ORIGINAL ARTICLE

CLINICAL CORRELATION OF ALTERATION OF ENDOGENOUS ANTIOXIDANT-URIC ACID LEVEL IN MAJOR DEPRESSIVE DISORDER

K Chaudhari, S Khanzode*, S Khanzode, G Dakhale****, A Saoji** and S Sarode***
Departments of Pharmacology, *Medicine, **Psychiatry and ***Physiology,
Government Medical College Nagpur, Maharashtra-440003, India.
****Department of Pharmacology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.

ABSTRACT
Derangement of antioxidant levels in major depressive disorder had been correlated with oxidative damage. The effect of Selective Serotonin Re-Uptake Inhibitors on endogenous antioxidant uric acid levels in major depressive disorder has never been examined. This was a prospective; open labeled, parallel, 12 weeks study, in which serum uric acid levels and Hamilton Rating Scale for Depression score were estimated in age and sex matched thirty-six healthy and forty major depressive disorder subjects before and after fluoxetine and citalopram treatment. Significant decrease in serum uric acid (P<0.0001) was observed in newly diagnosed major depressive disorder subjects when compared to healthy subjects. The trend was reversed after 6 weeks more significantly after 12 weeks of treatment with improvement in Hamilton Rating Scale for Depression score. Also, Significant and negative correlation was found between Hamilton Rating Scale for Depression score and serum uric acid level (r= -0.864, P<0.001) after 12 weeks of treatment. Treatment with fluoxetine or citalopram reverses endogenous antioxidants like uric acid and improves Hamilton Rating Scale for Depression score in major depressive disorder.

KEY WORDS
Uric acid, Citalopram, Fluoxetine, Hamilton Rating Scale for Depression score, Major depression, Selective Serotonin Re-Uptake Inhibitors.

INTRODUCTION
Mental health problems are among the most important contributors to the burden of disease and disability worldwide. A recent WHO report predicts that depression will be the leading cause of disability and premature death by 2020, second only to Ischaemic Heart Diseases (1). The illness has a poor outcome in spite of best available treatment. However the majority of patients respond to pharmacological treatment if diagnosed early. Hence development of novel strategies to improve outcome, which include early diagnosis and treatment, will be of great benefit to patient of major depression.

Several investigators have implicated the role of oxidative stress in major depression. Abnormal levels of antioxidant enzymes and lipid peroxidation in major depression further substantiates the role of free radical in major depression (2, 3). Neurons are especially vulnerable to free radical attacks. Insufficient defenses with exposure to excess reactive oxygen species (ROS) can lead to neuronal dysfunction and death of neuron. Oxidative stress is one of the important mechanisms that causes the destruction of nerve cells and decrease the volume of hippocampus in patients of major depression (4). The major antioxidative defenses include both enzymatic and non enzymatic antioxidants. The levels of enzymatic antioxidants like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSHPx) etc. are altered in major depressive patients (5).
Selective Serotonin Re-Uptake Inhibitors (SSRIs) modify both enzymatic antioxidants and lipid peroxidation (3). Albumin, bilirubin, uric acid and ascorbic acid are some of the non enzymatic antioxidants in the body (6, 7). The non enzymatic antioxidant levels are also modified in major depression. Accumulating evidence suggest lowering of these antioxidants in patients of major depression (8, 9, 10). SSRIs also modify some of the non enzymatic antioxidant levels (11, 12).

Although incidence of major depressive disorder (MDD) is increasing the knowledge about its early diagnosis is overlooked due to lack of organized data available to clinicians. Evaluation of such biochemical markers would certainly be of useful and supportive for early diagnosis and monitoring of treatment response.

In recent years SSRIs have been used as first line drugs in the treatment of major depression. They lack cardiac toxicity and anticholinergic effect present in the older generation of antidepressants like Mono-amine Oxidase (MAO) inhibitors and Tricyclic Antidepressants (TCAs). They are more effective antidepressants like Mono-amine Oxidase (MAO) inhibitors and anticholinergic effect present in the older generation of the treatment of major depression. They lack cardiac toxicity in long-term treatment as indicated by fewer cases of relapses in the patients taking these medicines (13).

So far the conducted studies did not bring unequivocal explanation of relation between non-enzymatic antioxidants and serotonin reuptake inhibitors. Non enzymatic antioxidants like albumin, globulin and total proteins were studied by some authors but in relation to acute phase response and MDD (9). Uric acid is a potent endogenous antioxidant in the body (6). As per our knowledge and recent internet search although alteration in the uric acid in MDD are reported (8, 10), no study has ever been reported the alteration of uric acid after SSRIs in particularly fluoxetine and citalopram treatment. Lack of conclusive information regarding the potential of such biochemical variable like uric acid as supportive prognostic indicator or predictor of treatment response in MDD has encouraged us to analyze changes induced by SSRIs on serum uric acid level in MDD.

**MATERIALS AND METHODS**

This prospective, open labeled, randomized, non-cross over 12 weeks trial was carried out in the Outpatient Department of Pharmacology and Department of Psychiatry, Government Medical College and Hospital (GMCH) Nagpur, India. The trial procedure was in accordance with the guidelines of 1964 declaration of Helsinki.

Study groups consist of a control group of healthy subjects and that of major depression. Healthy adult subjects more than 18 years of age, of both sexes, more than 50 Kilogram body weight, taking good diet, preferably vegetarian, non-smoker, non-alcoholic, free of medication for at least one month prior to study were selected as controls. Controls were excluded for history of any psychiatric illnesses. Subjects of MDD were maintained on their usual dietary pattern. Subjects were kept on self-selected diets and were instructed not to make any major change in dietary pattern during the trial period. Compliance to the dietary restriction was determined by obtaining a twenty-four hour dietary recall from the subjects on two occasions during each one-month period.

The subjects included in the study were of both genders between the age group of 18-65 years and were able to comprehend and provided written consent prior to study. MDD was diagnosed by trained psychiatrist using DSM IV criteria and 21-item Hamilton Rating Scale for Depression (HRSD) score to measure the severity of disorder. The subjects with score less than 14 in 21 item HRSD scale and associated psychiatric disorders accompanying major depression were excluded from the study. Medical illnesses including endocrine, metabolic disorders known to affect free radical status and uric acid levels were also excluded. Further, subjects with abnormal liver and kidney function and on non-vegetarian diet like meat, fish etc., which are rich sources of uric acid and taking any other medication, were excluded from the study.

The trial was started after approval of institutional ethics committee GMCH Nagpur. Informed consent material about the drug trial was prepared in English and the local vernacular language. The information was read out to all the potential participants and doubts regarding the trial procedure were clarified. Thirty-six healthy subjects and forty major depressive subjects participated in the trial. The sample size was calculated on the basis of previous similar studies (3, 5) by using Graph Pad Prism Version 3.02 software and considering future drop outs during the trial.

After taking consent and screening with routine investigations, physical examination and obtaining HRSD scale, subjects suitable for drug treatment were allocated randomly to either fluoxetine (20 mg/day) or citalopram (20 mg/day) groups depending upon a computerized randomization programmer. Fasting blood samples were obtained at week 0 and at the end of 6th week and 12th weeks from the start of the treatment. For the follow up, similar parameters and routine laboratory analysis were performed to explore any adverse event after drug treatment.