Efficiency of Transcranial Electrostimulation on Anxiety and Insomnia Symptoms During a Washout Period in Depressed Patients
A Double-Blind Study

P. Philip, J. Demotes-Mainard, M. Bourgeois, and J.D. Vincent

In order to test the efficacy of cerebral electrostimulation (electrosleep) as an alternative to drug therapy for the treatment of anxiety and insomnia, we conducted a double-blind study in a sample of 21 depressed inpatients submitted to a 5-day period of drug washout on admission to the psychiatric department. During this withdrawal period, anxiety and insomnia were exacerbated in the placebo group, whereas anxiety decreased and sleep duration improved in the active treatment group, with a divergent evolution during the 5-day washout period. The depressive criteria did not respond differentially to treatment, however. Thus, the effects of this drug washout period are markedly attenuated by cerebral electrostimulation, which is of possible interest in the management of psychotropic drug withdrawal.

Introduction

First investigated by Leduc (1902), and then widely studied by the Russian school (Giljarowski et al 1956), transcerebral electrotherapy, more commonly called electrosleep, consists of transcutaneous electrical stimulation with relatively low-intensity electrical pulses through the brain. The current is generally applied in an anteroposterior direction using electrodes bilaterally placed over the eyes and the mastoid or neck region. This nonpharmacological treatment has previously been used during opiate withdrawal in mice (Ho et al 1978) and as a naloxone-reversible analgesic in rats (Skolnick et al 1989). Electrosleep therapy has been studied as a nonpharmacological treatment for anxiety disorders and insomnia (Dymond-Cartwright et al 1975; Feighner et al 1973; Leduc 1902; Rosenthal and Wulfsohn 1970; Rosenthal 1972; Ryan and Souheaver 1976; Smith 1982; Tomsovic and Edwards 1973; Weiss 1973; Demotes-Mainard et al 1990), especially in chronic sleep disorders where hypnotic drugs become inefficient. It has also been proposed as an alternative treatment for hypnotic drug withdrawal in benzodiazepine-dependent patients (Demotes-Mainard et al 1990). Some trials involving heroin-dependent patients have yielded encouraging results (Daulouède et al 1980).

From UICA, Centre Hospitalier Spécialisé Charles Perrens, 121 rue de la Béchade 33000 Bordeaux, France (PP, MB) and Laboratoire de Sommeil, Hopital St André, 1, rue Jean Burguet, 33000 Bordeaux, France (JD-M, JDV).
Address reprint requests to Dr J. Demotes-Mainard, INSERM U 176, rue Camille St Saëns, 33077 Bordeaux, France.
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It is often difficult to evaluate the efficacy of such treatment on anxiety or insomnia symptoms in heterogeneous outpatient populations, since it interferes with life events or pharmacological treatment. Therefore, we have attempted to test, in a controlled double-blind study, the effect of electrosleep therapy under particular conditions using an acute model for anxiety and insomnia. Every inpatient suffering from a major depressive disorder was systematically submitted to a 5-day washout period upon admission to our psychiatric department. During this washout period, symptoms of anxiety and insomnia were exacerbated because of the sudden withdrawal of anxiolytic and/or antidepressant drugs. Such patients were invited to take part in this double-blind study.

Patients and Methods

Transcerebral electrostimulation was delivered through ambulatory placebo or active prototypic devices (Diastym), consisting of a semicircular frame surrounding the patient's head that holds electrodes made of cylindrical sponges impregnated with isotonic saline. An anode was placed on each eyelid and a cathode applied to the mastoids. Such a disposition allows rather low impedance levels (500–100 Ω for the anode–eyelid contact and 1500–2000 Ω for the cathode–mastoid contact). Rectangular monophasic pulses of 0.7 msec duration were delivered at a frequency of 350 Hz, the intensity of the stimulation being adjusted to just below the cutaneous perception threshold, which corresponded to approximately 1–1.2 mA. For the active device, the stimulation session lasted 30 min, whereas the placebo device delivered electrical stimulations for only 1 min, the time necessary for the intensity to be adjusted. A buzzer indicated the end of the session. Each patient received a 30-min stimulation twice daily (11 AM and 6 PM).

