The Influence of Electroconvulsive Therapy on the Level of Plasma Noradrenaline in Depressive Illness

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Abstract

This study was conducted with aim of studying the change in resting plasma noradrenaline as a marker of central noradrenergic activity in major depressive patients over a course of electroconculsive therapy (ECT) and relate this to their clinical state. In patients (6 male and 11 female) who suffered from DSM IV major depressive disorder, selected from psychiatric Inpatient Department in Zagazig University Hospital, blood samples were taken before and after each treatment, during a course of ECT, to measure plasma noradrenaline. Clincal rating were carried out before and after the course of ECT, using Zagazig Depression Scale and Hamilton Rating Scale for depression. The results revealed that plasma noradrenaline fell significantly in those patients with melancholic /psychotic depression, but increased with non-melancholic depressive illness. Also, there was a strong trend indicating that a fall in plasma noradrenaline was associated with improvement in depression ratings in the melancholic/ psychotic patients only. It therefore seems that ECT decrease plasma noradrenaline in melancholic/ psychotic depressive illness and this was to be associated with clinical improvement.

Introduction

Abnormalities of catecholaminergic function have been hypothesised to cause depressive illness (Kelly and Cooper 1997). If the catecholamine hypothesis of depressive illness is correct, it should be hypothesised that effective treatment might result in significant, clinically related change in some indices of central noradrenergic function. One such index may be plasma noradrenaline (NA), concentration of which may reflect central noradrenergic activity in controls and depressed patients. (Roy et al., 1988).

Studies examining resting plasma NA concentrations in depressed patients have found an increase compared with control populations (Lake et al., 1982), particularly in those with melancholic or psychotic depression (Roy et al., 1985). Electroconvulsive therapy (ECT) should be the method chosen to examine the influence of effective treatment on plasma NA, as it is applied principally to the brain and has no direct effects on peripheral plasma NA.

Aim of the Work

It is of interest to examine the change in resting plasma noraderenaline as a marker of central noraderenergic activity in patients with depressive illness over a course of electroconvulsive therapy (ECT) and relate this to their clinical state.

Subjects and Methods

(A) The study comprises seventeen patients (6 male and 11 female) with depressive illness, selected from the psychiatric Inpatient Department in Zagazig University Hospital.

* All patients were diagnosed according to

DSM-IV criteria (American psychiatric Association, 1994).

* Patients with diagnoses other than depressive iliness or dysthymia were not included.

* Patients were excluded if over 70 years of age, pregnant, suffering from any serious physical illness, drug misuse or if on drugs for physical illness which were known to interfer with plasma NA concentration.

* All 17 patients were free of psychotropic drugs for a period of two weeks before entry into the study and also during the study. (we use only diazepam 10 mg during the daytime for disturbed behaviour).

(B) All patients are subjected to the following:

1- Zagazig Depression scale (ZDS) (Fawzy et al., 1983) for the subjective severity of depression.

2- Hamltion Rating scale of Depression (HRSD) (Hamiltion 1967) for objective assessment of the severity of depression.

* Both ZDS and HRSD were made before the course of ECT and one week after the six ECT.

3- Modified ECT was given twice weekly using bifrontotemporal electrode placements. We gave every patient one ampoule diazepam (10mg) as a muscle relaxant before each ECT.

4- Blood samples were taken for measurement of plasma NA before and after each ECT.

* The patients were fasting before collection of blood samples. Blood was collected in 10-ml syringes and transferred to chilled plastic tubes containing sodium metabisulphite, which acted as an antioxidant. Tubes were stored on ice until centrifuged at 300 rpm at a temperature of 4 °C. The resulting supernatant was put into sterile plastic tubes and stored at -40°C for analysis later.

Concentrations of NA were measured in plasma samples by high-pressure liquid chromatography with electrochemical detection(Krstulovic et al., 1981; Nicholls et al, 1984).

(C) Statistical evaluation of the results.

Results

A- Clinical data:

As shown from table (1) patients are described as one group (n = 17) and subdivided into melancholic/psychotic depression (n=10: four psychotic and six melancholic) and non-melancholic depression (n=7).

Table (2) shows no significant difference in height or weight between the two subgroups. Although the melancholic/ psychotic patients were older, had a shorter duration of illness, these variables were not statistically significant in comparison with those for the non- melancholic group.

Table (3) shows that there was a statistically significant difference between the intial ratings and final ratings in both subgroups.

Table (4) shows that there was a statistically significant difference between the intial ratings and final ratings in both subgroups.

As shown from tables (5) and (6), there is a fall in the melancholic group as regards the comparion between the intial plasma NA value with the final value, which is statistically significant; but there is a non significant rise in plasma NA concentration in the non-melancholic group.

