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The impact of galantamine on cognition and mood during electroconvulsive therapy: A pilot study

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Abstract

Objectives: The purpose of this study was to: (1) assess the effectiveness of galantamine in the prevention of cognitive impairments during ECT treatment and (2) to explore the safety and tolerability of galantamine during ECT treatment.
Methods: Nine consecutive ECT patients were given galantamine 4 mg bid throughout the course of their ECT treatments followed by a second cohort of eight consecutive ECT patients who did not receive galantamine. Objective measures of cognitive functioning and depression severity were performed pre-ECT and post-ECT. Subjective ratings of depression, confusion, and side effects were obtained weekly.
Results: The two groups were similar in age, gender and admission Global Assessment Functioning (GAF) scores. There were no significant between group differences found with regards to mean seizure duration, energy administered to induce seizures, blood pressure, or heart rate during and post-ECT treatment. None of the patients discontinued galantamine due to side effects and there were no severe adverse drug reactions. Patients receiving galantamine performed significantly better on delayed memory and abstract reasoning following ECT. The galantamine group showed a greater but non-significant mood improvement (repeated measure ANOVA).
Conclusions: Our data support the hypothesis that galantamine may reduce cognitive impairment during ECT, especially with regards to new learning. In addition, galantamine may also enhance the antidepressant action of ECT. Galantamine was both safe and well tolerated during ECT.

Keywords: Electroconvulsive therapy (ECT); Acetylcholinesteras inhibitors; Galantamine (Reminyl); Nicotinic receptor

1. Introduction

Electroconvulsive therapy (ECT) is a highly effective treatment for severe major depressive disorder (MDD) (Sackheim, 1989). It has been estimated that approximately 10% of all patients admitted to the hospital for treatment of MDD receive ECT. However, one major complication of ECT is the potential for temporary mild to moderate cognitive impairment (McElhiney et al., 1995; Sackeim, 1992; Squire, 1986). The cognitive side effects of ECT include retrograde amnesia (reduced ability to recall recent events), anterograde amnesia (reduced ability for new learning), and prolonged postictal delirium and confusion (Frith et al., 1987; Squire et al., 1976; Steif et al., 1986; Devanand et al., 1989). Research has shown that the cognitive deficits associated with ECT are directly related to the treatment and not a side effect of the anesthesia that accompanies the treatment (Frith et al., 1983). For example, in a study comparing real ECT and sham ECT (general

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anesthesia with no ECT), the real ECT group achieved great recovery from depression but also evidenced impairments in attention, short-term memory, and new learning relative to the sham ECT group (Frith et al., 1983). Furthermore, at 6 months post-ECT the two groups showed no differences in cognitive functioning indicating that ECT-induced deficits were temporary. While little is currently known about the factors that contribute to ECT-induced cognitive deficits or their pathophysiology, recent studies have implicated the left temporal frontal region. A recent neurophysiological study has implicated increased activity in the left frontotemporal brain regions with longer recovery from post-ECT global cognitive impairment (Sackeim et al., 2000). A PET study has suggested that cognitive deficits of ECT are associated with decreased activities in the left temporal region (Mitchell et al., 2001). Other studies have shown that patients with treatment resistant depression and patients with elevated serum cortisol report more severe and persistent cognitive deficits when treated with ECT (Frith et al., 1983; Neylan et al., 2001). Currently, no interventions are available to protect against the development of ECT-related cognitive deficits and these cognitive side effects are, unfortunately, the primary reason that patients discontinue or refuse ECT.

Brain cholinergic systems have been implicated in the mediation of memory and cognitive processes. Bartus et al. have reviewed the data suggesting that Alzheimer's patients suffer from reduced cholinergic tone (reduced choline acetyltransferease activity in the cerebral cortex and possible loss of cholinergic innervation from the nucleus basalis of Meynert) (Bartus et al., 1982). Moreover, Lerer (1985) has demonstrated that chronic electroconvulsive shock (ECS) in rats lead to reduction of brain muscarinic cholinergic receptors and a diminished cataleptic response to the muscarinic agonist, pilocarpine. He further hypothesized that ECS effects on brain cholinergic functioning might underlie ECT-induced memory deficits (Lerer, 1985). Given this hypothesized mechanism of action, it would be expected that acetylcholinesterase inhibitors, which would increase brain cholinergic tone, might prevent or reverse memory and/or cognitive deficits. The well-documented ability of acetylcholinesterase inhibitors to slow the cognitive decline in patients with Alzheimer's disease also suggests that they may have the potential to slow or prevent cognitive deficits secondary to ECT. One study has shown that the administration of physostigmine (an acetylcholinesterase inhibitor) reverses memory impairment following ECT (Levin et al., 1987). While there have been some anecdotal reports suggesting the potential usefulness of combining cholinesterase inhibitor medications with ECT (Zink et al., 2002; Bowman, 2002) there is only one randomized controlled trial that systematically evaluated the effectiveness of an acetylcholinesterase inhibitor in improving ECT-induced memory loss. Prakash et al. examined the immediate post-ECT period, and demonstrated that donezepil (compared to placebo) was associated with more rapid recovery of personal memory (date of birth, workplace) and alertness (Prakash et al., 2006).

Galantamine (Reminyl[1]), a novel treatment for Alzheimer's disease, has a dual mechanism of action, providing both a reversible competitive inhibition of acetylcholinesterase and an allosteric modulation of nicotinic acetylcholine receptors (Sramek et al., 2000). Several randomized, placebo-controlled studies have demonstrated the effectiveness of galantamine in retarding cognitive impairment in patients with Alzheimer's disease for up to 12 months (Raskind et al., 2000; Tariot et al., 2000; Maelick, 2001). The dual action of galantamine may enhance its effectiveness for treating others forms of dementia such as vascular dementia (Maelick, 2001) as well as for treating memory deficits associated with psychiatric conditions like schizophrenia (Levin et al., 1996). Galantamine, with its broad spectrum of efficacy and its tolerability, appears to be an ideal agent with which to begin investigating the ability of this class of drugs to reduce or possibly prevent the development of cognitive side effects associated with ECT.

The purpose of this pilot study was to explore the potential adjunctive use of galantamine in patients receiving ECT. We were especially interested in evaluating the safety and tolerability of galantamine in patients undergoing ECT and to explore the potential cognitive and mood benefits that galantamine might offer.

2. Materials and methods

2.1. Study design

This study was carried out in accordance with the most recent Declaration of Helsinki. The study was reviewed by Massachusetts General Hospital Internal Review Board (MGH-IRB) and all subjects signed MGH-IRB approved consent forms after the study procedures were thoroughly explained. All subjects received a comprehensive psychiatric evaluation and were given a diagnosis based on DSM-IV criteria. They all received a physical examination and a comprehensive laboratory panel including electrolytes, BUN, creatinine, calcium, phosphorus, magnesium, LFTs, CBC with differential, TSH, serum B12, and folic acid levels. Potential subjects were excluded if they suffered from significant cardiac conduction abnormalities, brady arrhythmias, hepatic impairment, gastric ulcer disease, renal impairment, respiratory disease, seizure disorder, inflammatory disease or urinary tract obstructions. The diagnostic profile included: major depressive disorder (52%), bipolar disorder (35%), and schizoaffective disorder (12%). Medications with anticholinergic properties were avoided throughout the study.

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