Altering of Serum Levels of Interlukin 1 and Tumor Necrosis Factor in Depression Independent of Treatment or Overdose of Tricyclic Antidepressants

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The aim of this study was to evaluate the status of serum IL-1β and TNF-α in depressed patients who treated or non-treated or poisoned with tricyclic antidepressants (TCAs) in comparison to healthy subjects. In this prospective comparative study, patients were selected from those admitted at Loghman-Hakim Hospital from August 2007 to January 2008. Serum level of IL-1β and TNF-α were compared among group of subjects (10 in each) of healthy subjects, TCA-poisoned patients, TCA-treated depressed patients and non-treated depressed patients. Demographic and clinical data were collected by a questioner filled out by a trained practitioner in daily clinical management. Blood was tested for liver function, blood cells, electrocardiography and arterial blood gases. Complete blood analysis and demographic data did now show significant change between groups. IL-1β level was higher among females. The group of depressed patients non-treated with TCAs showed higher serum levels of IL-1β and TNF-α than other groups. No significant difference was observed in IL-1β and TNF-α values among healthy control, depressed TCA-treated and TCA-poisoned groups. It is concluded that depression and gender may influence the production of cytokines while neither TCAs treatment nor its overdose affect IL-1β and TNF-α.

Key words: Tricyclic antidepressants, poisoning, interleukin, tumor necrosis factor, cytokine

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INTRODUCTION

Tricyclic antidepressants (TCAs) are pharmacological agents widely prescribed in treatment of depressive disorders and other forms of psychiatric illness. These antidepressants continue to be a leading cause of both non-fatal/fatal morbidity and mortality in overdoses cases worldwide (Eizadi-Mood et al., 2005, Singh et al., 2002; Abdollahi et al., 1997; Shadnia et al., 2007; Talaie et al., 2007; Moghadamnia and Abdollahi, 2002). Most of TCAs have been registered in Iran and are available in Iran (Nikfar et al., 2005). In 2004, data of a US. poison center revealed 12,000 exposures to TCAs (Woelf et al., 2007). 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 positive immunomodulating effects by antidepressants as already reported by some researchers (Peng et al., 2008; Maes, 2001; Kubera et al., 2001a, b). A 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 by Xia et al. (1996) and Kubera et al. (1996). There is evidence that TCA-induced reduction of pro-inflammatory cytokines is usually accompanied with a rise in the production of the anti-inflammatory cytokine such as IL-10 (Castanon et al., 2002; Dredge et al., 1999). On the other hand, study of depressed patients exhibiting immune suppression before treatment has shown that the TCA (elomipramine) increases the production of IL-1b, IL-2 and IL-3 (Weizman et al., 1994). It is worthy to note that cytokines specially IL-1b and TNF-α have important role in pathogenesis of various disease in human (Rahimi et al., 2007a,b; Kajbaf et al., 2007; Vazin et al., 2005; Rezaei et al., 2007). One of the problems in overdose cases or those who use TCAs is lack of satisfactory biomarkers to estimate the severity of clinical conditions of patients. Present hypothesis is that determination of blood levels of cytokines can be suitable and convincing when blood TCA levels are not easily available.

Regarding above-mentioned reports we aimed to investigate whether depression or exposure to TCAs at normal doses or at overdosage might influences serum concentrations of IL-1b and TNF-α.

MATERIALS AND METHODS

The study conducted in poison center and psychology clinic of Loghman-Hakim Hospital during August 2007 to January 2008. In this prospective comparative study 40 subjects were included in four groups with 10 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 TCA by thin layer chromatography (TLC) by routine laboratory analysis. Group 2 included 10 age- and sex-matched controls who were recruited from healthy individuals of the hospital. Those with any history of psychiatric illness, substance or alcohol abuse, infectious diseases, chronic renal or liver diseases and malignancy were excluded. The psychopathological status of the patients was assessed by a trained psychiatric 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 (American Psychiatric Association, 2000). Group 4 included 10 outpatients who were first diagnosed for depressive disorder and not having previous history of TCA usage recruited from psychology clinic.

Ten milliliter venous blood was obtained from all subjects, serum was separated and frozen at -70°C until analysis. Serum concentrations of the IL-1b and TNF-α were assayd using enzyme-linked immunosorbent assay (ELISA) by BioSource kits (Belgium). The detection limits for IL-1b and TNF-α were 0-1400 and 0-1500 pg mL^-1, respectively. Results were expressed as pg IL-1b and TNF-α per milliliter 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 questionnaire filled out by a trained practitioner in daily clinical management. Tests for liver function, blood cells, electrocardiography (ECG) and Arterial Blood Gases (ABG) were performed. Patients who had history of any concomitant drug poisoning, substance or alcohol abuse, infectious diseases, chronic renal or liver diseases, malignancy, autoimmune disease, leukocytosis and fever were excluded.

