverse events.

Clinical trials are conducted to demonstrate the efficacy of an intervention. Placebo control groups in clinical trials are essential to minimise bias and to allow for discrimination of effects caused by the test treatment from effects caused by other factors, such as the natural course of disease and observer or patient expectations. The enrolment of patients in controlled groups is only permissible under well

defined conditions and both written and oral consent must be obtained. Therefore, participants in clinical trials have to be informed about the chance of being randomised into a control group (i.e. receiving placebo) and about the likelihood and potential severity of expected adverse events.

Since the introduction of the term 'placebo' in medical literature[1] there has been much debate about the definition of placebo and placebo effects, their magnitude and the underlying mechanisms. Recently, a systematic review that analysed randomised trials comparing placebo with no treatment found no significant pooled effects on binary and objective outcomes. However, in continuous outcomes and pain a small possible effect of placebo was seen.[2] In most of the trials included in this systematic review, the no-treatment group still involved some form of treatment. Furthermore, the study populations differed widely concerning the disorders and the active treatment used. Therefore, no definite conclusions about the clinical power of placebo interventions can be drawn.

Several theories, including conditioning,[3] expectation[4] and endorphin effects,[5] have been considered as possible explanations for the placebo effect. Expectancy, in turn, is clearly dependent on the information provided. Although these factors are not well defined and the proportion of their contribution is unclear, placebo is pragmatically used in controlled trials to demonstrate the efficacy and tolerability of medical interventions.

The influence of study design on efficacy and adverse effects of NSAID trials was discussed recently in a review by Rochon et al.[6] The investigators examined whether the inclusion of a placebo arm would affect the efficacy and frequency of adverse effects in clinical trials. Withdrawal because of inefficacy was found to be more likely in trials comparing drugs with placebo whereas withdrawal because of adverse effects was found to be more likely in trials comparing two active drugs. The investigators concluded that for a conservative appraisal of new drugs the appropriate study design for the evaluation of drug efficacy would be a placebo-controlled trial. Active controlled trials should be preferred when adverse effects are the major outcome of interest. However, in light of possible placebo effects, and assuming that factors, such as anxiety, expectancy, setting effects, conditioning, regression to the mean and the natural course of disease also influence the likelihood of occurrence of adverse effects, this conclusion seems unfounded.

In the present study we have investigated the influence of information on the frequency and severity of adverse events of a single oral dose of nifedipine in healthy volunteers. Based on the findings discussed previously by Rochon et al.,[6] we hypothesised that participants who have no reason to believe that they might be given an inactive agent will report adverse events more frequently than participants who know that they have a 50% chance of swallowing a 'dummy pill'. Although this assumption seems plausible, it has never been tested in a trial specifically designed to study the influence of information regarding treatment on adverse events in clinical trials.

Methods

The study was approved by the local ethics committee and was performed in accordance with the European Commission Good Clinical Practice guidelines.

Study Subjects

Twenty-five male and 37 female healthy volunteers were included in the study. Subjects were assessed to be healthy based on physical examination results and medical history. Two subjects had to be excluded because they did not meet the inclusion criteria: the first because of a suspicion of hypertension, and the second because of a chronic disease of the thyroid gland. Therefore, a total of 60 volunteers (24 men and 36 women, aged 19–46 years) completed the study.

Study Design

The study was conducted using a double-blind factorial design. All participants were randomly allocated into two study groups (figure 1). Participants in group A (n = 30) received the misleading information that two different formulations of the active study medication would be given to compare tolerability. Participants in group B (n = 30) were correctly informed about the 50% chance of receiving placebo to test the active drug for its tolerability

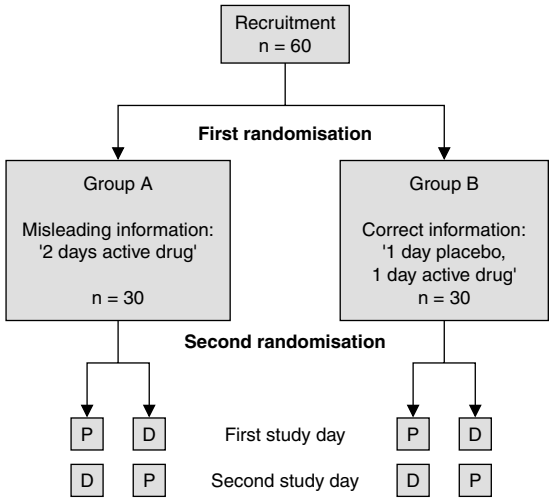

Fig. 1. Flow-chart illustrating study design and sequence of randomisation procedures. **P** indicates administration of placebo; **D** indicates administration of the active drug (nifedipine 20mg, single dose).

compared with placebo. Within each study group the active drug was alternated with the placebo in a crossover design. The sequence 'active drug-placebo' or 'placebo-active drug' was randomised (second randomisation). The washout period between the 2 study days was 4–10 days.

