Influence of the behaviour pattern on the nocebo response of healthy volunteers

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The occurrence of a nocebo effect after placebo administration to healthy volunteers in a Phase I trial was analysed according to their type of personality (Bortner Rating Scale). More subjects with a behaviour pattern A (competitive and aggressive) (50%) described subjective side effects of the placebo than type B subjects (17%, $P = 0.03$). The volunteers who had nocebo effect had a higher Bortner score (BS) than did placebo non-responsive subjects ($P = 0.05$). The BS was 205 for paramedical staff, 189 for medical and dentistry students, 173 for non-science students and 161 for science students ($P < 0.04$). The nocebo response was not statistically correlated with professional status. These results suggest that volunteer’s type of personality might influence the reporting of subjective symptoms after placebo, and therefore impair the evaluation of new drugs in Phase I clinical trials.

Keywords placebo nocebo personality clinical trial

Introduction

The placebo response depends greatly on the subject’s personality and psychological factors [1]. The opposite of the placebo effect is the nocebo effect, that can be activated by negative expectations [2]. It results in negative side effects instead of a positive or neutral response to a placebo [3] and may be most important in Phase I clinical trials. A high frequency of placebo-related side effects could impair the evaluation of a new drug and prevent its further clinical development [2]. A subject’s personality type might influence the reporting of subjective symptoms [4]. The Bortner Rating Scale (BRS) is widely used to measure behaviour patterns and identify two main types of personality, types A and B. Type A subjects are more competitive, hard-driving, hurried and aggressive than type B [5-6], and therefore more likely to respond to a placebo with subjective, negative side effects. Since most of the volunteers in Phase I studies are medical students or paramedical staff who usually have a type A personality [7], this study analyses the nocebo response of volunteers participating in a non-invasive Phase I clinical trial, according to their type of personality.

Methods

A total of 52 non-smoking healthy subjects (26 males, 26 females), mean age 23.5 ± 3.2 years [19-36] participated in a clinical Phase I trial of the tolerance of a new paracetamol eyedrop; they were selected after a standard medical examination and a biological screening, including evaluation of their personality type on the BRS. The Bortner self report consisted of 14 pairs of adjectives (not competing—very competitive) or phrases (can wait patiently—impatient when waiting), separated by a horizontal line. Each extreme represented a contrasting behaviour, type A or type B. The volunteers were asked to indicate the point on the line that best described their own behaviour. The Bortner questionnaire scale was 14–336: type A subject scores were above 196.5 and type B scores were below 196.5 [5].

Each subject received randomly a single drop of placebo in one eye and a single drop of the active drug in the other eye 4 times a day for 7 days. Subjective tolerance was evaluated from the self-assessed criteria: itching, burning, aching, ocular discomfort and photophobia, on verbal scales. The study was double-blind, and after volunteers were told they would be

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given randomly placebo in one eye and active drug in the other, further verbal interaction was kept to a minimum. Placebo formulation was a standard neutral one used in over the counter drugs and well tolerated in ocular pharmacology (sodium disulphite and sodium chloride in phosphate buffer, pH 6.9). Before and 2 h after the first administration and on the last day, each subject underwent an ophthalmic examination, including biomicroscope and slit lamp examinations, and measurement of visual acuity and aesthesiometry to evaluate the tolerance objectively. The study was approved by the Marseille Ethics Committee and all subjects gave their informed consent.

The scores are expressed as means ± s.d. Continuous data were compared by non parametric Mann-Whitney and Kruskal-Wallis tests; categorical data by the Chi-squared test with continuity correction. All tests were two-tailed and P values ≤ 0.05 were considered to indicate statistical significance.

