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The placebo effect on resting tremor in Parkinson's disease: an electrophysiological study

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ABSTRACT

Introduction: The aim of our study was to investigate the effect of apomorphine and placebo on resting tremor in tremor-dominant Parkinson's disease (tPD) patients.
Methods: Fifteen tPD patients were enrolled. Each patient underwent two treatments on two consecutive days: on day one the patients received a subcutaneous injection of placebo, while on day two they received apomorphine. On each day, the patients underwent three electrophysiological recording sessions: T0, T1, and T2: before, 30 min, and 60 min after the treatment respectively. Electrophysiological changes in tremor amplitude were evaluated using a triaxial accelerometer.
Results: Placebo was effective in improving resting tremor in all tPD patients ($p = 0.009$) at T1, but not at T2. Eight out of 15 tPD patients (53.3%) responded to placebo with an at least 70% reduction in tremor amplitude compared to the basal condition (responders). By contrast, seven out of 15 tPD patients (46.7%) did not show any variation in tremor amplitude after placebo administration (non-responders). Apomorphine induced a marked reduction in tremor amplitude at 30 min and 60 min in all investigated tPD patients. Of note, the decrease in tremor amplitude in placebo responders was similar to that achieved with dopaminergic stimulation induced by apomorphine.
Conclusions: Our study demonstrates that placebo was very effective in reducing resting tremor in about half of patients with tPD. The decrease in tremor amplitude in placebo responders was similar to that induced by apomorphine. The cerebral mechanisms underlying the placebo effect on resting tremor need further investigations.

1. Introduction

In the last fifteen years, a plethora of evidence from clinical trials has switched the focus, highlighting the potential application of placebo effects in medical care [1]. Parkinson's disease (PD) is one of the main clinical disorders for which placebo response rates are high. In fact, in PD up to 50% of patients have shown placebo responses characterized by significant improvements in motor symptoms [2]. In particular, all domains of parkinsonian disability seem to be subject to placebo-associated improvements, with a trend toward more effects on bradykinesia and rigidity than on tremor [3].

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Most studies have focused on the placebo-induced improvements in the hypokinetic symptoms of PD, such as rigidity [4–6] and bradykinesia [7–9]. The placebo-induced improvement of these hypokinetic symptoms in PD seems to be mediated by endogenous dopamine release in the striatum [10,11]. Resting tremor is one of the cardinal motor signs of PD, along with rigidity and bradykinesia [12], which occurs at a frequency of 4–6 Hz and mainly involves the distal limbs. Whether resting tremor can also be influenced by placebo treatment is still unknown.

In the current study, we investigated the effects of placebo administration on resting tremor in patients with tremor-dominant Parkinson disease (tPD). To quantitatively assess tremor modifications, we used a triaxial accelerometer comparing the subcutaneous injection of apomorphine with the subcutaneous injection of placebo in patients with tPD.

2. Methods

2.1. Subjects

We enrolled fifteen patients with a diagnosis of idiopathic tPD according to established clinical criteria [13]. Inclusion criteria consisted of: a history of resting tremor, a resting tremor score of $\geq$2 on the Unified Parkinson Disease Rating Scale (UPDRS) for at least one hand during physical examination [14], and damage to the nigrostriatal dopaminergic system on DATscan images [15,16]. Each patient underwent an accurate clinical history and a neurological examination. Exclusion criteria were: (1) cognitive impairment (MMSE score<24); (2) neurological, cerebrovascular or thyroid comorbidities; (3) moderate to severe dyskinesias; (4) normal dopamine transporter single-photon emission computed tomography (DAT-SPECT); (5) evidence of brain tumor, marked atrophy, and/or diffuse white matter hyperintensities on magnetic resonance imaging (MRI); and (6) treatment with deep brain stimulation and general exclusion criteria for MRI scanning. Imaging studies, including MRI and DAT-SPECT, were assessed in all patients, as described extensively elsewhere [15]. Basal motor evaluation was calculated in the “practically off” condition (at least 12 h after the last dose) according to the motor portion of the UPDRS (UPDRS-III). A levodopa equivalent daily dose was calculated for each patient under anti-parkinsonian therapy.

