Effects of Moclobemide on Event-related Potentials of Depressed Patients — a Preliminary Study

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Abstract

Objective: Moclobemide is a reversible inhibitor of monoamine oxidase-A and has become well established as an antidepressant, primarily because of its non-sedating effect and safety. This study was conducted to examine the effect of moclobemide on event-related potentials of depressed patients. Both P300 and contingent negative variation were tested.

Patients and Methods: P300 was elicited using an auditory 'oddball' paradigm. Contingent negative variation was elicited using a click-flashing paradigm. Fifteen unmedicated patients who met DSM-IV criteria for major depressive episode were examined. After initial event-related potential tests, they were administered moclobemide 150 mg/day. P300 and contingent negative variation were retested after 1 and 6 weeks of moclobemide treatment. The patients were also compared with 33 normal healthy controls. The N2 and P3 components of P300, and both the early and late contingent negative variation components were analysed.

Results: Before medication, the depressed patients presented a longer P300 latency and lower contingent negative variation amplitudes than the controls. After 1 week of moclobemide treatment, although the patients were not yet showing signs of symptom remission, an amplitude increase in N2 of P300 and in both early and late contingent negative variation components was found. After 6 weeks of treatment with moclobemide, the patients' depressive symptoms have mostly remitted, and a recovery in the latency of P300 and in reaction time to contingent negative variation paradigm was observed, but there was no further amplitude increase in event-related potentials.

Conclusion: While the amplitude increase in event-related potentials might be a direct effect of moclobemide on event-related potentials, the recovery in P300 latency and reaction time of contingent negative variation might be secondary to the remission of depressive symptoms.

Key words: *Contingent negative variation, Depression, Event-related potentials, Moclobemide, P300*

Introduction

Moclobemide is a reversible inhibitor of monoamine oxidase - A (RIMA). As a newer member of the monoamine oxidase inhibitor (MAOI) class, moclobemide is devoid of hepatic toxicity, and also has a very low liability for increasing the effect of dietary tyramine, so that strict diet restrictions may not be necessary.[1] The drug has become well accepted in the treatment of depression because of its non-sedating effect and safety.[2,3] Unique electrophysiological effects of moclobemide had been observed by some researchers,[4,5] who found that the drug could increase rapid eye movement (REM) sleep in patients with depression, throwing doubt on the assumption the reduction of REM sleep common many antidepressants was an important pharmacological requirement for therapeutic effects. To our knowledge, no study has yet examined the effect of moclobemide on event-related potentials (ERPs).

The auditory evoked potential P300 and contingent negative variation (CNV) are commonly measured ERPs in psychiatry.[6,7] P300 has often been obtained using an 'oddball' paradigm in clinical studies. Two major endogenous components in P300 are N2 and P3. N2 is related to the automatic and controlled discriminating processing of stimuli, and P3 reflects the memory updating and attentional

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Submitted: *15 November 2002 ;* **Accepted:** *4 August 2003*

allocation aspects of information processing. CNV consists of 2 different components, an 'early' and a 'late' CNV. Early CNV is related to the orienting response and exhibits a rapid habituation. The late CNV is associated with motor preparation and stimulus anticipation.[8,9] Application of ERPs in psychopharmacological studies showed considerable promise.[10] ERPs seemed to be a sensitive and timely indicator in reflecting some of the pharmacological effects of psychotropic drugs (including antipsychotic agents, antidepressants, etc.) on the brain. ERPs are excellent in temporal resolution. Acute (within 30 minutes), subacute, and superimposed effects of drugs on the brain can be studied using ERP measurements.[11-13]

In this study, both P300 and CNV tests were carried out in depressed patients, firstly in the unmedicated state and then after 1 and 6 weeks of treatment with moclobemide, in order to explore the subacute and therapeutic effects of the drug. Moclobmide has a intrinsichigh clearance that decreases during the first week and then remains constant.[14]

