Role of serotonin3 receptors in prolactin release induced by electroconvulsive therapy: A study with ondansetron

Lakshmi N. Yatham*, Athanasios P. Zis, Raymond W. Lam, Manit Srisurapanont, Kathleen McGarvey, Oluwafemi Agbayewa

Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, V6T 2A1, Canada

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Abstract

The effect of pretreatment with ondansetron 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 serotonin3 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...
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-HT2 receptor antagonists ketanserin (Zis et al., 1989a) and ritanserin (Papakostas et al., 1990) does not block the PRL rise following ECT; thus, 5-HT2 receptors do not appear to be involved. With regard to the role of 5-HT1A receptors, pindolol, a β-blocker with 5-HT1A 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-HT1A antagonists.

There is some evidence from animal studies to suggest that 5-HT3 receptors are involved in PRL release (Jorgensen et al., 1992a, 1992b). Ondansetron is a highly selective 5-HT3 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 semistruc-
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