

Alteration of serum levels of interleukin 1 and tumor necrosis factor in depression independent of treatment or overdose of tricyclic antidepressants

Haleh Talaie^{1*}, Mohammad Abdollahi^{1,2}, Abdolkarim Pajoumand¹, Reyhaneh Panahandeh¹, Behjat Barari³, Maryam Baeeri²

ABSTRACT

Introduction: Pro-inflammatory cytokines, such as IL-1b and TNF- α have been suggested to be involved in the pathophysiology of depression. Tricyclic antidepressants (TCAs) are also thought to influence immune functions and concentrations of cytokines. The aim of this study was to evaluate the status of serum IL-1b and TNF- α in depressed patients who were treated, not treated, or poisoned with TCAs in comparison to healthy subjects.

Material & Methods: In this cross-sectional study, 40 patients who were admitted at Loghman-Hakim Hospital from August 2007 to January 2008 were selected. They were divided into 4 groups: healthy individuals, TCA-poisoned patients, TCA-treated depressed patients, and non-treated depressed patients with 10 subjects in each group. Serum level of IL-1b and TNF- α were compared between groups and demographic and clinical data were collected by a questioner filled out by a trained practitioner. Liver function tests, blood cell count, electrocardiography, and arterial blood gases were also performed.

Results: Complete blood analysis and demographic data showed significant differences between groups. IL-1b level was higher among females. The group of depressed patients non-treated with TCAs showed higher serum concentrations of IL-1b and TNF- α than other groups. No significant difference was observed in IL-1b and TNF- α values among healthy control, depressed TCA-treated, and TCA-poisoned groups.

Conclusion: Depression and gender may influence the production of cytokines while neither TCAs treatment nor its overdose affects IL-1b and TNF- α .

Keywords: Tricyclic Antidepressants, Poisoning, Interleukins, Tumor Necrosis Factor-alpha, Cytokines

INTRODUCTION

Tricyclic antidepressants (TCAs) are pharmacological agents widely prescribed in the treatment of depressive disorders and other forms of psychiatric illnesses. These antidepressants continue to be a leading cause of both non-fatal/fatal morbidity and mortality in overdose cases worldwide (1-5). In 2004, data of a U.S. poison center revealed 12,000 exposures to TCAs (6). Previous

studies have demonstrated various immunomodulatory effects of antidepressants dependent on the immune status of the depressed patients at the initiation of the treatment. It is believed that inflammatory-response system is activated in depression and proinflammatory cytokines play a role in the etiology of depression.

Thus it is not surprising to expect beneficial immunomodulating effects by antidepressants as

1. Toxicological Research Center, Loghman-Hakim Hospital, School of Medicine, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

2. Faculty of Pharmacy, and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran.

3. Poison Center, Loghman-Hakim Hospital, Shaheed Beheshti University of Medical Sciences, Tehran, Iran.

* Corresponding Author: Toxicological Research Center, Tehran, Iran. Email: talaie@sbmu.ac.ir

already reported by some researchers (7-10). Spontaneous suppression of lipopolysaccharide (LPS)-induced secretion of pro-inflammatory cytokines such as IL-1b and TNF- α from monocytes by TCAs has been reported (11,12). There is some evidence that TCA-induced reduction of pro-inflammatory cytokines is usually accompanied by a rise in the production of the anti-inflammatory cytokine such as IL-10 (13,14). On the other hand, study of depressed patients exhibiting immune suppression before treatment has shown that the TCA (clomipramine) increases the production of IL-1 b, IL-2, and IL-3 (15).

Cytokines specially IL-1b and TNF- α have important role in pathogenesis of various diseases in human (16-19).

Regarding above-mentioned reports we aimed to investigate whether depression, exposure to TCAs at normal doses, or their overdoses could influence serum concentrations of IL-1b and TNF- α .

