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The Effect of Thiothixene Antipsychotic Drug on Serum Lipid Peroxidation Level in Rat

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ABSTRACT: Thiothixene is a first generation or typical antipsychotic drug. It has been proposed that reactive oxygen species play an important role in neurotoxic adverse effects induced by antipsychotics. In this study, the serum lipid peroxidation levelas a marker of oxidative stress was evaluated in rats' serum. Adult male Wistar rats received chronic administration of thiothixene by daily intraperitoneal injections (10 and 30 mg/kg) for 14 days. Normal control animals received vehicle. Carbon tetrachloride (CCl4) was administered in rats as positive control. Malondialdehyde as an end product of lipid peroxidation was measured in serum samples by spectrophotometric assay. CCl4 increased Malondialdehyde levels ($P<0.05$) but serum lipid peroxidation levels were not altered by any doses of thiothixene. There was also normal body weight gain after treatment with thiothixene unlike significant reduction in body weight in CCl4-treated animals ($P<0.05$). The results of present study revealed no undesirable effect on serum lipid peroxidation level and body weight gain after thiothixene treatment however more researches on various tissues especially brain tissue with different doses and durations and also evaluation of different markers of oxidative stress are required for better understanding the mechanism of thiothixene adverse effects.
KEYWORDS: Thiothixene**,** lipid peroxidation**,** rat

ORIGINAL ARTICLE

INTRODUCION

Schizophrenia is a severe and complex mental disorder and affects 24 million people worldwide according to the last report of World Health Organization (WHO) in 2011. This chronic disease is one of the most disabling disorders which requires long-term antipsychotic treatment (WHO, 2011). Typical and atypical antipsychotic medications are the most effective treatment for schizophrenia (Stargardtet al., 2008). First generation of antipsychotics, known as typical antipsychotic drugs are yet the most frequently used treatment for schizophrenia based on their lower cost (Tyrer and Kendall, 2009). Effective typical antipsychotic agents include phenothiazines, thioxanthenes, butyrophenones and diphenylbutylpiperidines. Thioxanthene derivates which is exemplified primarily by thiothixene, are chemically related to phenothiazines with a tricyclic structure. They have carbon atom in place of the nitrogen atom in the central ring of phenothiazines with the side-chain substituent linked through a double bond (Pedersen, 1996).

Antipsychotic medications are usually helpful in treating symptoms and behaviors associated with the disorder, but they can cause various side effects. Extrapyramidal adverse effects included acute dystonic reactions, neuroleptic-induced parkinsonism and akathisia are common with typical antipsychotics such as haloperidol, fluphenazine, thiothixene, and trifluoperazine. Long-term use of these antipsychotic medications may also increase risk for movement disorders such as tardive dyskinesia or dystonia (Malhotra et al., 1993). The blockade of nigrostriatal dopamine tracts and supersensitivity response to chronic dopamine blockade are implicated in these side effects (Glazer, 2000). However, new hypothesis suggest that increase in striatal glutamatergic neurotransmission and neuronal damage by oxidative stress induced by antipsychotics may be involved in extrapyramidal effects, tardive dyskinesia and also in other adverse effects (Tsai et al., 1998). The increased levels of lipid peroxidation products and decreased vitamin E levels have been reported in dyskinetic patients (Brown et al., 1998). Production of reactive oxygen species, decrease in antioxidant defense enzymes and oxidative damage has been reported in rat brain by some first generation antipsychotics such as haloperidol (Martins et al., 2008; Pillai et al., 2007). Long-term treatment with some phenothiazines such as fluphenazine has been also associated with increase in lipid peroxidation levels in liver and kidney homogenates of rats (Corte et al., 2009). Although there are many studies on phenothiazine and butyrophenone derivates of typical antipsychotics but since there is no any report

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about the effect of thiothixene on oxidative status, we evaluated lipid peroxidation level after treatment with thiothixene in animal model for better understanding the mechanism of side effects of thioxanthene derivates and preventing them in the treatment of psychosis.

MATERIALS AND METHODS

Adult male Wistar rats (150-200 g body weight), obtained from Pasteur Institute (Tehran, Iran) were used. Animals were housed in standard laboratory cages at room temperature and ambient humidity and had access to water and rodent laboratory chow *ad libitum*. The rats were acclimated to the laboratory conditions for at least 1 week prior to the experiments. All experiments were carried out in accordance with international guideline of the care and use of laboratory animals. Thiothixene and all reagents for biochemical assay were purchased from Merck (Germany).

Animals were divided into four experimental groups with six rats each. Groups 1 and 2 received chronic administration of thiothixene by daily intraperitoneal injections (i.p., 10 and 30 mg/kg, respectively) for 14 days (Florey, 1989). Normal or negative control animals in group 3 received vehicle. Carbon tetrachloride (CCl4) was administered i.p. at dose of 0.8 mg/kg, 30% in olive oil solution in group 4, twice a week for 2 weeks as positive control group (Morakinyo et al., 2012). Rats were weighed and killed by decapitation at the end of the second week; blood was collected and allowed to clot for preparation of serum. Thiobarbituric acid reactive substances (TBARS) were measured in serum samples as indicator of lipid peroxidation levelaccording to the method described by Thayer WS. In brief, serum was mixed with 20% trichloroacetic acid and the precipitate was dispersed in H_2SO_4 and mixed with freshly prepared 0.67% 2-thiobarbituric acid (TBA) solution in Na_2SO_4. After extraction with n-butanol, the absorbance of the chromogen formed between the end product of lipid peroxidation and TBA was measured at 532 nm and expressed as malondialdehyde (MDA) equivalents in nmol/ml (Thayer, 1984).