The study protocol was approved by review board of Pharmaceutical Sciences Research Center of TUMS and Toxicological Research Center of 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 are mean±SD unless otherwise stated.

RESULTS

Mean age of study population was 32.7±9.9 ranged from 17 to 56 years. Of 40 cases, 16 patients (40%) were male, while females were 24 (60%). Only in one case,
positive history of hyperlipidemia was reported (Table 1).

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 ranged from 57 to 120. Airway support and incubations were performed in 9 patients (22.5%). Majority of patients had normal arterial blood gas while acidosis was seen in 2 (5%) patients. ECG of 3 (7.5%) patients showed bradycardia, 2 (5%) tachycardia, 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⁻¹) and AST (27.9 U L⁻¹) within normal ranges. Moreover, subjects' WBC count was within the normal range with mean of 7637 per microliter while they were lower than that of controls (Table 2).

There was no significant difference in serum concentration of IL-1β and TNF-α between controls and TCA poisoned patients. Also no significant difference was found in serum concentrations of IL-1β and TNF-α among cases with TCA poisoning and those in other groups. The group of depressed patients non-treated with TCAs showed higher serum concentrations of IL-1β and TNF-α than other groups. No significant difference was observed in IL-1β and TNF-α values among healthy control, depressed TCA-treated and depressed non-TCA-treated groups (Table 2). Results revealed gender differences in IL-1β values with female predominance while no gender difference for TNF-α was observed.

**DISCUSSION**

Present data demonstrated that serum concentrations of pro-inflammatory cytokines such as IL-1β and TNF-α did not statistically differ among TCA-poisoned patients and depressed patients with or without previous history of TCA treatment meaning that TCA does not influence cytokine levels even in over dosage. Interestingly, results indicated higher serum concentrations of IL-1β and TNF-α in patients with depression. Some previous studies have reported higher levels of pro-inflammatory cytokines in depressed patients. They suggested that elevated cytokines might be considered as etiology of depression. To explain changes, they claimed that TCAs suppress immune system (Feng et al., 2008; Myint et al., 2005; Maes, 2001; Kubera et al., 2001a,b). In contrast, another study in depressed patients in 2007 reported no significant differences in plasma concentration of TNF-α between patients and healthy controls (Farid-Hosseini et al., 2007). In addition, a linear relationship between intensity of depression and indicators of cellular immunity and serum IL-1β has been shown (Herbert et al., 1993). As reported, over-stimulated production of cytokines is seen in melancholic and treatment-resistant depressions than in minor cases (Maes, 1999). In the present study, blood cytokines were measured without considering severity of depression and thus this can be numbered as a limitation to this work. On the other hand, most of animal studies support TCA-induced changes in cytokine levels. *In vitro* incubation of activated monocytes with TCAs inhibited production of inflammatory cytokines such as IL-1β and TNF-α (Xia et al., 1996). Furthermore, TCAs attenuated monocyte pro-inflammatory cytokine release in microglial cell cultures (Obuchowicz et al., 2006). Likewise, in another repot, 14-day treatment of rats with desipramine (75 mg kg⁻¹) impaired TNF-α secretion following an
in vivo challenge by LPS (Shen et al., 1999). Similarly in rats subjected to a chronic mild stress model of depression, daily administration of imipramine for 8 weeks, accompanied by a decrease in the ability of splenocytes to produce IL-1b while administration of imipramine alone did not alter splenocytes activity (Kubera et al., 1996). 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 (Dredge et al., 1999). On the contrary, increased rat hippocampus TNF-α was observed after 14 days administration of desipramine (Ignatowski et al., 1994). The controversy in different animal studies might also result from 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 female predominance was observed for serum IL-1b but not for TNF-α. In contrast, previous study, significantly lower TNF-α levels in female than male patients was reported. This difference was diminished after antidepressant treatment (Kim et al., 2007). In females, higher prevalence of Th2-mediated autoimmune diseases such as systemic lupus erythematosus has been shown (Rider and Abdou, 2001). There is evidence that in systemic inflammatory conditions mediated by mononuclear pro-inflammatory cytokines, females show better outcomes (De Maio et al., 2005). Meanwhile, reduced T cell proliferative responses and the pro-inflammatory cytokines production in women with depressive disorders have been reported by Miller et al. (1999) and Cyranowski et al. (2007). Moreover, female hormones such as estrogen may influence the immune response in women (Beagley and Goekel, 2003; Cutolo et al., 2004) and thus menstrual phase and consumption of oral contraceptive should be considered for any conclusion.

Taking collectively, there are many controversial reports on the cytokine levels and TCA treatment. In human studies, blood cytokines have not been measured in relation to severity of depression that is a limitation. In animal studies, source of controversy seems to be different sample sizes, in vivo or in vitro procedures, duration of treatment and methods of cytokine assays used in various studies. However, the present results show that depression and gender may influence production of cytokines while neither TCA treatment nor its overdose affect cytokine levels.

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