Sister-Chromatid Exchange Analysis in Women Treated With Fluoxetine for Depression*

Ruşen Dündaröz[1], A. Zafer Çalışkaner[2], Tümer Türkbay[3], Faysal Gök[1], Nesrin Dilbaz[4], Volkan Baltacı5

[1]Assist.Prof. Dept. of Pediatrics, Gülhane Military Medical Academy, School of Medicine, Ankara
[2]MD. Dept. of Internal Medicine, Gülhane Military Medical Academy, School of Medicine, Ankara
[3]Assist.Prof. Dept. of Child Psychiatry, Gülhane Military Medical Academy, School of Medicine, Ankara
[4]Assoc.Prof. Dept. of Psychiatry, Numune State Hospital, Ankara
[5]Assoc.Prof. Dept. of Genetics, Başkent University School of Medicine, Ankara

*This study was conducted at the Gülhane Military Medical Academy and Başkent University School of Medicine, Ankara, Turkey.

Abstract

Depression is a disease frequently seen in our times around the world. It is more common in women. Fluoxetine is one of the drugs widely used in the treatment of depression in recent years. However, there are not enough studies of its effects on DNA. This possible toxic effect is more important in women considering the possibility of pregnancy. In the present study, the potential toxic effects of long term fluoxetine therapy on DNA was investigated by means of incidence of sister chromatid exchange (SCE) using the peripheral blood lymphocytes of female patients with depression. The results showed that the frequency of SCE were significantly increased in women who have received fluoxetine for a long time compared to the control group ($p<0,0001$). As this is the first study in this subject, further large-scale experimental and clinical studies are needed to confirm these preliminary results.

Keywords: *Fluoxetine, depression, SCE, teratogenicity, DNA damage*

Depresyon İçin Fluoksetin Tedavisi Gören Kadınlarda Sister-Chromatid Exchange Analizi

Özet

Depresyon çağımızda dünyanın her tarafında sıklıkla karşılaşılan bir hastalıktır. Kadınlarda daha sıktır. Fluoksetin son yıllarda depresyonun tedavisinde en yaygın kullanılan ilaçlardan biridir. Buna rağmen DNA üzerindeki etkisi yeterince araştırılmamıştır. Hamilelik göz önüne alınırsa böyle bir toksik etki kadınlarda daha önemlidir. Bu çalışmada, depresyonlu kadın hastaların periferik lenfositlerinde Sister Chromatide Exchange (SCE) yöntemi kullanılarak uzun süre fluoksetin kullanımının DNA üzerine olası toksik etkisi araştırıldı. Sonuçlar, SCE sıklığının uzun süre fluoksetin kullanan kadınlarda kontrol grubuna nazaran istatistiksel olarak anlamlı derecede arttığını gösterdi. Bu çalışma bu konudaki ilk çalışma olduğundan, sonuçları doğrulamak üzere daha kapsamlı klinik ve deneysel çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Fluoksetin, depresyon, SCE, teratojenite, DNA hasarı*

Depression is a common health problem seen in the primary care setting. Depression affects more than 17 % of the population. It occurs twice as often in women as in men, and the lifetime burden of major depression in women is estimated to be as high as 21 % (1). Epidemiological studies have shown that women identify more total depressive symptoms, decreased sexual interest, increased appetite, and weight gain than do males. Women also have a greater tendency to report anxiety and multiple somatic complaints than males (2).

The main drugs currently used in treating major depression are agents that selectively inhibit the reuptake of serotonin (SSRI). They are used primarily to treat depression, anxiety, obsessive compulsive disorder and impulse control disorders, but they are also useful in the treatment of other psychiatric disorders. They have fewer anticholinergic and cardioarrhythmic effects (3), but cause anxiety, nausea, and insomnia in a substantial proportion of patients (4-6). Although fluoxetine is one of the most frequently prescribed SSRI, its toxicity on DNA has not been enough clear yet.

Sister Chromatid Exchange (SCE) is known to result from reciprocal DNA interchange in homologous loci of sister chromatids in the replication process and it occurs spontaneously at certain rates in all cells (7). Most chemical and

physical agents causing DNA damage, such as various chemotherapeutics, antineoplastic drugs and ultraviolet light have an influence on SCE frequency (8). Therefore, SCE analysis has come into use as a sensitive means of monitoring DNA damage. DNA damage is known as responsible from teratogenity and cancerogenesis.

The aim of this study is to evaluate the association of exposure to fluoxetine with DNA damage by SCE analysis in women with depression.