Twenty-one psychiatric inpatients, suffering major depressive disorders according to the DSM-III-R criteria, were included in this study. They were divided into two subgroups, "placebo" (n = 11) and "active treatment" (n = 10), adjusted for age (44.9 ± 10.3 years for placebo and 36.4 ± 13.8 years for active treatment), sex (6 of 11 men in placebo and 3 of 10 men in active treatment), previous drug treatment, and depressive or anxiety scores. The average length of the depressive illness before this study was 64 months (5–222 months) in the placebo group and 56 months (1–156) in the active treatment group. Eight patients in each group had a recurrent pathology. A family history of depressive disorders was noted in three placebo and two active treatment patients. The treatment withdrawn upon admission consisted of benzodiazepines (8 of 11 placebo and 9 of 10 active treatment), barbiturates (1 of 10 active treatment), antidepressant drugs (8 of 11 placebo and 5 of 10 active treatment), and neuroleptics (1 of 11 placebo and 1 of 10 active treatment).

Informed consent was obtained from each patient participating in this experimental study. As soon as the patient was admitted to the department, all psychotropic drugs were withdrawn (including hypnotics, anxiolytics, neuroleptics, and antidepressants) for at least 5 days, and the electrostimulation began on the first drug-free day. The depressive pathology was evaluated daily by the Montgomery and Asberg Depression Rating Scale (MADRS). Sleep was evaluated using a sleep diary and a daily sleep questionnaire including the following criteria: duration and appraisal of sleep onset, nocturnal arousals, self-evaluated sleep duration and sleep efficiency, and awakening time. In addition, daytime alertness was evaluated using analogic self-rating scales concerning anxiety, fatigue, and arousal, together with a questionnaire focusing on life events.

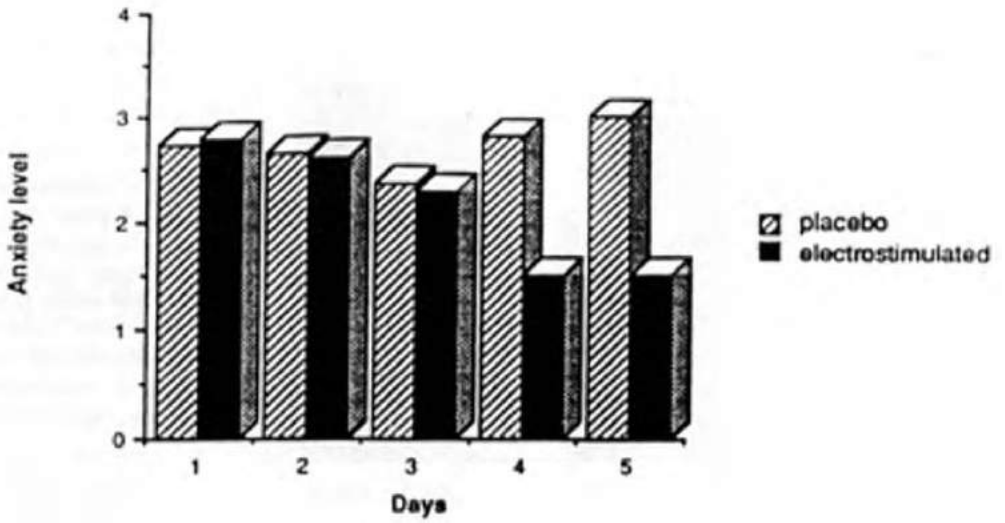

Figure 1. Development of anxiety levels during the 5-day washout period in placebo ($n = 11$) and active treatment ($n = 10$) groups, evaluated according to the third criterion of the MADRS scale. The significant improvement of anxiety symptoms observed in the active treatment group ($p < 0.01$) appears at the fourth day of treatment.

Statistical Analysis

The development of each criterion between the first and the fifth day of the withdrawal period was evaluated for the patients of the placebo and active treatment groups using Student's paired *t*-test.

Results

During the 5-day washout period, the natural development of symptoms consists of a rise in anxiety and an exacerbation of sleep disorders. In two cases, benzodiazepine withdrawal induced epileptic seizures in patients devoid of epileptic history. These seizures did not occur during electrostimulating sessions.