MATERIAL AND METHODS

The study conducted in poison center and psychology clinic of Loghman-Hakim Hospital during August 2007 to January 2008. In this cross-sectional study, serum concentrations of the IL-1b and TNF- α were compared between four separated groups of patients with 10 cases in each. Group 1 included 10 cases of TCA-poisoned patients diagnosed on the basis of history, clinical manifestations, and confirmation by urine analysis for TCAs using thin layer chromatography (TLC) (Clark identification Method). Group 2 included 10 age and sex-matched controls who were recruited from healthy individuals working in the the hospital. Those with any history of psychiatric illnesses, substance or alcohol abuse, infectious diseases, chronic renal or liver diseases, and malignancies were excluded. The psychopathological status of the patients was assessed by a trained psychiatrist through an interview. Group 3 included 10 outpatients with depressive disorder and previous history of TCA treatment who were

recruited from psychology clinic of the Hospital. Depressive disorder was diagnosed by trained psychiatric specialists using DSM-IV criteria (20). Group 4 included 10 outpatients from psychology clinic who were diagnosed with depressive disorder for the first time and did not have any previous history of TCAs. 10 ml venous blood was obtained from each subject and the serum was separated and frozen at -70°C until analysis. Serum concentrations of the IL-1b and TNF- α were assayed using enzyme-linked immunosorbent assay (ELISA) by BioSource kits (Belgium). The detection limits for IL-1b and TNF- α were 0-1400 pg/ml and 0-1500 pg/ml, respectively. Results were expressed as pg IL-1b and TNF- α per ml of serum.

The demographic (age, sex, history of underlying disease) and clinical data (pulse rate, respiratory rate, blood pressure, body temperature) were collected via a questioner filled out by a trained practitioner. Tests for liver function, blood cells, electrocardiography (ECG), and arterial blood gases (ABG) were performed too. Patients who had history of any concomitant drug poisoning, substance or alcohol abuse, infectious diseases, chronic renal or liver diseases, malignancies, autoimmune diseases, leukocytosis, and fever were excluded.

The study protocol was approved by the review board of Pharmaceutical Sciences Research Center of Tehran University of Medical Sciences (TUMS) and Toxicological Research Center of Shaheed Beheshti University of Medical Sciences (SBUMS).
Statistical analysis of data:

Data were analyzed by one-way ANOVA followed by Newman-Keul's test. P value less than 0.05 was considered statistically significant. Data were reported as mean \pm SD unless otherwise stated.

RESULTS

Table 1 presents the demographic data of study subjects. The mean age of study population was

32.7±9.9 and ranged from 17 to 56 years. Of 40 cases, 16 patients (40%) were males, while females were 24 (60%). Only in one case; a positive history of hyperlipidemia was mentioned. Mean body temperature was 37±0.3°C. Mean systolic pressure in the study population was 112.7 mmHg. Mean pulse rate was 84.3 per minute and ranged from 57 to 120. There was not statistically significant difference between the groups concerning age, body temperature, systolic pressure, and pulse rate. Airway support and intubations were

performed in 9 patients (22.5%). The majority of patients had normal arterial blood gases while acidosis was seen in 2 (5%) of patients. ECG of 3 (7.5%) patients showed bradycardia, 2 (5%) tachycardia and 1 (2.5%) T wave changes, whereas 34 patients (85%) had no abnormal ECG findings. Liver function tests showed mean ALT (28.5 U/L) and AST (27.9 U/L) within normal ranges and no difference between the groups was observed. Moreover, depressed subjects' WBC counts were within the normal range with a mean of 7637/μl which was lower than that of controls (Table 2).

Table 1: Overall demographic data of all study subjects

Demographic data	N (%)
Sex (male/female)	16/24
Age (years)	32.7±9.90, range of 17-56
Not existence of underlying disease	39 (97.5%)
Existence of underlying disease	1 (2.5%)

There was one case with a positive history of hyperlipidemia

Table 2: Paraclinical data of different groups

Paraclinical data of study subjects	TCA-poisoned patients (n=10)	Depressed patients without previous history of TCA treatment (n=10)	Depressed patients with previous history of TCA (n=10)	Healthy controls (n=10)	P-value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
IL-1b (pg/ml)	16±12.9	26±26.4	18±16.2	13±10.6	0.395
TNF-α (pg/ml)	14±8.3	21±9.3	22±7.7	14±9.9	0.062
Body temperature (C°)	37.2±0.53	36.9±0.06	36.8±0.15	37±0.10	0.077
Pulse rate	3.6±8.2	19.5±1.8	18.3±1.1	19.3±8.1	0.829
Systolic blood pressure (mmHg)	111±14.4	116±17.7	111±5.6	113±14.1	0.856
Diastolic blood pressure (mmHg)	70±10.5	68±7.8	67.5±5.4	70±8.1	0.169
White blood cell (number/μL)	11810±3771	6190±792.2	6930±1626	5620±1184	0.000
Serum glutamic oxaloacetic transaminase (U/L)	30.7±20.1	26.1±11.7	27.5±6.9	27.3±9.0	0.876
Serum glutamic pyruvate transaminase (U/L)	32.9±51.9	21.1±5.8	27.4±7.8	32.6±23.5	0.778
Alkaline phosphatase (U/L)	112±37.0	128.6±51.5	122.9±43.5	112.5±41.1	0.803

