EFFECT OF IMIPRAMINE AND ECT ON PLATELET MAO ACTIVITY IN DEPRESSIVES

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SUMMARY

Platelet monoamine Oxidase (MAO) activity was estimated in 30 depressed patients treated with Imipramine or ECT over a period of 5 weeks and pretreatment and post treatment values were compared. Imipramine and ECT caused significant reduction of platelet MAO, which after 7 days washout period comes to the pretreatment level while subjects clinical status remained unchanged. The percentage blockade in platelet MAO values by Imipramine and ECT was 51.40±13.43 and 34.73±24.27 respectively.

Tricyclic antidepressant drugs are generally considered to act effectively in the treatment of depression by increasing the functional levels of biogenic amines at specific brain receptor sites. Recently various studies, considering in vitro and in vivo effect of tricyclic on monoamines have appeared in the literature (Edwards and Burns, 1974; Roth and Gillis, 1974 a; Sullivan, 1977). These studies have demonstrated that inhibition of monoamine oxidase (MAO) plays a role in the clinical action of tricyclic anti-depressants.

Various hypotheses—neurochemical, neuroanatomical, neuroendocrine and psychological have been propounded to understand the mechanism of action of electroconvulsive therapy (ECT) (Ottason, 1980; Miller, 1976; Weaver et al., 1976) but it is not possible to pinpoint a single mechanism of action. The present work is an endeavour in this area.

Indian literature is short of studies conducted in this specific area (Trivedi et al, 1988 b) and the ones reported are in Schizophrenics (Sen Gupta et al., 1981; Gupta et al., 1985; Trivedi et al., 1987, 1988 a):

**Aim :** to study the effect of treatment (Imipramine and ECT) and clinical response on monoamine oxidase activity in depressed patients.

**Material and Methods**

Thirty male depressed patients (according to ICD-IX-296) and fulfilling research diagnostic criteria (Spitzer et al., 1978) and meeting predefined selection criteria were selected. These patients were randomly assigned to imipramine (Group A) or ECT (Group B) treatment.

Only those subjects were chosen for study who were between 17-60 yrs, had minimum of 17 score on Hamilton Psychiatric Rating Scale for depression (HRSD) (Hamilton, 1960), had haemoglobin not less than 10 gm%, had absence...
of major physical illness, papilloedema, glaucoma or prostatic hypertrophy, had no immediate danger of suicide and had not received ECT in the past 3 months.

Procedure

All the experimental group subjects were kept drug free for 7 days and score on HRSD was assessed on the day of starting treatment (day 0).

**Group A:** The patients received tablet imipramine on a fixed dosage of 225 mg/day in divided dosage which was achieved within a week starting from 75 mg/day followed by 150 mg/day for next 3 days and 225 mg/day thereafter and continued till the end of 3 week study periods provided there were no serious side effects of imipramine which were assessed clinically.

**Group B:** Patients were given direct ECT; first 3 on alternate days starting from day one, and on every fourth day thereafter to a maximum of 10 at the end of 3 weeks treatment phase.

In both the above groups (A & B) the treatment was stopped at any assessment point at which clinical improvement occurred i.e. HRSD score falls on or below 5 point. Subsequent to the completion of treatment, all the patients (Group A and B) were kept drug free of imipramine and ECT for seven days so as to abolish immediate effect of ECT and imipramine on platelet MAO.

Patients were assessed on Hamilton Psychiatric Rating Scale for Depression at the time of inclusion in the study, then at weekly interval and after 7 days of posttreatment washout period. Blood was drawn at the beginning of study, then at the completion of the treatment and after 7 days of post treatment washout. Details regarding sample collection and estimation of platelet MAO activity is given elsewhere (Trivedi et al., 1988 b).

**Results**

The mean age of the group was 40.3 years (range 24-57). In the Imipramine group (N=15) 2 patients had shown improvement after 3 weeks, 4 patients after 4 weeks and in 9 patients treatment was continued till 5 weeks. The mean duration of Imipramine treatment was 4.47 weeks. In ECT treatment group (N=15) 3 patients had shown improvement after 3 weeks, 5 patients after 4 weeks and in 7 patients the treatment was continued till 5 weeks. The mean duration of ECT treatment was 4.27 weeks.

| Pre- Treatment | Post- Treatment | Post- Treatment after washout |
|---------------|----------------|-------------------------------|
|               | (N=15)         | (N=15)                        |
| (A) ECT treated group | Mean | 28.47 | 4.73 | 5.87 |
|               | s.d.           | 4.11 | 4.09 | 4.30 |
|               | Range          | 22-39 | 0-14 | 0-14 |
| (D) Drug treated group | Mean | 28.26 | 5.00 | 5.07 |
|               | S.D.           | 3.94 | 4.23 | 4.40 |
|               | Range          | 22-36 | 0-13 | 0-13 |

Significant comparisons:

A Vs. B: t = 13.80; d.f. = 14; p < 0.001
A Vs. C: t = 13.93; d.f. = 14; p < 0.001
D Vs. E: t = 18.46; d.f. = 14; p < 0.001
D Vs. E: t = 15.07; d.f. = 14; p < 0.001
E. C. T. and Imipramine produced significant improvement in depression but there was no significant difference between the treatment modalities.

