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Comparative study of efficacy of L-5-hydroxytryptophan and fluoxetine in patients presenting with first depressive episode

Purushottam Jangid [a], Prerna Malik [a,*], Priti Singh [a], Minakshi Sharma [b], Anil kumar D. Gulia [a,c]

[a] Department of Psychiatry, Post Graduate Institute of Medical Sciences, Rohtak 124 001, Haryana, India
[b] Department of Biochemistry, Maharishi Dayanand University, Rohtak, Haryana, India
[c] BPS Govt. Medical College, Khanpur Kalan, Sonepat, Haryana, India

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ABSTRACT

Introduction: Role of L-5-hydroxytryptophan (L-5-HTP) in depression is relatively less studied but the literature has shown its robust role in depression. The present randomized double blind study was undertaken to assess the role of L-5-HTP as an antidepressant and to compare its antidepressant efficacy with fluoxetine in first depressive episode patients of Indian population.

Methods: A total of 70 patients of first depressive episode, all of whom were diagnosed with ICD-10 criteria, were recruited but only 60 patients completed the study and were randomly divided into two groups, receiving L-5-HTP and fluoxetine, respectively, for a period of 8 weeks. All patients were administered Hamilton Rating Scale for Depression (HAM-D) to assess severity of depression at baseline, 2 weeks, 4 weeks and 8 weeks. The efficacy of treatment was assessed by comparing HAM-D scores obtained at these examinations with the baseline examination; final evaluation of both efficacy and tolerance was assessed using the Clinical Global Impression (CGI) scale at the end of study.

Results: Both treatment groups showed significant and nearly equal reduction in HAM-D scores beginning at week two and continuing through week eight. Twenty-two patients (73.33%) in the L-5-HTP group and 24 patients (80%) in the fluoxetine group showed positive response at the end of the study.

Conclusion: L-5-HTP has definitely got antidepressant effect in patients of depression. Antidepressant effect was seen within 2 weeks of treatment and was apparent in all degrees of depression. The therapeutic efficacy of L-5-HTP was considered as equal to that of fluoxetine.

1. Introduction

Affective disorders are one of the most common psychiatric disorders and account for nearly 30–40% of the case load at various psychiatric facilities in India (Varma and Das, 1995). There is a marked variability in the prevalence rate of depression across the studies in India which range from 1.5 per 1000 (Sethi and Gupta, 1972) to 37.74 per 1000 (Nandi and Ajmany, 1975). The Epidemiological Catchment Area and National Co morbidity Survey studies suggested that the current rate of major depression is in the realm of 2 – *t*. It is believed that the true life time rate of major depression is probably in the realm of 10–20 per 100 (Joyce, 2009).

A response to a single antidepressant medication, classically measured as an attenuation of 50% or more in the intensity of depressive symptoms, is generally obtained in about 50–75% of patients with a first trial (Lonnqvist et al., 1994). Remission rates, in contrast are generally around 30% with a single agent (Blier et al., 2010). This is a disappointing result indicating that additional treatment measures must be taken in about two-third of patients after using an antidepressant medication at an adequate dose for a sufficient time.

Tryptophan depletion is widely used paradigm to study the role of the serotonergic system in the pathophysiology and treatment of depression (Neumeister, 2003). There are several reports that plasma tryptophan is significantly lower in patients with major depression than in normal controls or in patients with only minor symptoms of depression (Coppen et al., 1973; Cowen et al., 1989). In humans, several studies have shown that reducing serotonin synthesis (by depriving the brain of tryptophan) can induce depression within hours (Neumeister et al., 1998; Delgado et al., 1990; Lam et al., 1996).

Furthermore, administration of tryptophan has been used as an antidepressant but due to its side effects profile, it was no longer used (Shaw et al., 2002).

L-5-Hydroxytryptophan (L-5-HTP) is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan. Therapeutic use of L-5-HTP bypasses the conversion

Abbreviations: L-5-HTP, L-5-hydroxytryptophan; HAM-D, Hamilton Rating Scale for Depression; CGI, Clinical Global Impression.

* Corresponding author. Tel.: +91 9992275525.
E-mail address: pm.malik@yahoo.co.in (P. Malik).

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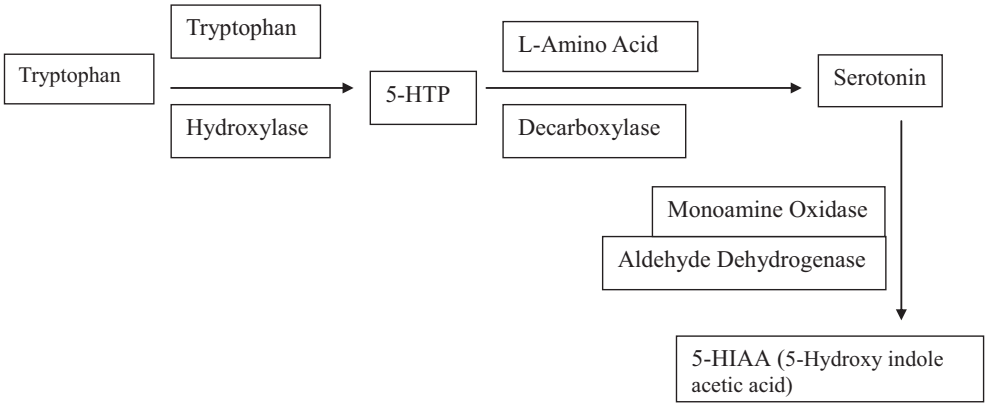