All volunteers were recruited by a single investigator (M. Ossege). Volunteers were contacted by the investigator, and those who spontaneously asked about ongoing studies at the study centre were informed about the study medication, dose and schedule (2 study days). All volunteers who expressed interest in participating in the trial were randomly assigned to one of the two study groups according to a computer-generated list. The volunteers were not informed about the real purpose of the study, the randomisation or the fact that there were two groups.

Different informed consent protocols were designed for the two groups. The informed consent for both groups was identical for the aim of the study (tolerability of nifedipine in a new formation), time exposure and health risks. In the chapter about health risks, the volunteers were informed about the adverse effects of nifedipine, namely dizziness, heat sensation, flushing of the head, headache, weakness, nausea, tremor, nervousness, fatigue, palpitation, dyspnoea and sore throat and that these are transient in nature. The informed consent for group B included the information that the volunteers would be given either two capsules of nifedipine 10mg or two capsules of placebo (corn starch) each study day in random order, whereas group A was informed that they would receive two capsules of nifedipine 10mg on both study days. Actually, both groups received placebo and nifedipine in randomised order. Therefore, group A was misleadingly informed and group B was correctly informed.

The participant information and the informed consent form (as randomised) were given to the subjects. No subject resigned from participation after reading the informed consent.

Study Medication

Nifedipine immediate release, a widely used antihypertensive agent with a well known spectrum of adverse drug effects, was chosen as the study medication. No health risk was expected from a single dose of nifedipine 20mg. Minor adverse drug reactions (e.g. headache) were not only expected but were intended as the main outcome variable.

Assessments

The two groups of participants were asked to fill out a standardised checklist of 13 frequent adverse events associated with the study drug (dizziness, heat sensation, flushing of the head, headache, weakness, nausea, tremor, nervousness, fatigue, palpitation, dyspnoea, sore throat or other) in order to assess the difference between the severity and frequency of reported adverse events. The assessment was done 1 hour after drug administration. Participants who had questions regarding the checklist were answered by a single investigator who was masked concerning the assignment to treatment (drug or placebo). All the reported symptoms were quantified using a 100mm visual analogue scale. For safety reasons heart rate and blood pressure were measured during the trial.

Statistical Analysis

An adaptive (flexible) two-stage design was chosen to access the 'learning-from-experience' paradigm in the present study.[7] This seemed to be reasonable, because little is known about the re-

sponse pattern of healthy volunteers in such an experimental environment. A classical approach would have been to run a sufficiently large pilot study and plan the follow-up main study based on the observed results. Instead we planned an internal pilot study as a first stage where the results would be used in the statistical analysis along with the results of the forthcoming second stage. In this article the data from the pilot study are not 'wasted' but are incorporated in the statistical analysis. The principle was to calculate test statistics from each stage and to combine them in a predefined way. It allows mid-trial design modifications based on all the information collected at the interim analyses from inside or outside the trial without compromising on overall type I error probability.[8,9] Potential adaptations in this design were prescheduled to modify the primary outcome variable for the second stage (in case the first stage definition of the outcome scores seemed to be improvable),[10-12] and sample size re-assessment (since there was very little knowledge on the distribution and variability of the outcome variables) was performed. Sample sizes of 60 and 140 subjects for the two stages were planned in advance, with the option to reassess the second-stage sample size of 140 subjects in the interim analysis.

The sum of the values over the 13 items of the analogue scale of the 'adverse effect case record form' was pre-defined as the primary endpoint in the interim analysis after the first stage. A comparison between the groups was performed on sums of these scores over both treatments (active drug/placebo) per patient by the one-sided Wilcoxon rank sum test leading to a p-value p_1.

For the final analysis a p-value p_2 was to be calculated from the data of the second stage for the primary endpoint (which could have been suitably modified in the interim analysis). The overall final test will use the 'inverse-normal' combination function of one-sided p-values.[9]

O'Brien and Fleming[13] boundaries for an overall one-sided level $\alpha = 0.05$ were applied for early stopping in the interim analyses.

Beyond the scheduled protocol an explorative analysis of variance was performed after stopping the trial for futility. The sum of the values of the analogue scale over all adverse effects per day was calculated by analysis of variance with the fixed factors: information (correct or misleading), study day (1, 2), treatment (placebo, active drug), sequence (placebo-active drug versus active drug-placebo), the interactions between information and treatment, the interactions between information and day, and the random factor participant. Two-sided p-values were reported throughout for this explorative analysis.

