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Lithium addition in antidepressant-resistant depression: Effects on platelet 5-HT, plasma 5-HT and plasma 5-HIAA concentration

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Abstract

The efficacy of the addition of lithium to an established course of antidepressant treatment can be explained by a synergistic effect of the two drugs on central 5-HT neurotransmission. In the present study we investigated the effect of lithium addition on the 5-HT concentration in plasma and platelets and the concentration of 5-HIAA. Thirty-nine depressed inpatients who fulfilled the DSM-IV criteria for major depressive disorder and who did not respond to monotherapy with either imipramine or fluvoxamine participated in this study. Concentration of 5-HT in both plasma and platelets did not change significantly during lithium addition. The 5-HT ratio (plasma concentration/platelet concentration) shows a small non-significant increase after 3 weeks lithium addition. The mean concentration of 5-HIAA shows a significant increase during lithium addition; with no difference between the imipramine and the fluvoxamine sample. The increments in 5-HIAA concentration during lithium addition are indicative of an increased 5-HT turnover.

Keywords: Lithium addition; Major depression; Plasma 5-HIAA; Plasma 5-HT; Platelet 5-HT

1. Introduction

Many open studies and at least 11 double-blind studies have suggested that the addition of lithium to an established course of an antidepressant may convert 50–60% of patients who have failed to respond into responders; these studies were included in a meta-analysis that confirmed the efficacy of this strategy (Bauer and Dopfmer, 1999). The antidepressant efficacy of the antidepressant–lithium combination can be explained by a synergistic effect of the two drugs on central serotonin (5-HT) neurotransmission (de Montigny et al., 1981).

Animal studies showed that prolonged antidepressant administration increases the sensitivity of postsynaptic 5-HT_{1A} receptors in the hippocampus (van Praag, 2005; de Montigny and Aghajanian, 1978), and lithium treatment facilitates the release of 5-HT in hippocampal neurons (Blier and de Montigny, 1985).

The effect of lithium on human central 5-HT neurotransmission has been studied in neuroendocrine studies. The pharmacological challenge test used most frequently to study central 5-HT function is the prolactin response to the 5-HT precursor, L-tryptophan (Price et al., 1990). Intravenous administration of L-tryptophan leads to an increase of plasma prolactin (Cowen et al., 1989, 1991), presumably by increased central 5-HT neurotransmission. Lithium treatment results in an even larger increment of plasma prolactin by L-tryptophan (Cowen et al., 1991).

In addition, lithium treatment results in a higher plasma cortisol response to the 5-HT agonist fenfluramine (Muhlbauer and Muller-Oerlinghausen, 1985). The above-mentioned studies provide evidence that lithium increases central 5-HT function.

Abbreviations: 5-HT, serotonin; 5-HT_{1A} receptor, serotonin receptor; 5-HIAA, 5-hydroxyindoleacetic acid; HRSD, Hamilton Rating Scale for Depression; SADS, Schedule for Affective Disorders and Schizophrenia; MAO, monoamine oxidase; ANOVA, Analysis of Variance.

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The human platelet is frequently used as a peripheral model for the central 5-HT neurons. This has been based on striking similarities between neurons and platelets with regard to serotonin uptake, storage and release. Although platelet 5-HT, and to a lesser extent, plasma 5-HT have been extensively studied in investigating the effects of antidepressants on 5-HT neurotransmission, we are not aware of a previous study on the effect of lithium addition on platelet and plasma 5-HT levels, and 5-HIAA levels. Presynaptic reuptake of 5-HT is considered to be reflected by the 5-HT content in platelets (Fekkes et al., 1997; Mann et al., 1992), while plasma 5-HT levels might be a peripheral indicator of central 5-HT activity (Sarrias et al., 1990).

Prolonged administration of 5-HT reuptake inhibitors/mixed reuptake inhibitors leads to large decrements in the platelet 5-HT content. Therefore, during lithium addition, there are only small amounts of 5-HT that could be released into the plasma. A shift in the equilibrium of peripheral 5-HT may be reflected by a change in the 5-HT plasma/platelet ratio.

