British Journal of Psychiatry (1984), **144,** 643–645

Prolactin Levels after Bilateral and Unilateral ECT

CONRAD SWARTZ and RICHARD ABRAMS

Summary: Serial post-ictal serum prolactin levels were obtained over a period of one hour after bilateral or unilateral electroconvulsive therapy (ECT) in six patients. Bilateral ECT yielded significantly higher mean post-ictal prolactin levels than unilateral ECT at the 15, 20, 30 and 60 minute sampling times. These findings demonstrate a greater hypothalamic-stimulating effect of bilateral than unilateral ECT, and may explain the reported therapeutic advantage of bilateral over unilateral ECT in the treatment of patients with melancholia.

Serum prolactin levels typically increase many-fold after *grand mal* seizures, whether due to epilepsy (Trimble, 1978), or induced by electroconvulsive therapy (ECT) in man (Ohman *et al,* 1976; O'Dea *et al,* 1978; Balldin, 1982) or electroconvulsive shock in animals (Swartz and Dunbar, in press). Such elevations last for about an hour; they do not occur after hysterical fits (Trimble, 1978) or anaesthesia alone (Arato *et al,* 1980). The hypothalamus appears to regulate prolactin release from the anterior pituitary through a dopamine-mediated tonic inhibitory mechanism (MacLeod and Lamberts, 1979); other neurotransmitters (serotonin, endorphins) also appear to elevate prolactin levels (Kordon *et al,* 1973; Garthwaite and Hagen, 1979; Guidotti and Grandison, 1978). Post-ictal prolactin release reflects the aggregate effects of several hypothalamic neurotransmitters (Swartz and Dunbar, in press), and ECT-induced post-ictal changes in serum prolactin levels provide an indirect measure of hypothalamic stimulation. The quantity of neurotransmitters released in the hypothalamus during ECT may depend upon local electrical or seizure activity as well as seizure-induced changes in other parts of the brain.

The present study was designed to compare the difference between the hypothalamic stimulation achieved with bilateral and unilateral ECT by measuring serial post-ictal prolactin levels.

Methods

Consecutive male patients referred for ECT to a university psychiatric service were included for study if they provided informed consent and had not received neuroleptic or other drugs known to affect prolactin release during the prior three weeks. Six patients were studied: five unipolar depressives and one with a chronic delusional disorder. Each patient received a course of at least six ECT administered at the rate of one treatment three times a week. Samples were taken only following the first six treatments. Patients alternately received unilateral and bilateral ECT as the initial treatment. Subsequent treatments alternated between unilateral and bilateral electrode placements. In this way, we were able to compare the difference between the effects of unilateral and bilateral ECT within each subject.

Treatments were given 30–45 minutes after a pre-anaesthetic dose of atropine 1.0 mg intramuscularly. A base line blood sample was drawn and then anaesthesia was induced by a bolus of 50 to 100 mg methohexitone followed by 40 to 80 mg succinylcholine. Bilateral ECT was administered through standard bi-fronto-temporal electrodes and unilateral ECT was given according to the placement of d'Elia and Raotma (1975). In each case a pulsed bi-directional square-wave stimulating current of 70 Hz and 1.5 ms pulse width was passed for two seconds (0.21 s of current) resulting in a fully generalized bilateral tonic-clonic *grand mal* seizure. Seizure activity was recorded through bi-frontal EEG leads and the duration of visually observed muscular convulsive activity was also recorded. Repeat blood samples for prolactin were obtained through an indwelling venous catheter at 5, 10, 15, 20 and 30 minutes after termination of visible muscular convulsive activity while the patient remained supine. A 60 minute sample was obtained by routine venipuncture after the patient had returned to his hospital ward. Samples were allowed to clot at room temperature, then centrifuged and the serum was stored at −20° centigrade. All samples were analyzed at the same time within three months of collection. Only barbiturate or benzodiazepine sedatives were to be permitted during the study period and one subject did receive a parenteral neuroleptic following his third

ECT, but only the data from his first three seizures were included.

Prolactin concentrations were determined in duplicate by radio-immunoassay (coefficient of variation = 7.8 per cent), and the samples averaged for analysis. Separate mean prolactin levels after unilateral and after bilateral ECT were calculated for each patient and the resultant values combined across the six patients. The difference between the mean prolactin levels obtained with the two treatment methods was tested by one-tailed paired t-tests with five degrees of freedom.