Results

Demographic data of the study participants were equally distributed over both study groups (table I). No noticeable difference (one-sided Wilcoxon test, $p_1 = 0.48$) in the primary endpoint between the misleadingly informed group and correctly informed group was found. The analysis for interaction between the treatment and information, based on intra-individual treatment differences of the sum scores, was also not statistically significant (one-sided Wilcoxon rank sum test, $p = 0.16$).

As a result of the very small effect found for the influence of information, there was not sufficient probability of obtaining a significant result in the final analysis when applying a reasonably small sample size at the second stage. For a calculation we optimistically assumed that, despite the very small observed effect, the effect of information would be half of the between-treatment effect observed at the first stage. Under this assumption the probability of obtaining a significant result with the adaptive combination when performing a second stage (140 subjects, 70 per group) would be 25%. On the other hand, under this optimistic assumption the probability of observing an unconvincing p-value >0.48 for the primary question at the first stage, as found in our study, was only 20%. (Both calculations were based on normal approximations using the observed

Table I. Demographic data of the study participants

Characteristic	Correct information group	Misleading information group
Number of volunteers	30	30
Men (%)	65	55
Women (%)	35	45
Age (mean ± SD)	27.7 ± 5.8	27.4 ± 5.7
BMI (mean ± SD)	22.3 ± 2.9	22.6 ± 3.1

BMI = body mass index.

first-stage variability.) An enlargement of the sample size could not be justified on ethical and economical reasons. Therefore, we decided to stop the trial for futility.

While performing the explorative analysis of variance, assay sensitivity could be established with a clear treatment effect (all following p-values two sided, p = 0.002). Larger scores were found on the first treatment day (p = 0.014). Figure 2a (placebo) and figure 2b (active control) show the severity of reported adverse events per day, treatment and information (means ± standard error of the mean).

The largest contribution to the treatment effect was dizziness. Eleven subjects only reported dizziness when taking the drug, one subject when only taking the placebo and eight subjects reported dizziness when taking either treatment. Further major contributions were flushing of the face, heat sensation and fatigue. Reporting of the item 'other adverse effects' was practically equal under both treatments. The mean severity of adverse events for the different study groups is presented in table II.

On the first day higher adverse event scores were reported by the participants. Contrary to the treatment effect, the major contribution to the day effect was the category 'other adverse effects'. Ten subjects reported other adverse effects on the first day but no such adverse effects on the second day, two subjects reported other adverse effects only on the second day and two reported other adverse effects on both days. The day effect seemed to arise mainly when the first day treatment was the placebo. Although there were hints of noticeable interactions, we performed two-way analyses of variance separately per treatment, with the factors information, day and their interaction. For the placebo the day effect was clearly significant (p = 0.012), with higher scores on the first day. A further explorative finding in patients given placebo was a tendency for higher scores in the group with the misleading information (p = 0.08). Nothing of that sort was found in the analysis for active treatment. The day effect collapsed and the factor information did not show any tendency of being a potential influence. Taking the square roots of the sum scores for the analyses in order to reduce skewing of the distribution or using the number of adverse effects as dependent variables did not substantially change these findings.

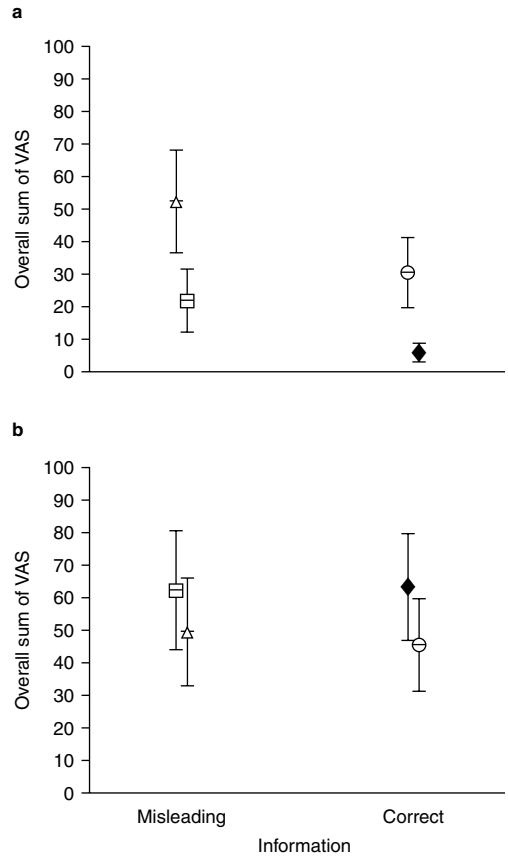

Fig. 2. (a) Mean ± standard error (SE) of the sum of severity of adverse events to placebo. **(b)** Mean ± SE of the sum of severity of adverse events to active drug. In each information group, left bars show the first day, right bars show the second day. Data coming from the same group of persons are denoted by identical symbols. Triangle and circle patients received the sequence placebo-active drug. Diamond and square patients received the sequence active drug-placebo. **VAS** = visual analogue scale.