Scheme 1. Mechanism of action of 5-hydroxy indole acetic acid (5-HIAA).

of L-tryptophan into L-5-HTP by the enzyme tryptophan hydroxylase, which is the rate limiting step in the synthesis of serotonin as shown in Scheme 1 (O'Neil and Moore, 2003). L-5-HTP has been used clinically for over 30 years. In addition to depression, the therapeutic administration of L-5-HTP has been shown to be effective in treating a wide variety of conditions, including fibromyalgia, insomnia, binge eating associated with obesity, cerebellar ataxia, and chronic headaches (Birdsall, 1998).

The first large clinical open trial using L-5-HTP in the treatment of depression was done in 1972 with 107 patients having unipolar or bipolar depression using daily oral dosages of L-5-HTP from 50 to 300 mg. Significant improvement was observed in 74 of the patients (69%), and no significant side effects were reported. The response rate in most of these patients was quite rapid (less than 2 weeks) (Sano, 1972).

After this, many double blind, placebo controlled trials with L-5-HTP showed that L-5-HTP was superior to placebo. A double blind study compared L-tryptophan with amitriptyline over a 3 month period among 115 outpatients diagnosed with mild or moderate depression. Based on scores from the Hamilton Rating Scale for Depression (HAM-D) and a global rating of depression, L-tryptophan at a dose of 3 g per day was more effective than the placebo, as effective as amitriptyline, and produced significantly fewer side effects (Thomson et al., 1982).

Other double blind placebo controlled trials evaluated L-5-HTP in comparison with tryptophan in 15 patients with endogenous unipolar or bipolar depression at a daily oral dosage of 200 mg over 4 weeks. Marked improvement was observed in eight of the patients and L-5-HTP was found more effective than tryptophan or placebo (Van Praag, 1984).

It is amply clear that L-5-HTP has potential for being used as alternative to the traditional forms of therapy in depressive disorder; further work needs to be undertaken because no study has been done in the Indian population till date. This raises the question whether results of a western population could be generalized to the Indian population. Therefore, carrying out such studies in the Indian population is mandatory. The present study aims at comparing the efficacy of L-5-HTP and fluoxetine in patients presenting with first depressive episode.

2. Methods

2.1. Sample

This randomized, double-blind, parallel group study was started in May 2009 for 8 weeks in a tertiary center of northern India. The study group consisted of first depressive episode patients attending the Psychiatry Outpatient Department of Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India. Approval from the ethical board of this institute was granted and a sample of 70 outpatients with ICD-10 diagnosis of first depressive episode was recruited. After explaining the purpose and nature of the research, written informed consent to join the study was obtained from the patient, emphasizing that they could withdraw from the study whenever they wished to do so and that withdrawal from the study will no way affect the treatment, ensuring confidentially of the information.

Inclusion criteria included age from 20 to 50 years; patients fulfilling ICD-10 criteria for first episode depression. Exclusion criteria included patients with history of epilepsy, mental retardation, substance use disorder or any other organic brain disease or having taken any form of psychiatric treatment for current episode during the previous month, patients having active suicidal ideas, patients with psychotic symptoms, pregnant females or females planning pregnancy during the study period and refusal to give informed consent.

2.2. Measures

A semi-structured clinical interview: Designed by the author to tap into different socio-demographic variables, duration of illness and medications received.

HAM-D (Hamilton, 1960): This is a multiple choice questionnaire that clinicians may use to rate the severity of depression.

Clinical Global Impression (CGI) scale (Guy, 1976): This is a standardized assessment tool that allows clinician to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI scale consists of three global subscales formatted for use with the Global Scoring Sheet: severity of illness subscale, global improvement subscale and efficacy index subscale.

2.3. Study design

All patients were randomly allotted to two groups by a pharmacist using simple random sampling (34 patients in group A receiving L-5-HTP capsules and 36 patients in group B receiving fluoxetine capsules). To avoid bias, similar looking capsules of both drugs were given along with placebo, so that neither the investigator nor the patients knew which medicines were being used for the treatment. All patients in group A received L-5-HTP capsules 150 mg in three divided dosages during the first 2 weeks and then the dose was doubled (300 mg) after the second week. The dosages were increased to 400 mg in three divided dosages after the fourth week. Thereafter, the same dosages were continued. All patients in group B were given fluoxetine 20 mg capsules along with two placebo dosages during the first 2 weeks