Results

Of the potential 252 serum prolactin samples (seven samples for each of six seizures in six patients), 21 were dropped due to neuroleptic administration, 18 were not obtained or lost in handling, and 11 were rejected because they were out of assay range.

The Figure shows the post-ictal time course of prolactin levels for the two treatment methods. The shapes of the curves are similar, but the mean values after bilateral ECT are higher at each post base line sampling time. These mean bilateral-unilateral differences are significant at 20 and 30 minutes post-seizure ($P = .03$ and $P = .02$, respectively), and they approach significance at the 15 and 60 minute sampling times ($P = .09$ in both instances).

The time of appearance of the peak post-ictal prolactin concentration averaged 15.3 minutes for both unilateral and bilateral treatments but there was a negligible difference between the groups in the temporal distribution of the peak levels (44 per cent of peak levels occurred at 15 minutes, 25 per cent at 10 minutes, 16 per cent at 20 minutes, 9 per cent at 30 minutes, 6 per cent at 5 minutes, and none at 60 minutes.

In all but two of 32 seizures (both in the same subject), the smallest 15-minute post-ictal prolactin elevation showed a 173 per cent increase over the baseline level.

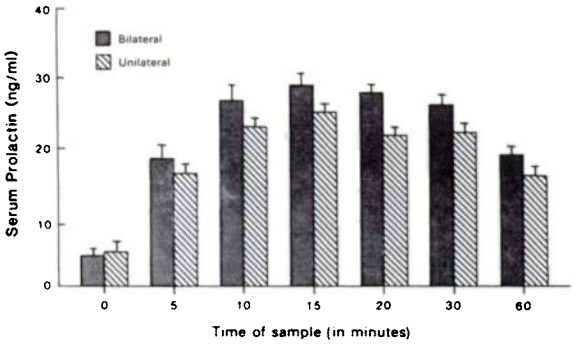

FIG. Prolactin levels after bilateral and unilateral ECT.

The mean seizure duration for unilateral and bilateral ECT was 41.3 and 40.0 seconds respectively and the correlation coefficient between seizure duration and serum prolactin levels was 0.16 (NS).

Discussion

The total amount of hypothalamic stimulation induced by an ECT seizure is presumably reflected by the total quantity of prolactin released. The prolactin elevations seen at five and 60 minutes after the seizure were far below peak elevations, suggesting that the blood levels at these two particular times largely reflect influences other than total hypothalamic stimulation (e.g. rates of hormonal transport and metabolism).

These observations demonstrate that bilateral ECT stimulates the hypothalamus more than unilateral ECT. The absence of a correlation between seizure duration and post-ictal prolactin levels suggests that this difference in stimulating activity depends upon differences in the cerebral distribution of electrical currents or seizure activity.

Using a mathematical model of intracerebral current densities, Weaver *et al* (1976) proposed that bilateral ECT would produce more hypothalamic stimulation than unilateral ECT in an hypothetical homogeneous spherical brain. Our data are consistent with this proposal and with the recently reported therapeutic advantage of bilateral over unilateral ECT (Abrams *et al*, 1983). Several signs and symptoms of melancholia (anorexia, insomnia, constipation, decreased libido, amenorrhea, diurnal variation) reflect dysfunction of systems regulated by the hypothalamus (Pollitt, 1965); Carney and Sheffield (1975) hypothesized that ECT relieves melancholia through a direct stimulating effect on diencephalic structures. A therapeutic advantage for bilateral ECT may therefore result from its greater ability to stimulate the hypothalamus (Abrams and Taylor, 1976).

That the therapeutic essence of hypothalamic stimulation may be electrical is suggested by a recent report (Robin and deTissera, 1982) that high-energy ECT currents were more therapeutic than low-energy ones in the treatment of depressed patients, even though the seizures were equivalent in duration. On the other hand, our finding that more hypothalamic neurotransmitter release follows bilateral ECT suggests that change of synaptic contents in the hypothalamus is the therapeutic mechanism of ECT. That ECT selectively induces release of some but not all neurohormones (Whalley *et al*, 1982; Arato *et al*, 1980) and raises some but not all hypothalamic neurotransmitter concentrations (Woo *et al*, 1980) implies that such changes are

more specific than simply a general disruption by either the electric current or the seizure.