Discussion

The present study tested the hypothesis that being informed about receiving a placebo might influence the perception of adverse effects in volunteers participating in a clinical trial. The main finding was the absence of a difference in the primary endpoint between the groups, indicating that information regarding the placebo did not influence reported adverse events. However, when performing an explorative analysis of variance, assay sensitivity could already be established in the rather small first-stage sample. There was a clear difference between the

Table II. Severity of adverse events recorded by the participants given placebo and drug subdivided by information. Values are expressed as millimetres of a visual analogue scale (range 0–100mm)

Medication information	Placebo				Drug			
	misleading information		correct information		misleading information		correct information	
	mean	SE	mean	SE	mean	SE	mean	SE
Dizziness	1.73	0.9	3.33	1.88	4.4	1.62	7.83	3.03
Heat sensation	2.17	1.3	0.3	0.22	7.73	3.88	9.13	3.13
Flushing of the head	1.1	0.78	0.1	0.1	7.13	3.72	4.03	1.84
Headache	3.93	2.04	2.8	1.04	10.67	3.53	6.5	2.57
Weakness	3.7	2.08	0.83	0.6	3.23	1.52	4.83	1.71
Nausea	1.13	0.84	2.83	2.83	0.13	0.13	2.6	2.07
Tremor	0	0	0.13	0.13	1.17	0.85	0.8	0.48
Nervousness	1.47	0.91	0.13	0.13	0.03	0.03	1.13	0.9
Fatigue	15	4.59	4.17	1.79	12.83	4.04	12	3.68
Palpitation	0	0	0.6	0.6	2.37	1.01	2.27	1.9
Dyspnoea	0	0	0	0	0.23	0.23	0	0
Sore throat	0	0	0	0	0.07	0.07	1.4	1.05
Other	6.83	3.62	2.97	1.81	5.77	2.57	1.77	1.77

SE = standard error.

active treatment and placebo in the primary variable. This indicates that the trial was not underpowered despite the small number of participants and the large variances.

On the first day higher adverse event scores were reported by the participants. Contrary to the treatment effect with dizziness as the largest contribution, the major contribution to the day effect was the category 'other adverse effects'. Carry-over effects, defined as the residual effect of the previous treatment, cannot explain these findings because no pharmacological interaction is expected. It may be explained by a lower level of anxiety due to habituation. Furthermore, in the subjects that received the drug on the first day and placebo on the second, classical conditioning might have occurred. In classical conditioning an association is developed between the neutral stimulus (placebo) and the unconditioned stimulus (active drug). On the second day a conditioned response could be seen, although only one conditional stimulus-unconditional stimulus pairing is sub-optimal for conditioning to take place. However, it is not possible in the present design to investigate the role of conditioning, since we do not know how the participants would score on reactions such as headache, weakness, nausea, tremor, nervousness or other effects just by being exposed to the environment in which the study was conducted, in the absence of the administration of any tablets. Therefore, it is not known whether the adverse events to placebo reported in the present study are in fact due to the placebo tablets or merely reflect the novel situation of the study environment.

The evidence of a differential information effect confined to the placebo or the active drug alone may indicate that averaging over both treatments has led to a dilution of the information effect. After the volunteers received correct information, a high level of reported adverse events was observed. Therefore, there may not have been enough leeway for those receiving misleading information. In addition, the large treatment and day effects observed make it difficult to detect a potentially small information effect. The influence of information in a crossover design is compared against the between-subjects variability and, moreover, may depend on the day and the treatment in a way too complicated to be recovered from statistical analysis.

A number of clinical trials have been conducted to investigate the effect of information on outcomes. They provided inconsistent results that appear to be attributable to the different study settings: in a randomised controlled trial it was found that changes in the adverse events frequency information in a patient information leaflet affects the number of adverse events reported.[14] Sedative medication was

given to participants in a clinical trial crossed with information that was agonistic or antagonistic, and it was found that the reported tension was modulated by the stimulant information.[15] The interaction of psychological stimuli and pharmacological agents on airway reactivity in patients with asthma has also been investigated and a correlation between airway reaction and information given about the effect of the inhalant was found.[16] However, in patients with chronic pain, no difference between positive and neutral expectancy groups regarding the analgesic effect of the medication was observed.[17]

Conclusion

In the present study we did not find a statistically significant effect of misleading information about the likelihood of receiving placebo on reported adverse events. The large treatment and day effects observed made it difficult to detect a potential small information effect. Furthermore, classical conditioning might have occurred, which could not be adequately assessed in the present study because of the lack of information on the base rate of adverse events. However, this study excluded a strong and relevant effect of information on the frequency and severity of reported adverse events.

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