Table (7) shows a trend linking fall in plasma NA with Fall in HRSD in melancholic group which is statistically significant.

Table (8) shows that there is no statistically significant association between plasma NA and HRSD for the non-melancholic subgroup.

Table (9) shows that there is no statistically significant relationship between plasma NA and ZDS ratings for any group.

Table (1) No. and % of depressive groups

	Melancholic/ psychotic group		Non-melancholic group	Total group
	Melancholic	Psychotic		
No.	6	4	7	17
%	35.3	23.5	41.2	100

Table (2): Demographic data of patients

Items	Total	Melancholic psychotic	Non-melancholic
No. of patients selected	17	10	7
Sex (M/F)	6/11	4/6	2/5
Mean age			
(years)	51.2	52.5	45.0
(range)	(31-63)	(35-63)	(31-57)
In first episode of illness	5	3	2
Upipolar / Bipolar	15/2	8/2	7/0
Drug-free (2 weeks)	17	10	7
Mean height			
(cm)	169	172.6	163.5
(range)	(156-196)	156-196	(162-165)
Mean weight			
(kg)	68.83	71.71	64.8
(range)	(46-91)	(46-91)	(52-76)
Mean length of illness			
(weeks)	15.7	11.4	21.6
(range)	(4-52)	(4-36)	(8-52)

Table (3): HRSD ratings for the both groups

Item	No.	Initial rating mean ± SD	Final rating mean ± SD	Z	P
Melancholic/psychotic group	10	30.5± 7.3	6.2 ± 5.9	-2.8	0.005
Non-melancholic group	7	26.3 ± 4.5	11.7 ± 8.4	-2.3	0.01

Table (4): ZDS ratings for both groups

Item	No.	Initial rating mean ± SD	Final rating mean ± SD	Z	P
- Melancholic/psychotic group	10	21.9 ± 8.1	4.7 ± 3.3	-2.7	0.005
- Non-melancholic group	7	27.6 ± 8.7	12.5 ± 9.6	-2.28	0.01

Table (5): Resting plasma noradrenaline (NA) concentrations (mean ±SD) Pg/ml in patients undergoing ECT.

Stage of treatment	Melancholic	Non-melancholic
Initial NA	785.2 (184.4)	349.1 (87.7)
	(n=10)	(n=7)
Pre ECT 1	874.9 (219.5)	280.8 (90.9)
Pre-ECT 2	674.1 (153.6)	278.6 (57.1)
Pre-ECT 3	516.2 (214.9)	309.1 (63.7)
Pre-ECT 4	472.7 (71.7)	340.5 (43.3)
Pre-ECT 5	546.9 (91.7)	399.2 (116.9)
Pre-ECT 6	409.0 (84.8)	370.6 (88.7)
24 h post ECT	372.7 (75.3)	450.0 (149.7)
7 days post ECT	350.8 (35.0)	448.0 (233.9)
Final NA	347.0 (61.3)	450.0 (144.5)

Table (6): Comparison between the intial plasma NA value with the final value in both subgroups

Subgroups	Intial NA value mean ±SD	Final NA value mean ±SD	Z	P
Melancholic group	785.2 ± 184.4	347 ± 62.3	-2.7	0.006
Non-melancholic group	349.1 ± 87.7	450±143.5	-0.85	0.39

B- Biochemical data:

Table (7): Relationship between plasma NA and HRSD in Melancholic /psychotic group.

Item	Intial NA value mean ±SD	Final NA value mean ±SD	Z	P
Melancholic group (HRSD)	30.5 ± 7.3	6.2 ± 5.9		
Melancholic group (Plasma NA)	785.2± 184.4	347 ± 62.3	- 1.8	0.07

Table (8): Relationship between plasma NA and HRSD in non- melancholic group.

Item	Intial NA value mean ±SD	Final NA value mean ±SD	Z	P
Non-melancholic (HRSD)	26.3 ± 4.5	11.7 ± 8.4		
Non-melancholic (Plasma NA)	349 ± 87.7	450 ± 143.5	- 1.18	0.23

Table (9): Relationship between plasma NA and ZDS ratings for both groups.

Item	Intial NA value mean ±SD	Final NA value mean ± SD	Z	P
Melancholic group (ZDS)	21.9 ± 8.1	4.7 ±3.3		
Melancholic group (Plasma NA)	785.2± 184.4	347± 62.3	- 0.85	0.39
Non- Melancholic group (ZDS)	27.6± 8.7	12.6 ± 9.5		
Non-melancholic group (Plasma NA)	349.1± 87.7	450 ± 143.5	-1.16	0.21

Discussion

Methodology

All patients were diagnosed, independently of the decision to give ECT, with DSM IV criteria. Allocation to subgroups of depressive illness was made strictly according to the presence of operationally defined clinical symptoms.