Data were presented as mean $\pm$ S.E.M (standard error of mean) and statistical analysis was made by one-way ANOVA followed by Dunnett analysis. *P* value <0.05 was considered statistically significant.

RESULTS

CCl4 as an inducer of oxidative stress increased MDA levels (P<0.05). However, the results from determination of serum lipid peroxidation level in other groups showed that MDA levels were not altered by any doses of thiothixene in comparison with vehicle treated animals (Figure 1). The results of body weight measurement also showed significant reduction in body weight in CCl4-treated animals (P<0.05) while there was normal body weight gain in other groups (Table 1).

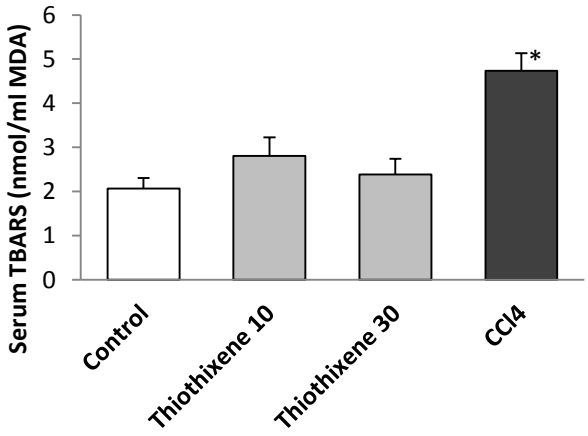

Figure 1. The effect of thiothixene on serum lipid peroxidation level. Thiothixene (10 and 30 mg/kg, i.p.) was administered in rats for 14 days. Normal control animals received vehicle. CCl4 was administered as positive control. Lipid peroxidation was determined by measuring thiobarbituric acid reactive substances (TBARS) and expressed as MDA equivalents in nmol/ml. Data are presented as mean $\pm$ SEM of n = 6. * = $P < 0.05$ versus normal control.

Table 1. Effect of thiothixene and CCl4 on body weight in rats

Treatment	Initial body weight (g)	Final body weight (g)	Weight gained (g)
Normal Control	170.5 $\pm$ 5.2	185.5 $\pm$ 4.1	15
CCl4	172.2 $\pm$ 3.5	174.7 $\pm$ 3.7	2.5*
Thiothixene 10	167.3 $\pm$ 4.7	183.5 $\pm$ 5.3	16.2
Thiothixene 30	173 $\pm$ 3.8	187.5 $\pm$ 5.1	14.5

Weight values are mean ± S.E.M of six rats per group. *Significant difference (p<0.05) with control value.

DISCUSSION

Oxidative stress has been implicated in the pathogenesis of schizophrenia and also antipsychotics toxicity (Martins et al., 2008; Corte et al., 2009; Do et al., 2009). Although short-term antipsychotic treatment has been associated with reduced oxidative stress in schizophrenia but long-term administration has been shown to induce oxidative stress (Brown et al., 1998; Pillai et al., 2007; Chittiprol et al., 2010). It has been proposed that oxidative stress may be involved in various side effects caused by antipsychotics such as extrapyramidal adverse effects and metabolic derangements (Roberts and Sindhu, 2009).

Our findings showed no difference in serum oxidative status after treatment with thiothixene in normal animal model. The results of researches suggest dual

activity for antipsychotic medications. While some phenothiazines are able to act as an antioxidant by scavenging of free radicals and inhibiting of lipid peroxidation, they are also able to release free radicals during the several oxidation processes following the metabolism in the human body or photoionization (Jeding et al., 1995; Souza dos Santos et al., 2007; Dhaunsi et al., 1993). It is possible that dosage and treatment duration, adaptive response or the result of compensatory biological processes may be involved in this paradox activity of neuroleptic drugs (Venkatasubramanian, 2012). These responses may also be tissue dependent since some antipsychotic-induced oxidative stress has been reported only in rat brain (Martins et al., 2008).

Our results also showed normal body weight gain after thiothixene treatment. The mechanisms of significantly reduced the gain in body weight from CCl4 toxicity have not been clearly established. However there are some reports that dopamine antagonism with thioxanthenes can inhibit anorectic behavior, improved body weight gain and increased food intake (Verhagen et al., 2009).

In conclusion, the results of the present study revealed no undesirable effect on serum lipid peroxidation level and body weight gain after thiothixene treatment normal serum lipid peroxidation level and normal body weight gain may be resulted after thiothixene treatment however for better understanding the mechanism of thiothixene side effects, more researches on various tissues especially brain tissue with different doses and durations and also evaluation of different markers of oxidative stress are needed.

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