Efficacy of Placebo in the Treatment of Patients with Amenorrhea

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Abstract
Thirty-two amenorrheic patients were treated with a tablet oral placebo preparation for a period varying from 30 to 180 days. Another 24 amenorrheic patients were also treated with a placebo administered i.m. for a period varying from 30 to 120 days. As a consequence of the treatment, 27 patients (48%) had menstrual bleedings. The progestogen withdrawal test responsive patients were more responsive to placebo (73 vs. 14% in the progestogen withdrawal test nonresponsive, p < 0.001). The time lag between starting the medication and the first bleeding varied between 4 and 120 days with a mean value of 3.9 (SD 26.3). Oral placebo was more effective than the intramuscular form (56 vs. 38%, p < 0.05).

Placebo is an effective and probably the safest treatment for many symptoms including amenorrhea. Its mechanism, however, is still unknown and the success rate obtained by amenorrheic patients treated with placebo appears quite variable [1,4]. It was therefore of interest to further evaluate the effect exerted by placebo in a larger group of amenorrheic patients not wishing to be treated with replacement therapy. In particular, our goals were the study of the relationship between efficacy and the way of administration and the coherent or discordant individual response to a two-subsequent-placebo course.

(PWT responsive). Thirty-two patients (18 PWT responsive) were treated with a tablet placebo preparation administered twice for a period varying from 30 to 180 days. Among these patients 8 underwent a second cycle of placebo treatment after a mean of 18 weeks (range: 8-30) from the first one. The other 24 patients (15 PWT responsive) were also treated with an intramuscular placebo daily for a period varying from 30 to 120 days. The patients were controlled monthly and the occurrence of uterine bleeding was recorded. The significance of the association between response to placebo treatment and (a) PWT test and (b) route of administration was assessed by means of the Man-tel-Haenszel chi-square test [5], after stratification for age and, in turn, route
and PWT test. The Mantel-Haenszel odds ratio (OR) stratified as above, was used as a measure of the strength of the associations.

Subjects and Methods
Fifty-six patients with secondary amenorrhea were included in the study. All patients had normal FSH and prolactin concentrations and were of normal weight. None of them showed clinical hyperandrogenism. The length of amenorrhea varied from 6 to 60 months (median 12, mean 15.8, SD 11.6 months). All patients underwent progestogen withdrawal test (PWT) and 33 of them had a bleeding

Results
The PWT responsive patients resulted younger (p > 0.01) than the nonresponsive ones while the length of amenorrhea was not different in the two populations, although the PWT responsive group included more patients with shorter amenorrhea. As a consequence of the treatment (table 1), 27 patients (48%) had menstrual bleedings; 6 had a single bleeding while 11 had 2 and 10 had 3 or 4 menstruations. The PWT+ patients were more responsive to placebo (73 vs. 14% in the PWT- OR = 54.2, 95% confidence interval (CI) 9.2-321.1, p < 0.001).

The time lag between starting the medication and the first bleeding varied between 4 and 120 days with a mean value of 33.9 (SD 26.3) and a median of 28 days. The PWT+ patients were significantly more responsive using both routes of administration. Oral placebo was more effective than the intramuscular form (56 vs. 38% OR = 8.0, 95% CI 1.5-41.9, p < 0.05). Three of the 8 patients treated two times had bleedings during both treatments while 1 of these subjects menstruated only after the first and 2 only after the second placebo administration.

Table 1. Menstrual response to placebo treatment in amenorrheic women

Mantel-Haenszel $\chi^2$ adjusted for age, PWT test and route of administration (when appropriate):
for PWT $\chi^2 = 19.4$, 1 d.f. (p < 0.001); for route $\chi^2 = 6.1$, 1 d.f. (p = 0.01).

Discussion
The present data confirm [1,3] the existence of an important effect of placebo in amenorrheic women and provide a more reliable quantification of the effect. The expected higher rate of menses in PWT-responsive patients confirms previous observations [1]. On the contrary, there is no obvious explanation for the significantly higher efficacy of oral placebo in comparison with the parenteral form. This apparent discrepancy and the quite variable time lag between the starting of treatment and the first bleeding suggest different mechanisms of action. Interestingly, the vast majority of responsive patients had two or more menstrual bleedings indicating the occurrence of a change in hypothalamic cyclicity as a consequence of placebo treatment. Unfortunately, the beneficial effect disappeared almost constantly after placebo withdrawal showing the close temporal relationship between the ‘treatment’ and some related biochemical change in the regulatory mechanism of ovarian function. Among the possible mechanisms for this substantial placebo effect opiateergic neurotransmission has been suggested following the restoration of menses and ovulation in patients treated with naltrexone [3]. However, this drug was found as active as placebo in another study [4]. Finally, since approximately 50% of amenorrheic women respond to placebo and this effect can, for many reasons, probably occur
quite often, gynecologists and general practitioners cannot disregard the need for an accurate
counselling of these young women including information on the risk linked to unwanted fertility.

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