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Role of serotonin$_3$ receptors in prolactin release induced by electroconvulsive therapy: A study with ondansetron

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Abstract

The effect of pretreatment with odansetron on prolactin (PRL) release induced by electroconvulsive therapy (ECT) was examined in 16 depressive patients in a double-blind, placebo-controlled crossover study. Ten patients were pretreated with 4 mg and the other six with 8 mg of ondansetron. The order of administration of study medication (ondansetron and placebo) was counterbalanced. The failure of ondansetron to attenuate ECT-induced PRL release suggested that serotonin$_3$ receptors are not involved in mediating this response.

Keywords: Affective disorder; 5-Hydroxytryptamine; Ondansetron; Psychoendocrinology

1. Introduction

It has long been held that a generalized tonic/clonic seizure of adequate duration must be produced if electroconvulsive therapy (ECT) is to be effective (Cronholm and Ottosson, 1960; APA Task Force, 1990). This view has been recently questioned by Sackeim et al. (1993), who argued that low-dose right unilateral ECT produces 'adequate' seizures as reliably as bilateral ECT, yet it is therapeutically ineffective. Therefore, other biological measures that might reflect the physiological impact of ECT and indicate that an effective stimulus has been delivered should be sought. Prolactin (PRL) release offers such a possibility as the levels of this hormone rise sharply and consistently following ECT. Although a direct relationship between PRL release and clinical outcome has not been established (Whalley et al., 1987; Clark et al., 1995), the PRL rise has been shown to be greater following bilateral than unilateral ECT, and high-energy compared with low energy stimuli (Papakostas et al., 1984; Swartz and Abrams, 1984; Zis et al., 1991, 1993). Since electrode placement and stimulus energy appear to be critical factors in determining not only the magnitude of ECT-induced PRL release but also the therapeutic efficacy and side effects of ECT, understanding the neurotransmitter receptors

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involved in PRL release following ECT is of considerable interest. Such an understanding may provide some insights about the mechanism of action of ECT.

The fact that pretreatment with naloxone, an opioid antagonist, does not abolish the PRL rise after ECT (Haskett et al., 1985), suggests that the opioid system is not involved in this response. Methysergide, a nonselective 5-hydroxytryptamine (5-HT) receptor antagonist, blocks the ECT-induced PRL rise when given before ECT (Papakostas et al., 1988; Zis et al., 1989b). This might suggest the involvement of a serotonergic system in the PRL response to ECT, but a role for the dopaminergic system cannot be excluded because methysergide has dopamine receptor agonistic effects (Lamberts and Macleod, 1979). Pretreatment with the selective 5-HT_2 receptor antagonists ketanserin (Zis et al., 1989a) and ritanserin (Papakostas et al., 1990) does not block the PRL rise following ECT; thus, 5-HT_2 receptors do not appear to be involved. With regard to the role of 5-HT_{1A} receptors, pindolol, a β-blocker with 5-HT_{1A} antagonistic properties, has been reported to attenuate the PRL response to ECT by one group (Zis et al., 1992), but another group (Papakostas et al., 1993) could not confirm this effect. Although methodological differences (e.g., dose of pindolol used) may account for the discrepant findings, resolution of the issue may await the development of more specific 5-HT_{1A} antagonists.

There is some evidence from animal studies to suggest that 5-HT_3 receptors are involved in PRL release (Jorgensen et al., 1992a, 1992b). Ondansetron is a highly selective 5-HT_3 receptor antagonist with little affinity for other 5-HT receptors (Tyers et al., 1989; Hoyer et al., 1994). In the present study, we used a double-blind, placebo-controlled experimental design to examine the effects of pretreatment with ondansetron on ECT-induced PRL release.

2. Methods

Patients who met *DSM-III-R* criteria for major depressive disorder (American Psychiatric Association, 1987), as determined by a semistructured clinical interview, and who had been referred for ECT were recruited. All study patients had been drug free with the exception of benzodiazepines for ≥ 1 week before the first day of their participation in the study. Patients who had received fluoxetine within the previous 5 weeks or monoamine oxidase inhibitors within 2 weeks were excluded. Patients who had received a course of ECT within the previous 6 months were also excluded. The study was approved by the Ethics Committee of the University of British Columbia. All subjects gave written informed consent for participation in the study.

Patients were studied while receiving two consecutive treatments during a course of ECT. Anesthesia was induced with sodium thiopental and muscle relaxation with succinylcholine. Doses were individually adjusted during the first two treatments and remained unchanged for the duration of the study. A Thymatron ECT apparatus with flexdial controller (Somatics, Inc.) was used to deliver the electrical stimulus. The stimulus parameters included a frequency of 70 Hz, pulse width of 1 ms, and current of 0.9 A as set by the manufacturer. The duration of the stimulus was the only variable manipulated to determine seizure threshold and deliver treatments. Seizure duration was monitored with the pressure-cuff method (Fink and Johnson, 1982).

Seizure threshold (defined as the least amount of electrical energy necessary to produce a bilateral seizure lasting ≥ 30 s) was estimated during the first treatment. In subsequent treatments, a stimulus that was just above threshold (for bilateral ECT) or 3 times the seizure threshold (for unilateral ECT) was used. Further adjustments to maintain an adequate seizure duration (≥ 25 s) were performed as necessary but before the first of the two study treatments. The stimulus parameters used to elicit a seizure were similar during both treatments.

A total of 16 patients (11 women and 5 men) took part in two separate studies. The first 10 consecutive consenting patients (7 women and 3 men) participated in study 1, and the next six (4 women and 2 men) participated in study 2. The mean age of subjects was 53.30 years (SD = 14.61) in study 1 and 39.67 years (SD = 19.60) in study 2. In study