Table 2. Comparison of platelet MAO values in E. C. T. and Imipramine treated group of patients in pretreatment, post treatment and post-treatment after washout period.

|                  | E.G.T. treated Group (N=15) | Imipramine treated Group (N=15) |
|------------------|-----------------------------|---------------------------------|
|                   | (A)                         | (B)                             |
| **Pre-treatment** |                             |                                 |
| Mean             | 42.52                       | 41.82                           |
| s.d.             | 21.20                       | 21.68                           |
| Range            | 1.13—91.31                  | 16.17—116.60                    |
|                   | (C)                         | (D)                             |
| **Post treatment**|                             |                                 |
| Mean             | 29.03                       | 20.79                           |
| s.d.             | 18.05                       | 15.45                           |
| Range            | 4.16—68.56                  | 9.13—73.38                      |
|                   | (E)                         | (F)                             |
| **Post treatment after washout period** |                       |                                 |
| Mean             | 42.97                       | 31.90                           |
| s.d.             | 26.85                       | 20.67                           |
| Range            | 12.91—104.37                | 14.04—110.33                    |

*MAO values were represented in nkat/mg/min/mg protein.

Significant comparisons:
- B Vs D: t=9.60; d.f. = 14; p < 0.001
- D Vs F: t=9.30; d.f. = 14; p < 0.001
- A Vs C: t=2.96; d.f. = 14; p < 0.05

There was significant decrease in mean post-treated platelet MAO values when compared to pretreatment values both in Imipramine and ECT group. There was again a increase in platelet MAO values at post treatment washout period which was significant in imipramine group and insignificant in ECT group. Thus, it is evident that Imipramine and ECT had reduced platelet MAO values in depressed patients which tended to return more or less to pretreatment values.

**Discussion**

To study the effect of Imipramine and ECT on platelet monoamine oxidase activity of depressed patients, the pre-treatment and post-treatment monoamine oxidase values were compared and a significant decrease was observed in post treatment period. The percentage blockade (decrease) of platelet monoamine oxidase activity was studied comparing the post-treatment after 7 days washout period values with that of post-treatment values. The pre-treatment values were not considered because in that period although patients were drug free for 7 days, the disease process i.e. depression was there, which could have caused a faulty interpretation as it has already been seen that platelet MAO is increased in depressed patients (Mann, 1979; Trivedi et al., 1988b). Whereas taking into account, the post-treatment (after 7 days washout period) values, the effect of depression on platelet MAO values was eliminated. The mean percentage blockade of MAO activity by Imipramine and ECT was found to be 51.40 ± 13.43 and 34.73 ± 24.27 respectively.

In vitro inhibition of the enzyme monoamine oxidase has also been reported in several animal studies (Roth and Gillis 1974, a & b). Sullivan et al. (1977) reported 40% decrease in platelet MAO activity in 11 male patients of primary depression after 3 weeks of treatment with imipramine or amitryptiline. Edwards and Burns (1974) reported in vitro inhibition of platelet MAO acti-
activity by amitryptiline. Roth and Gillis (1974 a) working on mitochondrial preparations of rabbit lung and brain observed that Oxidase deamination of tyramine, 5HT and beta-phenylethylamine (PEA) was inhibited by imipramine. The same workers in another study (Roth and Gillis, 1974 b) determined the ability of several structurally related tricyclic antidepressant drugs to inhibit both the type A form of the MAO (5HT determination) and the type B form of the enzyme (PEA deamination). However, several reports challenge the proposal that tricyclic antidepressants affect MAO activity (Reveley et al., 1979; Davison et al., 1978; Giller et al., 1980). Reveley et al. (1979) did not find any significant inhibition of platelet MAO activity in depressives treated by amitryptiline for 4 weeks. Thus, the present observation of significant inhibition of MAO activity by imipramine supports other workers' observation of inhibition of both types of mitochondrial MAO and suggests that ‘imipramine inhibition’ of the oxidative deamination of NE, 5HT, PEA and other biogenic amines may contribute to the clinical action of this drug. There has been very little work on the effect of ECT on MAO activity. The only human study, investigators could come across has been done by Mann (1979), who did not find any significant change in pretreatment and posttreatment values. However, Pryor and Otis (1970) and Pryor et al. (1972) working on animal brain MAO activity observed that multiple ECT causes increased enzyme activity persisting for several weeks.