Patients and Methods

Patients

Eighteen patients were recruited from the Outpatient Department of Shanghai Mental Health Center, Shanghai, China. All patients met the DSM-IV criteria for major depressive disorder or bipolar I disorder with the most recent episode being depression according the joint consultation of 2 of the authors (JW and QB). Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D).[15] Eleven patients visited the hospital for the first time and were drug-naive when enrolled into this study. The other 7 patients had not taken any psychotropic medication for more than 1 month prior to being recruited. They had previously stopped medication themselves, without consulting their doctors, after taking psychiatric medication for about 2 years (19.4 ± 10.6 months), in the belief that they were completely recovered. Their first psychiatric diagnoses were depression (4), mania (2), and schizophrenia (1). After the patients undertook the initial P300 and CNV tests, moclobemide 150 mg/day was initiated. The ERP tests were carried out again at 1 week and 6 weeks post-treatment. Within the follow-up period, no change of medication was made. Three of the drug-naive patients were visiting the hospital from remote areas, and were not followed up; therefore, data for 15 patients were reported.

Data were also obtained from 33 healthy control volunteers whose age and gender ratio matched the patient group (Table 1). All subjects were screened for hearing impairment, substance abuse, and organic brain impairment. Control subjects were also screened for past history and family history of any psychotic disorder. Informed consent was obtained from all subjects. All subjects were right-handed. The background characteristics of patients and control subjects are shown in Table 1.

Recording Procedure

P300 and CNV tests were carried out in the Department of Electrophysiology at Shanghai Mental Health Center. ERPs were recorded from 3 silver chloride disk electrodes placed on the scalp (Fz, Cz, and Pz), according to the international 10/20 system. All electrodes were referred to linked earlobes. Electrode impedance was maintained under 5 kW. The electro-oculogram (EOG) was recorded from electrodes placed above and below the right eye. Amplifiers gains were set at 10,000 with a band pass of 0.5 to 50 Hz. The electroencephalogram and EOG were sampled at the rate of 250 samples every second with a Nicolet Spirit device (Compact 4 model, Nicolet Biomed Inc., USA). ERPs were averaged online using VERSION 1.70. Trials were automatically rejected if at any point during the averaging epoch the voltage exceeded ± 100 mV in the EOG lead.

P300 was elicited using an auditory 'oddball' paradigm, which consisted of non-target stimuli (frequent 1000 Hz tone burst at 75 dB SPL) and target stimuli (rare 1600 Hz tone burst at 85 dB SPL). The duration of both tones was 90 ms with a rise time and a fall time of 10 ms. Target and non-target stimuli were delivered binaurally in a random sequence through a headphone (TDH-39P, Nicolet Biomed Inc., USA). The probabilities of occurrence of target and non-target stimuli were 0.2 and 0.8, respectively. The stimulus interval was 1.5 ± 0.1 ms. Subjects were instructed to count silently the number of rare tones, and were excluded from the study upon failure to achieve an accuracy of 90%.

Table 1. Background characteristics of patients and control subjects.

	Patients	Controls	p Value
Cases (n)	15	33	-
Gender (M/F)	10/5	18/15	0.320
Age (mean ± SD) [years]	40.3 ± 12.7	38.0 ± 9.8	0.503
Biological features (with/without)*	5/10		
Psychological stress (with/without)†	2/13		
Past mania episode (with/without)	7/8		

* *Biological features referred to weight loss, weight gain, decrease or increase in appetite, decreased sleep, reversed diurnal variation, psychomotor agitation, or retardation.*

† *Loss of job and divorce, respectively, were identified as the psychological stress eliciting current episode of depression in 2 patients. While one had had previous episodes of depression, the other had previously experienced an episode of hypomania.*

The recording threshold required 40 artifact-free trials of target stimuli. No subject was excluded because of failure in the counting task. Peak amplitudes and latencies of N200 and P300 were measured from the ERPs to the target stimuli. While the peak amplitude was measured from a baseline, which was calculated as the amplitude value of the first sampling point within the recording window, peak latency was calculated relative to stimulus onset. The N200 component was defined as the negative peak 180 to 280 ms after stimulus onset, and the P300 component as the positive peak 260 to 450 ms after stimulus onset.