In the present study we investigated the effect of short-term (1 week) and prolonged (3 weeks) lithium addition on both the concentration of 5-HT in plasma and platelets and the plasma level of 5-HIAA. Our hypothesis was that the addition of lithium would increase plasma 5-HT, the 5-HT plasma/platelet ratio and the 5-HIAA plasma level, and that these increments are correlated with the level of improvement of depression as measured with the Hamilton Rating Scale for Depression (HRSD).

2. Methods

The study was performed at the inpatient depression unit of the Department of Psychiatry at the Erasmus University Medical Centre Rotterdam. It is routine practice to discontinue psychotropic drugs after admission. Depressed patients were screened for in- and exclusion criteria. The study protocol was approved by the medical ethical board of the University Hospital Rotterdam, and the study was carried out in accordance with the ethical standards laid down in the World Medical Association Declaration of Helsinki. Eligible patients provided written informed consent after study procedures were fully explained.

2.1. Patient population

Eligible for inclusion were patients aged 18 to 65 years who fulfilled the DSM-IV criteria for major depressive disorder which was diagnosed by the administration of the depression part of the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott, 1978) and who had a 17-item HRSD score ≥ 17. Subject exclusion criteria were schizophrenia, schizoaffective disorder, bipolar disorder, organic brain syndrome, chronic alcohol or drug abuse, relevant somatic illness (e.g. thyroid disease) and pregnancy or inadequate contraception for women in the fertile age group.

2.2. Study design

After a washout period of 7–10 days, patients received 75 mg/day of imipramine or fluvoxamine during days 1–2 and then 150 mg/day for days 3–8, unless severe side-effects emerged. Plasma levels of both antidepressants were monitored weekly, and doses were adjusted to obtain plasma levels of 200–300 ng/ml for imipramine plus desmethylimipramine and 150–200 ng/ml for fluvoxamine. Scoring of the 17-item HRSD was performed weekly. The use of concomitant psychotropic medication was prohibited, with the exception of lorazepam (maximum: 3 mg/day), although its use was strongly discouraged. Four weeks after achievement of an adequate plasma level of imipramine or fluvoxamine, lithium was added to the antidepressant for patients scoring ≥ 14 on the HRSD.

Patients receiving lithium addition continued their double-blind medication and had lithium added in an initial dose of 600 mg at 8.00 p.m. Blood lithium level was measured on day 7 and weekly thereafter, 12 h post dose. The dose was adjusted to achieve a lithium level of 0.6–1.0 mmol/l as soon as possible. Response was evaluated by the final HRSD assessment; 3 weeks after patients reached the target lithium level.

2.3. Blood sampling and biochemical analysis

Blood sampling was carried out at the end of the washout period (T1), after patients had received antidepressant monotherapy with predefined plasma levels for 4 weeks (T2), and during lithium addition, both after 1 week (T3) and 3 weeks (T4) predefined lithium plasma level. Ten milliliters of blood was drawn between 8.00 and 8.30 a.m. from the anterocubital vein using K_3-EDTA Vacutainer tubes. Immediately after sampling the blood was centrifuged for 20 min at 90 $\times g$ (room temperature). The platelet-rich plasma was carefully pipetted and aliquots were frozen at −80 °C for 5-HT determination. The remaining platelet-rich plasma was centrifuged for another 20 min at 2650 $\times g$ (room temperature) and the platelet-poor plasma was subsequently frozen until 5-HT determination. The concentrations of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were measured in duplicate by high performance liquid chromatography combined with electrochemical detection (assay detection limits in plasma are: 1 nmol/l for both substances). For further details the reader is referred to Fekkes et al. (1997) and Borgdorff et al. (2002).

2.4. Statistical analyses

For intergroup comparisons *t*-tests were used for continuous variables and χ^2 tests for categorical variables.

The 5-HT ratio was calculated by dividing the 5-HT plasma concentration by the 5-HT platelet concentration. The change in mean plasma 5-HT and 5-HT ratio at T4 and T3, respectively as compared with T2, were analysed with repeated measures ANOVA. As a further measure of increased 5-HT activity, levels of 5-HIAA at T2, T3 and T4 were analysed with repeated measures ANOVA, comparing 5-HIAA at T2 with 5-HIAA at both T3 and T4.

All repeated measures ANOVA analyses were performed with baseline values and type of antidepressant (imipramine or fluvoxamine) as covariables. The influence of antidepressant response to lithium addition, as measured by the change in HRSD