All patients were recruited after providing written informed consent which included authorized deception. All the experimental procedures were conducted according to the policies and ethical principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the University “Magna Graecia” of Catanzaro.

2.2. Electrophysiological examination

The upper limb with the dominant rest tremor was recorded. Rest measurements were performed with the patient's arm flexed at 90°, fully supported against gravity. A triaxial accelerometer (3D Acceleration Sensor MR, Brain Products, Gilching, Germany), was placed on the dorsal side of the patient's hand. Amplitude and frequency of resting tremor were analyzed. For each patient, the changes in the tremor amplitude at the frequency characteristic of PD (3–5 Hz) during T1-and T2 sessions were normalized to values recorded at the basal condition (T0), and expressed in percentage units (%). The placebo response was defined as a decrease in tremor amplitude at T1 or T2 of at least 70% compared to the basal condition (T0) recorded on two out of 3 axes (x, z, and y) of the accelerometer. An additional measure was obtained by calculating the amplitude tremor decrease in relation to the most involved axis (MIA).

To calculate amplitude tremor, the signal peak-to-peak amplitude (A_{pp}) on each axis was measured as $A_{pp} = M/(4^{*}N_{samples})$, where M was the amplitude peak in principal tremor frequency in the signal amplitude spectrum (Fig. 1).

All acceleration signals were recorded at a 5 KHz sampling frequency using a BrainAmp MR acquisition system and filtered in the 1–12 Hz frequency band before being processed. Digital Signal Processing was performed using the GNU/Octave computing environment, version 3.8.2.

Twelve hours prior to experimental sessions, all medications except domperidone were withdrawn. Electrophysiological examination was performed by an investigator who was blind to the patient's diagnosis.

2.3. Experimental design

Using a repeated-measures design, each patient was tested on two consecutive days. The patient underwent three electrophysiological recording sessions on each day, using a triaxial accelerometer: at baseline (T0), just before treatment administration, at T1-and a T2 sessions, 30 min and 60 min after drug or placebo administration, respectively. Each recording session lasted about 1 min. On the first day, the patients received the placebo (subcutaneous injection of 1 mL saline solution), whereas on the second day they received a subcutaneous injection of 1 mg apomorphine. In both conditions patients were informed that they had received an active treatment for their tremor, but the patients did not know when they were receiving a placebo or apomorphine (all patients received both treatments). As apomorphine could induce vegetative symptoms, placebo and apomorphine conditions were not applied in a counterbalanced order. In fact, patients were not randomly assigned to one of two possible orders, in order to prevent possible side effects induced by apomorphine that might reduce expectations in the placebo condition.

Drug and placebo injections were performed by a nurse. Motor evaluation before and after drug/placebo administration was performed by a blinded neurologist who did not know anything about the purpose of the study, the nature and the sequence of the subcutaneous injections. Moreover, patients were asked to abstain from reporting any side effects to the blinded neurologist that performed the motor evaluation.

All patients had never received apomorphine subcutaneous injections before this experiment and they were given domperidone (60 mg/daily) for 48 h before the experimental sessions, in order to prevent vomiting and/or nausea [10]. The apomorphine-induced side effects were also minimized using a low-dose apomorphine. Previous studies [17] have shown that a 1 mg subcutaneous injection of apomorphine induced a significant improvement in tremor without side effects. Furthermore, all patients underwent routine electrocardiography in order to exclude the presence of domperidone-induced QT prolongation.

2.4. Statistical analysis

To compare sex distributions among tPD subgroups, we used the χ^2 test, whereas differences in demographic, clinical, and DAT-SPECT data between tPD subgroups were assessed using the unpaired t-test or the Mann-Whitney U test, for normally or non-normally distributed variables, respectively.

Differences between apomorphine and placebo T0 measurements were assessed by the Wilcoxon rank sum test, while the one-sample t-test was used to assess differences in amplitude percentage change at a tremor frequency between T0 and T1, between T0 and T2 and between treatments, in tPD total group and in tPD subgroups.

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