Journal of Psychiatric Research 45 (2011) 1165–1169

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Post-dexamethasone cortisol as a predictor for the efficacy of electroconvulsive therapy in depressed inpatients

Miljana Vukadin [a], Tom K. Birkenhäger [a,*], André I. Wierdsma [a], Theo H.N. Groenland [b], Walter W. van den Broek [a]

[a] Department of Psychiatry, Erasmus Medical Center, PO Box 2040, 3000CA Rotterdam, The Netherlands
[b] Department of Anaesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 13 December 2010
Received in revised form
23 February 2011
Accepted 20 March 2011

Keywords:
Major depression
Electroconvulsive therapy
Dexamethasone suppression test
Prediction

ABSTRACT

Background: Although several variables have been studied as a possible predictor for the efficacy of ECT, results regarding hypercortisolism have been inconsistent. This prospective study evaluates the relation between pre-treatment cortisol levels and the efficacy of ECT in a population of drug-free inpatients with severe major depression.

Methods: At the inpatient depression unit, 18 patients meeting the DSM-IV criteria for depressive disorder, and with scores of at least 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D), were treated with bilateral ECT twice weekly. The HAM-D evaluated depression severity and was performed within 3 days prior to ECT, weekly during the course of ECT, and within 3 days after the last treatment. The outcome criterion was defined *a priori* as the change on the HAM-D score. Salivary cortisol was assessed within 3 days prior to ECT at two time points, followed by 0.5 mg dexamethasone ingestion. The following day, salivary cortisol was again assessed at two time points. The generalized linear model was used to assess the relation between salivary cortisol levels and reduction in HAM-D score as continuous variables.

Results: Higher levels of salivary cortisol at 9 AM after 0.5 mg dexamethasone ingestion are associated with a greater reduction in HAM-D score ($B = -0.279$, 95% CI: -0.557 to -0.01, s.e. $= 0.13$, $p = 0.049$; R square $= 0.23$; adjusted R square $= 0.13$).

Conclusion: This study suggests that higher levels of post-dexamethasone salivary cortisol at 9 AM are predictive of ECT efficacy.

1. Introduction

Electroconvulsive therapy (ECT) is considered to be the most effective treatment for patients with major depression, with a reported response rate of 60–90% (UK ECT ReviewGroup, 2003). Several clinical variables have been studied as possible predictors for the efficacy of ECT. Although identifying predictors for response has proven difficult, the most convincing clinical predictors are the presence of delusions (Petrides et al., 2001; Birkenhäger et al., 2003), psychomotor retardation (Hickie et al., 1996) and pharmacotherapy failure prior to ECT (Heijnen et al., 2010).

However, data on potential biological predictors for the efficacy of ECT are scarce. Hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis, as indicated by hypercortisolism and non-suppression of cortisol on the dexamethasone suppression test (DST), has been reported in many studies of depression. It occurs most frequently among inpatients with more severe psychotic or melancholic depression (Nelson and Davis, 1997; Fink, 2005).

Hyperactivation of the HPA-axis could be a predictor for ECT response, although in a meta-analysis no clear predictive value of the DST for response to either antidepressants or ECT was found (Ribeiro et al., 1993)

This apparent lack of predictive value of the DST might be due to studies including heterogeneous populations of depressed patients and, with regard to ECT, the use of low-to-moderate dose unilateral ECT, or administering ECT with benzodiazepines as concomitant medication, both of which may result in limited antidepressant efficacy. Less effective forms of ECT may result in a relatively large proportion of 'placebo' responders and a relatively small proportion of 'true' responders, leading to a relatively high efficacy in less severely depressed patients without hypercortisolism.

* Corresponding author. Tel.: +31 10 7040139; fax: +31 10 4633217.
E-mail address: t.birkenhager@erasmusmc.nl (T.K. Birkenhäger).

0022-3956/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2011.03.012

1.1. Aim of the study

Knowledge on the relation between baseline hyperactivity of the HPA-axis and ECT response is limited. Since ECT is particularly effective in severe forms of depression, such as melancholic depression (Hickie et al., 1996), and high levels of cortisol are often present in patients with severe depression (Murphy, 1991; Nelson and Davis, 1997), we hypothesized that pre-treatment cortisol levels may predict the efficacy of ECT, as measured with a reduction in the Hamilton Rating Scale for Depression (HAM-D) score (Bech et al., 1986), in a population of drug-free inpatients with severe major depression.

The findings of this study may be clinically relevant because identifying a useful predictor for ECT efficacy might facilitate a more adequate prescription of ECT and improve its risk–benefit ratio.