Though the development of depressive criteria in the active treatment group paralleled that in the placebo group, the anxiety and sleep criteria showed divergent changes between these groups during the withdrawal period. The third criterion of the MADRS scale (anxiety level) was exacerbated in the placebo group (NS) but reduced in the treatment group ($p < 0.01$) (Figure 1). The same was true of the ninth criterion (pessimism about the future and feelings of guilt and of failure). None of the other criteria of the MADRS scale exhibited divergent development during either the placebo or active treatment. Sleep duration appeared to be significantly worsened in the placebo group ($p < 0.05$) but not in the active treatment group (Figure 2), this being mainly related to divergent developments of awakening time, which was advanced in the placebo group ($p < 0.05$) and delayed in the active treatment group ($p < 0.01$) (Figure 3). The feeling of fatigue and alertness, evaluated by a daily analogic scale, revealed a positive change in the treatment group ($p < 0.05$) but not in the placebo group.

Discussion

Some particularities of our results are probably a function of our patient sample, a group of depressive inpatients whose anxiety and insomnia are increased by the acute withdrawal

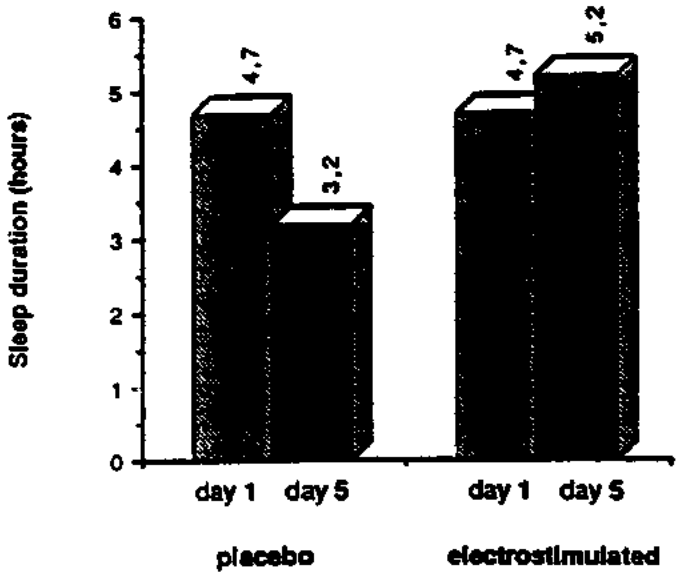

Figure 2. Comparison of sleep duration between the first (day 1) and the last day (day 5) of electrotherapy in the placebo (n = 11) and active treatment (n = 10) groups. Sleep duration is significantly reduced in the placebo ($p < 0.05$) but not in the active treatment group.

of all psychotropic drugs, including antidepressants, anxiolytics, and hypnotics. Under quasi-experimental conditions such as this double-blind study, it was possible to better evaluate the efficacy of cerebral electrostimulation on symptoms of anxiety and insomnia.

In fact, our results exhibit a combination of the anxiolytic and hypnogenic effects of cerebral electrostimulation, without concomitant action on depressive criteria. The anxiolytic effects include an improvement of the self-reported and behavioral symptomatology, diurnal fatigue but also, surprisingly, feelings of guilt, failure, and pessimism about the future. Conversely, the appetite, concentration, sadness, or suicide criteria are not affected by electrotherapy.

This study also shows an interesting effect on sleep in these depressive patients. Whereas in the placebo group, sleep duration largely decreased during the 5-day with-

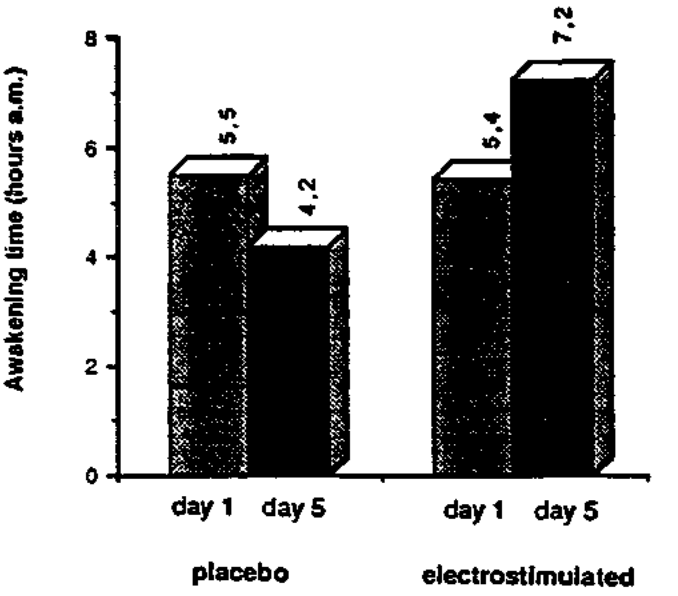

Figure 3. Comparison of the awakening times between the first day (day 1) and the last day (day 5) of electrotherapy in the placebo (n = 11) and active treatment (n = 10) groups. The awakening time is significantly advanced in the placebo group ($p < 0.05$) and delayed ($p < 0.01$) in the active treatment group.