P-value ≥0.05 considered significant

There was no significant difference in serum concentration of IL-1b and TNF- α between controls and TCA poisoned patients. Also no significant difference was found in serum concentrations of IL-1b and TNF- α among cases with TCA poisoning and those in other groups. The group of depressed patients not treated with TCAs showed higher serum concentrations of IL-1b and TNF- α than other groups. No significant difference was observed in IL-1b and TNF- α value among healthy controls, depressed TCA-treated, and depressed non-TCA-treated groups. Results revealed gender differences in IL-1b values with higher levels in females, while no gender difference for TNF- α value was observed.

DISCUSSION

Our data demonstrated that serum concentrations of pro-inflammatory cytokines such as IL-1b and TNF- α did not statistically differ among TCA-poisoned patients, healthy cases, and depressed patients with or without previous history of TCAs treatment indicating that TCAs do not influence cytokine levels even in overdose. Interestingly, we found higher serum concentrations of IL-1b and TNF- α in patients with depression which was in accordance with some previous studies that have reported higher levels of pro inflammatory cytokines in depressed patients. They suggested that elevated cytokines might be considered as an etiologic factor in depression. To explain the changes, they claimed that TCAs suppress the immune system (7-10,21). In contrast another study in depressed patients in 2007 noted no significant difference in plasma concentration of TNF- α between patients and healthy controls (22). In addition, a linear relationship between intensity of depression and indicators of cellular immunity and serum IL-1b has been shown (23,24). As reported, elevated production of cytokines is seen in melancholics and treatment-resistant depressed patients as compared to in minor

cases (25). In the present study, blood cytokines were measured without considering depression severity and which could be considered a limitation of our work. Most previous animal studies support TCA-induced changes in cytokine levels. In vitro incubation of activated monocytes with TCAs has inhibited the production of inflammatory cytokines such as IL-1b and TNF- α (11). Furthermore, TCAs attenuate monocytic proinflammatory cytokine release in microglial cell cultures (26). Likewise, in another report, 14-day treatment of rats with desipramine (75 mg/kg) impaired TNF- α secretion following an in vivo challenge by lipopolysaccharide (LPS) (27). Similarly in rats subjected to a chronic mild stress model of depression, daily administration of imipramine for eight weeks, was accompanied by a decrease in the ability of splenocytes to produce IL-1b while administration of imipramine alone did not alter splenocytes activity (12). Imipramine also inhibited LPS-induced increases in serum concentrations of TNF- α both 3 and 6 hours following administration. However, LPS-induced interleukin IL-1b secretion was not significantly altered following imipramine treatment at either of the time points examined (14). On the contrary, increased rat hippocampus TNF- α was observed after 14-days administration of desipramine (28). The controversy in different animal studies might have been a result of different sample sizes, in vivo or in vitro procedures, duration of treatment, and methods of cytokine assays used in various studies.

In the present study, gender difference with higher levels of serum IL-1b in females was observed but TNF- α levels were similar. In contrast, a previous study by Kim et al noted significantly lower TNF- α levels, in female than male patients. This difference was diminished after antidepressant treatment (29). In females, higher prevalence of Th2-mediated autoimmune diseases such as systemic lupus

erythematosus has been shown (30). There is also some evidence that in systemic inflammatory conditions mediated by monocytic proinflammatory cytokines, females show better outcomes (31). Reduced T cell proliferative responses and the proinflammatory cytokines production in women with depressive disorders have also been reported (32,33). Moreover, female hormones such as estrogen may impact the immune response in women (34,35) and thus menstrual phases and consumption of oral contraceptive should be considered before reaching any conclusions.

All in all, there are many controversial reports on the cytokine levels and TCAs treatment. In human studies, blood cytokines have not been measured in relation to the severity of depression which limits their accountability. In animal studies, the source of controversies seems to be different sample sizes, in vivo or in vitro procedures, duration of treatment, and methods of cytokine assays used in various studies.

CONCLUSION

However our results show that depression and gender might influence the production of cytokines while neither TCAs treatment nor its overdose affects cytokines levels.

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