The patients studied were moderately and severly ill, also all of them were free from antidepressants for at least two weeks before entry into the study. Moreover, patients receiving benzodiazepines were equally distributed between the two subgroups of depressive illness, which suggests that this did not influence the out come.

Longer drug free periods might have been ideal but would have resulted in an atypically mildly ill study group (Kelly and Cooper. 1997).

Subtyping of depressive illness, while defined in this study, has not been accepted as of worthwhile clinical significance with respect to melancholia. (Roy et al., 1985).

Effects of ECT: melancholic/psychotic depression but not in patients with non-melancholic depression. In addition, this change in plasma NA shows a strong trend to correlate with a decrease in the HRSD rating of the melancholic/psychotic patients.

Two previous studies, Gravenstein et al. (1965) and Cooper et al. (1985), have reported a fall in resting plasma NA during a course of ECT in depressed patients. These studies, however, used limited sampling points, did not subdivide depressive illness and failed to examine the relationship between change in plasma NA and clinical response.

Mechanism of action:

Plasma NA appears to be elevated in depressive illness. Physiologically this relates to increased spillover of NA from synapses in the peripheral sympathetic nervous system to plasma. As stated earlier, plasma NA correlates with central indicators of noradrenergic function such as cerebrospinal fluid NA, and since the locus ceruleus is the origin of both central and peripheral noradrenergic systems, it would perhaps not be surprising if central overactivity were reflected peripherally. Using this model, the data presented would suggest a decrease in central presynaptic activity with ECT. Siever and Davis (1985) suggested a dysregulated noradrenergic system producing excessive pre-synaptic NA release, followed by postsynaptic adaptation, leading to a progressively reduced response (and possibly to reduced ability to respond to stress). This argument is supported by decreased beta-adrenoceptor function in the platelets of depressed patients (Mann et al., 1990a). ECT, by decreasing NA production, would allow noradrenergic systems to re-regulate toward a greater post synaptic response to decreased NA production.

Therapeutic implications

The above results suggest that melancholic/ psychotic depression involves disturbance of noradrenergic systems and that this is not evident in non-melancholic depressions. The marked effects of ECT on noradrenergic systems (Cooper et al., 1995) may explain its therapeutic benefit. Also, in melancholic depression there is evidence to suggest that antidepressant drugs with mixed noradrenergic/serotonergic activity are more effective than those with

predominantly serotonergic effects (Danish University Antidepressant Group, 1990; Roose et al., 1994). Melancholic/psychotic forms of depression may benefit more from antidepressant treatments with effects on noradrenergic systems.

Conclusion

ECT decreases noradrenergic activity as measured by plasma nor adrenaline, only in depressed patients with melancholic or psychotic forms of illness.

Clinical improvement with ECT shows a strong trend associated with fall in plasma noradrenaline in melancholic or psychotic depressed patients.

Melancholic/psychotic forms of depressive illness may show preferential benefit from treatments which act via noradrenergic systems.

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تأثير العلاج الكهربائي على مستوى النورادرينالين في الدم في اضطراب الاكتئاب

يهدف هذا البحث إلى دراسة التغيرات التي تطرأ على مستوى النور أدرينالين في الدم باعتباره مؤشرا للنشاط المركزي للنور أدرينالين في مرضى الاكتئاب أثناء علاجهم بالجلسات الكهربائية ومن ثم ارتباط ذلك بالحالة الإكلينيكية. تضمنت الدراسة ٦ رجال و ١١ إناث من مرضى الاكتئاب (تبعا للتقسيم التشخيصي الإحصائي الأمريكي الرابع للاضطرابات النفسية) والمحجوزين بالقسم الداخلي للأمراض النفسية بجامعة الزقازيق، حيث تم أخذ عينات من الدم من كل منهم قبل وبعد كل جلسة كهربائية لقياس النور أدرينالين في الدم. كما تم تقييم المرضى بواسطة مقياس الزقازيق للاكتئاب ومقياس هاميلتون للاكتئاب. وقد أظهرت النتائج حدوث انخفاض دال إحصائيا في مستوى النور أدرينالين في الدم في المرضى المصابون باكتئاب الذهان الميلانخولي وارتفاع له في مرض الاكتئاب غير الميلانخولي. كما كان هناك مؤشرات قوية تشير إلى أن انخفاض مستوى الأدرينالين في الدم كان يصاحبه تحسن في قياسات الاكتئاب بين مرض اكتئاب الذهان الميلانخولي فقط. ومن ثم فهناك ما يشير إلى أن جلسات الكهرباء تؤدي إلى انخفاض النور أدرينالين في الدم في مرض اكتئاب الذهان الميلانخولي وان هذا عادة ما يصاحبه تحسن إكلينيكي.