Subjects rested for 15 minutes before the CNV test. The CNV paradigm consisted of a simple reaction time (RT) to an imperative stimulus, which had been preceded by a warning tone stimulus at an interval of 1 second. The warning stimulus was a 1000 Hz tone at 75 dB SPL with a duration of 60 ms. The imperative stimulus was a red flash of 80 luxes stopped by the subject's motor response. Subjects were instructed to press a button to stop the visual flash as soon as possible when they saw it. The inter-trial interval was randomised from 5 to 10 seconds. The CNV was averaged from 16 artifact-free trials. Early CNV component (M1) was measured as the voltage difference between the baseline and the highest point within the time range of 400 to 600 ms after the warning stimulus, and late CNV amplitude (M2) was obtained in the same way within a 400 ms range before the imperative stimulus.

Data from Cz were reported in this study were presented as means ± SD. The group difference of ERP measures between unmedicated depressives and controls was assessed using analysis of variance. The differences in depressives' ERP measures recorded from different medication phases were assessed using paired t-test.

Results

The results for ERP measures in controls and depressed patients before and after moclobemide treatment are shown in Table 2.

Event-related Potential Variations in Unmedicated Depressed Patients

Before treating depressed patients, the P3 latency of P300 was delayed compared to control subjects ($F_{1,46}$ 5.05, p = 0.029). Amplitudes of both early and late CNV components decreased in the patient group (for M1 amplitude: $F_{1,46}$ = 7.15, p = 0.01; for M2 amplitude: $F_{1,46}$ = 4.68, p = 0.036). The RT to CNV paradigm also showed a tendency of prolongation among patients ($F_{1,46}$ = 3.07, p = 0.086).

Event-related Potential Measures and Moclobemide Treatment

After 1 week of treatment with moclobemide, the patients' current depression episodes had not yet shown any sign of remission; however, both P300 and CNV had exhibited some normalisation compared with the unmedicated state. Amplitude increase was found with the N2 of P300 (t = 2.53, p = 0.024), and with both M1 and M2 components of CNV (for M1 amplitude comparison: t = 4.12, p = 0.001; for M2 amplitude comparison: t = 3.43, p = 0.004).

After 6 weeks treatment with moclobemide, these patients' depression had mostly remitted. At this time, a recovery in the P3 latencies of P300 and RT of the CNV was found (for P3 latency comparison: t = 4.57, p < 0.001; for RT comparison: t = 2.64, p = 0.02). However, no further amplitude increase was found in either P300 or CNV.

Discussion

In this study, the unmedicated depressives showed longer P3 latency, as well as lower amplitudes and longer RT in CNV compared with control subjects. Essentially, these results were consistent with our previous study and studies by other researchers.[16-23] However, some studies did not find ERP changes among depressed patients.[24-26] Recently, it was emphasised that some, if not all, depressed patients exhibit ERP abnormalities. ERP abnormality has also been related

Table 2. Mean (± SD) event-related potential values of control subjects and of depressive patients in the unmedicated state and after moclobemide treatment for 1 and 6 weeks.

	Controls (n = 33)	Depressed patients (n = 15)		
		Unmedicated	1 week	6 weeks
HAM-D score		18.5 ± 3.5	17.8 ± 3.0	7.5 ± 2.6¶
P300				
N2 latency (ms)	195.0 ± 20.3	194.1 ± 26.9	194.9 ± 23.9	197.7 ± 18.1
N2 amplitude (mV)	3.64 ± 2.10	3.32 ± 1.60	4.79 ± 1.93‡	4.51 ± 1.70
P3 latency (ms)	316.0 ± 26.4	334.1 ± 24.4*	339.4 ± 16.6	323.1 ± 21.2¶
P3 amplitude (mV)	6.55 ± 3.78	5.55 ± 0.96	4.78 ± 1.72	5.28 ± 1.45
CNV				
M1 amplitude (mV)	11.14 ± 7.24	6.02 ± 2.22†	9.45 ± 2.63§	9.94 ± 3.39
M2 amplitude (mV)	11.51 ± 7.31	7.32 ± 2.19*	9.57 ± 2.17§	9.54 ± 3.18
Reaction time (ms)	243.4 ± 80.8	298.7 ± 137.3	260.9 ± 77.7	211.4 ± 30.6xx