Results

The Bortner scores indicated that 36 subjects (69%) had a type B behaviour pattern (mean 167.4 ± 19.6) and 16 (31%) had a type A pattern (mean 223.2 ± 23.3) (Table 1). Fifty per cent of type A subjects described mild to moderate subjective side effects in the eye receiving placebo, while 17% of type B subjects described side effects (P = 0.03). There was no objective abnormality at any time in either group. The subjects asymptomatic after placebo or describing nocebo effect were statistically comparable for age, sex ratio, professional status, social level and motivation for participation in clinical studies. However the 14 subjects (both type A and B) describing nocebo effect had a higher mean BS than the 38 placebo non-responsive subjects (201.1 ± 42.2 vs 178.5 ± 27.4, P = 0.05). Fifty per cent of the type B subjects felt no sensation at all in the eyes whatever the substance administered and 12.5% of the type A subjects felt no sensation (P < 0.03). About half (52%) of the volunteers were medical or dentistry students, 15.5% were paramedical staff (nurse, laboratory technician), 15.5% were science students and 17% were non-science students (law, psychology, sport). Almost half (43%) of the paramedical, medical and dentistry subjects were type A, compared with 6% of the other subjects. The paramedics had the highest average BS (205.9 ± 30.6); that of the medical and dentistry students was 188.9 ± 35.6, that of the non-science students was 173.9 ± 18.0 and for the science students it was 161.1 ± 23.2 (P < 0.04). Most of the volunteers were medical, dentistry and paramedical students (67%) and they accounted for 94% of the type A population. Their average BS was 192.7 ± 34.9, vs 167.9 ± 22.0 for the remaining subjects (P < 0.02). Although 79% of placebo-responsive subjects belonged to this group, the incidence of nocebo response (31%) was not statistically different from that of the others (18%).

Discussion

A placebo is an inactive substance that was formerly given to please a patient, but now indispensable for determining the intrinsic tolerance and efficacy of medical substances. The placebo response remains poorly understood, especially when dealing with a nocebo response. This study indicates that almost one third (27%) of healthy volunteers included in this ophthalmic drug trial described nocebo effects after the placebo. This placebo responsiveness is linked to type A behaviour (hard driving psychological pattern) as assessed by a Bortner test performed prior to inclusion of volunteers in the study. Type A subjects are aggressive, competitive, have a sustained drive for achievement and a sense of urgency and are hostile. They lead more stressful working lives than type B people, and it has been suggested that type A people are more likely to report side effects than type B subjects [8]. This could explain the prevalence of type A among the subjects describing side effects under placebo.

Healthy volunteers are necessary for Phase I trials to evaluate the tolerance of new drugs. To avoid any bias, these drugs are compared with a placebo. While there is agreement on the usefulness of a placebo in controlled Phase III studies, there are few data on its role in Phase I studies. This raises a major problem as volunteers participating in clinical trials in the European Community must be clearly told they are being given a placebo. Since conditioning and verbal expectancy are involved in the creation of a placebo response [9–10], verbal interaction was kept to a minimum to avoid any suggestibility. Education type can also play a role, although the education of the subjects is not predictive of the placebo response [11].

Table 1 Incidence of nocebo effect after placebo administration and personality type in 52 volunteers involved in a Phase I study

<table>
<thead>
<tr>
<th>Nocebo effect (n)</th>
<th>Asymptomatic (n)</th>
<th>Bortner score (mean)</th>
<th>Incidence of nocebo effect (n/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A (n) 8</td>
<td>8</td>
<td>223***</td>
<td>8/16**</td>
</tr>
<tr>
<td>Type B (n) 6</td>
<td>30</td>
<td>167***</td>
<td>6/36**</td>
</tr>
<tr>
<td>Total (n) 14</td>
<td>38</td>
<td>184</td>
<td>14/52</td>
</tr>
<tr>
<td>Bortner score (mean) 201*</td>
<td>178*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*** P = 0.001; **P = 0.03; *P ≤ 0.05.
fact that most of the subjects participating in Phase I studies are medical and paramedical subjects may influence the appearance of symptoms, because of their knowledge of reactions to drugs. While some authors suggest placebogenic processes in patients such as suggestibility and expectancy [12], that are characteristic of a type B psychological pattern, resistance to placebo treatment is undoubtedly linked to a psychologically predisposed resistance to relief from drugs. This occurs in individuals who get worse while on a placebo [13], or are resistant to placebo and display an authoritative, aggressive behaviour [1]. The resistance to relief could correspond to a nocebo effect when therapeutic efficacy is not the goal, as in Phase I studies on healthy subjects.

The nocebo response undoubtedly deserves more study; a biased sample of subjects exhibiting a more frequent nocebo response could cause drug tolerance to be underestimated. Careful screening of healthy volunteers, including a psychological evaluation, should be done prior to placebo administration in clinical pharmacology. When clinical trials are expected to be particularly emotional and stressful, and especially when they include healthy volunteers, type A subjects could be excluded to avoid bias, if no objective evidence corroborates the subjective side effects.

References

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