2. Methods

2.1. Subjects

The study was performed at the inpatient depression unit of the Dept. of Psychiatry of the Erasmus Medical Center. This unit has a supraregional function for the treatment of treatment-resistant depressed patients. The study protocol was approved by the local Medical Ethical committee and the study was conducted in accordance with the Declaration of Helsinki. Eligible patients, or their legal relatives in case of incapacity, provided written informed consent after study procedures were fully explained.

It is routine practice to discontinue psychotropic drugs after admission and prior to ECT. Patients were included if they met the DSM-IV criteria (American Psychiatric Association, 1994) for depressive disorder, based on the depression part of the Schedule of Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott, 1978) and had a score of $\geq$18 on the 17-item HAM-D (Bech et al., 1986). Furthermore, only patients aged 18–65 years with an indication for ECT treatment were included. Patients with dementia, Parkinson's disease, other neurological and endocrinological disorders, and alcohol or drug dependence, were excluded.

2.2. Electroconvulsive therapy

Patients were withdrawn from all psychotropic drugs at least 5 days before the first ECT treatment and were maintained medication free during the course of ECT. In case of severe agitation incidental use of haloperidol was allowed.

All patients were treated with bilateral ECT, administered with a brief-pulse, constant-current apparatus (Thymatron, Somatics, IL, USA). Seizure threshold was determined during the first session with stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 s duration as measured with the cuff method, stimulus charge was increased according to the titration schedule and the patient was restimulated after 30 s. Seizure threshold was defined as the stimulus dosage that elicited a seizure of at least 25 s according to the cuff method. For the second treatment, the stimulus dosage was set at 1.5 times the seizure threshold.

Anesthesia during an ECT treatment was administered with intravenous propofol (1.0–1.5 mg/kg), alfentanil (7–10 μg/kg) and succinylcholine (1.0 mg/kg) after premedication with 0.2 mg glycopyrrolate. During the procedure patients were ventilated by mask with a FiO_2 1.0 and end tidal CO_2 was monitored to achieve normoventilation. Patients were ventilated until resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, non-invasive blood pressure, electrocardiogram and electroencephalogram.

ECT was administered twice weekly. The number of ECT treatments was determined by clinical observation, and a minimum of 10 bilateral treatments was required before evaluation as a non-responder. ECT was continued until patients were either asymptomatic, or had not shown any further improvement over the course of four consecutive treatments.

2.3. Additional treatments

The study was performed on a ward almost exclusively reserved for patients with severe major depression. The day programme on the ward includes activation therapy, psychomotor therapy and psycho-education. Patients are seen by their treating physician (a resident in psychiatry) twice weekly.

2.4. Evaluation of treatment outcome

The 17-item HAM-D evaluated the severity of the depression and was routinely performed within 3 days prior to ECT, weekly during the course of ECT, and within 3 days after the last treatment. The reduction in HAM-D score post-treatment compared to pre-treatment was the outcome criterion for the efficacy of the ECT course.

2.5. Salivary cortisol measurement

Baseline salivary cortisol was assessed within 3 days prior to ECT at 11 AM and 10 PM, followed by 0.5 mg dexamethasone ingestion. We used the low dose (0.5 mg) DST, since this is the most commonly used when cortisol is measured in saliva (Lieb et al., 2004; Vreeburg et al., 2009a). The next day post-dexamethasone salivary cortisol was assessed at 9 AM and 4 PM. The collection of salivary cortisol took place in a standardized environment. Instructions prohibited eating, smoking, drinking or brushing teeth within 15 min prior to collection. Saliva samples were obtained using Salivettes (Sarstedt, Germany).

Salivary cortisol measurement is considered to be a reliable and minimally invasive method to assess the active, unbound form of cortisol (Kirschbaum and Hellhammer, 1994).

Since we considered it not feasible to measure the cortisol awakening response (CAR) in these severely depressed patients, we chose to do the baseline morning cortisol assessment at 11 AM, thus avoiding the effect of awakening on cortisol level.

2.6. Statistical analysis

Generalized linear models were used to assess the relation between post-dexamethasone salivary cortisol levels at 9 AM and 4 PM and reduction in HAM-D score. The post-dexamethasone cortisol level was chosen as predictor, since the response of the HPA-axis to dexamethasone is more informative on HPA-axis functioning than baseline cortisol.

Data imputation was used for three missing values. Missing cortisol levels at 10 PM and 9 AM were estimated based on the cortisol levels at 11 AM and 4 PM, respectively. Post-treatment HAM-D score was the outcome variable in an analysis of covariance, with the prior to treatment HAM-D centered score and cortisol level as predictor variables.

Statistical significance was defined at $p < 0.05$. Data were analyzed using IBM SPSS 17.0 for Windows.

3. Results

3.1. Patient characteristics

Of the 84 patients receiving ECT for major depressive disorder, 50 fulfilled one or more exclusion criteria, 8 refused participation, and 26 (31%) patients were included in the study (Fig. 1). Of those, 6