**p < 0.05, † p < 0.01 versus control subjects.*
‡ p < 0.05; § p < 0.01 versus unmedicated state.
xx p < 0.05; ¶ p < 0.01 versus 1 week.
Abbreviations: *HAM-D = Hamilton Depression Rating Scale; CNV = contingent negative variation.*

to the presence of psychotic symptoms or suicide ideation/behaviour, etc.[21,27-30]

However, ERPs might be more sensitive in reflecting the pharmacological effects of antidepressants on the brain because of their excellent temporal resolution. The study by Blackwood et al reported full recovery in ERPs accompanied by the clinical remission of patients' depression.[31] The present study attempted to observe whether ERPs could precede the symptom remission among depressed patents. Eight patient were drug naive, with the current episode being the first one for which they were seen by a psychiatrist. The other 7 patients had inadvertently been drug-free for 4 weeks or more, because they had decided they were completely recovered and without consulting their doctors had stopped medication. Thus, these patients had had a suitable drug-washout period before this study. After 1 week of moclobemide treatment, despite there being no significant clinical remission of these patients' depression, an amplitude increase was found in the N2 component of P300, and both early (M1) and late (M2) components of CNV.

We believe that this kind of amplitude increase might result from a direct effect of moclobemide on ERPs, which could be termed a 'primary effect'. After 6 weeks of medication, when the patients' depression had almost remitted, ERPs showed a corresponding recovery in P3 latency of P300 and in RT of CNV. These changes could be regarded as a 'secondary effect' of moclobemide on ERPs, as it was possibly secondary to the clinical remission of the depressed state. It is necessary to differentiate these 2 kinds of effects in the clinical application of ERPs. The primary effect of a drug, that precedes the remission of clinical symptoms, might help in predicting the response of patients to the drug (therapeutic effects, side effects, etc), while the secondary effect, which often parallels or lags behind the remission of clinical symptoms, might be applied to objective evaluation of the therapeutic response.

Some studies reported that tricyclic antidepressants or selective serotonin-reuptake inhibitors (SSRIs) might directly decrease ERP amplitude among normal controls.[19,32] The acute effect of another RIMA, befloxatone, on ERPs of normal subjects has been reported by Luthringer et al.[12] An amplitude decrease of both P300 and CNV was seen in subjects within a time period as short as 0.5 to 2 hours after befloxatone administration, a result apparently inconsistent with that of the present study. However, this discrepancy could be accounted for by interindividual variation among study subjects. For instance, amitriptyline has been observed to decrease CNV amplitudes among normal controls but to increase CNV amplitudes among depressed patients.[19] In addition, even among the same subject sample, one drug could still present bi-directional effects because of the 'law of initial value'. For instance, sulpiride had been reported to increase the P300 amplitude in 'low-amplitude' subjects but decrease it in the 'high-amplitude' subjects.[33] Similarly, bi-directional effects have been found with bromocriptine and sodium valproate.[34,35]

The amplitude increase in ERPs seen shortly after the administration of moclobemide suggests that the recovery in ERPs might precede the clinical remission, raising the possibility that ERPs might be applied to predict patients' response to medication. However, almost all of our patients had obtained good remissions at 6-week medication follow-up, so that a retrospective ERP comparison between good responders and poor responders to moclobemide was not possible. Therefore, whether an early amplitude increase in ERPs could predict the response to the medication still needs further evaluation.

In conclusion, the present study demonstrated the effects of moclobemide on ERPs of depressed patients. The primary and secondary effects on ERPs might be applied usefully in different settings. However, the authors maintain that the results of the present study are preliminary because of the relatively small sample size, and also because analysis of data from Fz and Pz has not been performed. Confirmation of these results in additional subjects and at multiple recording sites is needed in future studies.

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