References

ABRAMS, R. & TAYLOR, M. A. (1976) Diencephalic stimulation and the effects of ECT in endogenous depression. *British Journal of Psychiatry*, **129**, 482–5.

—— —— FABER, R. *et al*, (1983) Bilateral versus unilateral electroconvulsive therapy: efficacy in melancholia. *American Journal of Psychiatry*, **140**, 463–5.

ARATO, M., ERDOS, A., KURCZ, M. *et al*, (1980) Studies on the prolactin response induced by electroconvulsive therapy in schizophrenics. *Acta Psychiatrica Scandinavia*, **61**, 239–44.

BALLDIN, J. (1982) Factors influencing prolactin release induced by electroconvulsive therapy. *Acta Psychiatrica Scandinavia*, **65**, 365–9.

CARNEY, M. W. P. & SHEFFIELD, B. F. (1973) Electroconvulsive therapy and the diencephalon. *Lancet*, **1**, 1505.

D'ELIA, G. & RAOTMA, H. (1975) Is unilateral ECT less effective than bilateral ECT? *British Journal of Psychiatry*, **126**, 83–9.

GARTHWAITE, T. L. & HAGEN, T. C. (1979) Evidence that serotonin stimulates a prolactin-releasing factor in the rat. *Neuroendocrinology*, **29**, 215–20.

GUIDOTTI, A. & GRANDISON, L. (1978) Participation of hypothalamic endorphins in the control of prolactin release. In *Advances in Biochemical Pharmacology, Vol. 18*, (eds. E. Costa and M. Trabucchi). New York: Raven Press.

KORDON, C., BLAKE, C. A., TERKEL, J. *et al*, (1973) Participation of serotonin-containing neurons in the suckling-induced rise in plasma prolactin levels in lactating rats. *Neuroendocrinology*, **13**, 213–23.

MACLEOD, R. M. & LAMBERTS, S. W. J. (1979) Clinical and fundamental correlates in dopaminergic control of prolactin secretion. In *Neuroendocrine Correlates in Neurology and Psychiatry* (eds. E. E. Muller and A. Agnoli). Amsterdam: Elsevier.

O'DEA, J. P. K., GOULD, D., HALLBERG, M., *et al*, (1978) Prolactin changes during electroconvulsive therapy in acute schizophrenia. *American Journal of Psychiatry*, **135**, 609–11.

OHMAN, R., BALLDIN, J., WALLINDER, J. *et al*, (1976) Prolactin response to electroconvulsive therapy. *Lancet*, **1**, 936–8.

POLLITT, J. D. (1956) Suggestions for a physiological classification of depression. *British Journal of Psychiatry*, **111**, 489–95.

ROBIN, A. & DETISSERA, S. (1982) A double-blind controlled comparison of the therapeutic effects of low and high energy electroconvulsive therapies. *British Journal of Psychiatry*, **141**, 357–66.

SWARTZ, C. & DUNBAR, E. (1984) Postictal prolactin elevations in rats. *Neuropsychobiology* (in press).

TRIMBLE, M. A. (1978) Serum prolactin in epilepsy and hysteria. *British Medical Journal*, **ii**, 1682.

WEAVER, L., WILLIAMS, R. & RUSH, S. (1976) Current density in bilateral and unilateral ECT. *Biological Psychiatry*, **9**, 303–12.

WHALLEY, L. J., ROSIE, R., DICK, H. *et al*, (1982) Immediate increases in plasma prolactin and neurophysin but not other hormones after electroconvulsive therapy. *Lancet*, **2**, 1064–8.

WOO, J.-I, PARK, C.-W. & LEE, C.-K. (1980) Effect of electroconvulsive shock on the contents of norepinephrine, dopamine and serotonin in rat brain. *Soul Uidae Chapchi*, **21**, 122–32.

*Conrad Swartz, PH.D., M.D., *Associate Professor*

Richard Abrams, M.D., *Professor and Vice-Chairman*

Department of Psychiatry and Behavioral Sciences, University of Health Sciences/The Chicago Medical School, 3333 Green Bay Road, North Chicago, Illinois 60064, U.S.A.

*Reprints and correspondence

(Received 15 April; revised 1 July 1983)