A significant decrease in platelet MAO activity in post-treatment phase, as found in this investigation, supports the hypothesis of increased post synaptic activity of catecholamines after ECT (Grahame-Smith et al., 1978). There is still more research to go in establishing the exact mechanism of action of ECT.

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REFERENCES

Davidson, J. Mcleod, M., Linnolla, M., Kenland. A. and White, H. L. (1978). Platelet MAO inhibition following tricyclic antidepressant therapy. American J. Psychiat., 135, 603.

Edwards, D. J. and Burns, M. (1974). Effects of tricyclic antidepressants upon human platelet monoamine oxidase. Life Sciences, 15, 2045.

Giller, E., Jatlow, P., Bilados, D., Harkness, L. and Docherty, J. P. (1980). Platelet MAO and amitryptiline treatment. Psychiatric Res., 2, 259.

Grahame-Smith, D. G., Green, A. R. and Costain, D. W. (1978). Mechanism of the antidepressant action of electroconvulsive therapy. Lancet, 1, 254.

Gupta, A. K., Sethi, B. B. and Trivedi, J. K. (1985). Platelet MAO activity in chronic schistomia. Indian J. Psychiat., 27, 279-286.

Hamilton, M. (1960). A rating scale for depression. Journal Neurol. Neurosurg. Psychiat., 23, 56.

Mann, J. (1979). Altered platelet MAO activity in affective disorders. Psychological Med., 9, 729.

Manual of the International Statistical Classification of diseases, injuries and causes of death. Ninth revision. Section V, Mental Disorders. World Health Organization, Geneva, 1977.

Miller, L. (1976). Psychological theories of E. C. T.—A review. British J. Psychiat., 113, 301.

Ottason, J. O. (1980). Experimental studies of the mode of action of electroconvulsive therapy. Acta Psychiat. Scand., 141, 1.

Pryor, G. T. and Otis, L. S. (1970). Persisting effects of chronic electroshock seizures on brain and behaviour in two strains of rats. Physiological Behav., 5, 1053.

Pryor, G. T., Peachie, S. and Scott, M. K. (1972). The effect of repeated electroconvulsive shock on avoidance conditioning and brain monoamine oxidase activity. Physiological Behav., 9, 623.

Rafaelson, O. J. (1980). Biology of manic melancholic disorders. Medical J. Aust., 1, 627.
Roth, J. A. and Gillis, C. N. (1974a). Some structural requirements for inhibition of type A and B forms of rabbit monoamine oxidase by tricyclic psychoactive drugs. Molecular Pharmacol., 11, 28.

Roth, J. A. and Gillis, C. N. (1974b). Deamination of beta phenylethylamine by monoamine oxidase inhibition by imipramine. Biochemical Pharmacol., 23, 2537.

Reveley, M. A., Glover, V., Sandler, M. and Coppen, A. (1979). Absence of platelet MAO inhibition during amitryptiline or Zimelidine treatment. British J. Psychiat., 8, 375.

Sen Gupta, N., Datta, S. C. and Sen Gupta, D. (1981). Monoamine Oxidase: studies of normal and psychiatric populations in a tropical environment. Enzyme, 26, 191.

Spitzer, R. L., Endicott, J. and Robins, E. (1978). Research Diagnostic criteria: Rationale and reliability. Archives Gen. Psychiat., 35, 773.

Sullivan, J. L., Dackis, C. and Stanfield, C. (1977). In vivo inhibition of platelet MAO activity by tricyclic antidepressants. American J. Psychiat., 134, 188.

Trivedi, J. K., Tandon, S. K., Viswanathan, P. N., Gupta, A. K. and Sethi, B. B. (1987). Platelet MAO activity in chronic schizophrenia. Indian J. Med. Research, 86, 79-83.

Trivedi, J. K., Gupta, A. K., Saxena, A., Viswanathan, P. N. and Sethi, B. B. (1988a). Platelet MAO activity in first degree relatives of chronic Schizophrenics. Indian J. Med. Research, 86, 327-328.

Trivedi, J. K., Lal, N., Singh, R. P. and Viswanathan, P. N. (1988b). Platelet MAO in Unipolar and Bipolar depression. Indian J. Med. Research, 88, 165-168.

Weaver, L., Williams, R. and Rush S. (1976). Current density in bilateral and unilateral ECT. Biological Psychiat., 111, 303.