drawal period, in the active treatment group we observed a slight improvement of sleep in spite of drug washout, leading to divergent development between these two groups. A more focused analysis of sleep parameters indicates that, in this sample of depressive patients, the worsening or improvement of sleep duration seems to be related to changes in awakening time, which appears significantly delayed in the treatment as compared to the control group. Other sleep parameters (sleep latency, nocturnal arousals) are not affected by the electrostimulation. This could be due to the lack of delayed sleep onset in this sample of depressive patients, in which insomnia mainly affects the second part of the night and results in early morning awakening.

Interestingly, insomnia during the second part of the night, observed in depressed patients, is commonly considered to be independent of the anxiety level, which instead influences sleep latency. Therefore, we might assume that the action of cerebral electrostimulation is dual, affecting both anxiety symptoms and sleep disorders by independent mechanisms.

In this study, sleep was autoevaluated by a sleep diary and a sleep questionnaire including both quantitative parameters (sleep latency, sleep duration, nocturnal arousals, and awakening time) and subjective criteria (appraisement of sleep onset and quality of sleep). A bias in such studies of self-reported sleep could be due to the underestimation of sleep duration by insomniacs (Frankel et al 1976). Nevertheless, the improvement of sleep parameters observed under electrostimulation seems not to be related to an isolated modification of subjective evaluation of sleep, since changes in the quantitative parameters of sleep evaluation significantly differ in the placebo and treatment groups, whereas the subjective appraisement of sleep remains identical in both groups. However, the lack of modification of this subjective appraisement of sleep in the treatment group appears surprising and could possibly be attributed to an impaired capacity for positive feelings caused by the depressive state.

Methodological considerations led us to restrict the electrotherapy to the 5-day period of drug washout systematically prescribed on admission of depressive patients, in order to rule out possible interactions with the subsequent antidepressant or electroconvulsive treatment. The effects of electrostimulation on sleep and anxiety appear after the third day of treatment (Figure 1), and it would certainly be interesting to evaluate the actions of more prolonged therapies, for example, 2- or 3-week studies, as are often described in the literature devoted to electrosleep.

Previous double-blind studies of cerebral electrostimulation in anxiety or sleep disorders have yielded positive (Dymond-Cartwright et al 1975; Feighner et al 1973; Rosenthal and Wulfsohn 1970; Ryan and Souheaver 1976, Weiss 1973) as well as negative results. These discrepancies could be attributed to methodological problems related to the heterogeneity of patient samples, which we have attempted to reduce in this study of psychiatric inpatients whose anxiety and insomnia were exacerbated during the wash-out period. A second possible explanation for this variability of results could depend on the parameters of cerebral electrostimulation. The 1-mA current pulses delivered induce an electric field of magnitude 6–16 mV/cm in brain tissue (Dymond et al 1975). Beyond a threshold of 10 mV/cm, an electric field is able to induce changes in spontaneous firing of central neurones (Terzuolo and Bullock 1956), especially if its orientation parallels the axodendritic polarity of the cell. Therefore, the intensity of electrostimulation, the quality of electrode-skin contacts and the position of stimulating electrodes are critical parameters in this method, and slight modifications of these criteria could alter the results (Wilson et al 1989).

This study emphasizes the possibility of using cerebral electrostimulation to treat anxiety and insomnia symptoms, particularly during the withdrawal period of psychotropic drugs, as previously reported for methadone (Gomez and Mikhail 1978). This is of particular relevance regarding the hypnotic drugs which rapidly decrease in efficacy during long-term administrations, and which induce a drug-dependence with a rebound insomnia when the treatment is interrupted (Kales et al 1983). Cerebral electrotherapy could constitute an alternative method to benzodiazepines in the management of insomnia and a tool in hypnotic drug withdrawal.

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