Materials and Methods

Subjects

Thirty female patients between the ages of 21 to 31 years (mean 28.36 years) diagnosed as major depression (by DSM-IV) who have been treated with fluoxetine for 6-19 months (mean 13.3 months) were included in the study. Only depressed patients who received fluoxetine and had not used any other drug within one year, had regular menstrual cycles, were in otherwise good health, and those who did not smoke were accepted. The control group was selected from the healthy non-smoker females matched to the patient group according to their age. They have normal menstrual cycles and were without long-term drug usage. The study was approved by the hospital's research ethics board and informed consent was provided from all patients. The blood samples were taken from the control and patient groups within 20th and 27th days following the beginning of their menstrual cycle. To our knowledge, neither the patients receiving fluoxetine nor the control group were exposed to any other mutagenic agents (e.g. radiation, chemicals, lifestyle, smoking, drugs, or viruses) at least one year prior to study. Neither did any of them presented any chronic or neoplastic diseases. All subjects were healthy at the time of sampling.

SCE analysis

Peripheral venous blood was drawn aseptically into heparinized tubes from each subject. 200 µl of the whole blood was added within the same day of sampling to 5 ml medium TC 199 (Gibco) supplemented with 10 % fetal calf serum (Gibco), 2 % phytohemagglutinin (Sigma), 5 µg/ml 5-bromodeoxyuridine (Sigma), 150 U/ml penicillin and 150 µg/ml steptomycin. Culture were incubated in the dark for 68 h at 37° C. After the treatment with demecoline (Colcemide, Gibco, 0.1 µg/ml) for 3 hours, microscope slides were prepared by a conventional method and stained by fluorescence plus the Giemsa technique of Perry and Wolff (9). The mean SCE frequency was calculated as SCE per cell from 20 selected cells per individual. Student's t test were used in the statistical evaluations of the data.

Results

Data on the mean frequency of SCE per cell in depressive and control women are presented in Table. The patient group had a mean SCE per cell of 6.5±1.94, whereas, the controls had a mean SCE per cell of 9.06±1.95. This difference was statistically significant ($p<0.0001$). The statistical comparison of the ages in two groups showed no significant difference ($p>0.05$).

Table. Clinical data and SCE frequencies in depressive women treated with fluoxetine and in healthy controls.

	Control Group		Patients Treated With Fluoxetine			
No	Age (years)	SCE (%)	No	Age (years)	Usage period (mo's)	SCE (%)
1	27	9	1	23	9	8
2	27	6	2	25	16	9
3	29	8	3	27	18	10
4	29	5	4	31	13	9
5	31	7	5	35	11	8
6	30	9	6	39	6	7
7	25	9	7	25	9	7
8	29	6	8	26	13	8
9	28	5	9	22	11	8
10	28	8	10	21	13	7
11	21	7	11	25	11	6
12	26	10	12	33	10	11
13	30	6	13	34	18	14
14	27	4	14	26	15	12
15	30	5	15	25	18	12
16	32	3	16	28	19	13
17	26	7	17	24	15	11
18	31	9	18	29	12	8
19	25	7	19	24	11	7
20	33	6	20	22	13	9
21	32	4	21	39	15	10
22	36	8	22	38	12	9
23	30	3	23	38	15	8
24	29	5	24	31	18	9
25	22	8	25	22	15	11
26	23	6	26	25	16	9
27	24	7	27	24	14	9
28	29	3	28	23	12	8
29	31	7	29	22	11	7
30	31	8	30	22	10	8
Mean	28.4±3.4	6.5±1.9		27.6±5.7*		9.0±2.0**

*p>0.05
**p<0.0001

Discussion

Depression occurring during pregnancy is not uncommon. One of the main concerns with psychotropic drugs during pregnancy is teratogenicity. Caution is recommended in using

antidepressants since they may carry risk to fetus. The outcomes of 128 and 228 fluoxetine-exposed pregnancies were investigated and it has been suggested an increased incidence of major malformations resulting from fluoxetine exposure. In addition, it has been noted that a decrease in body weight, an increase in prematurity, and an increase in newborn complications in infants from late fluoxetine exposed compared with early fluoxetine-exposed pregnancies. In some studies, it has been reported that an increased rate of miscarriage, an association with infants large for gestational age, one reported case of perinatal toxicity, and one case of an infant who was colicky while receiving breast milk from a mother taking fluoxetine (10-12).

On the other hand, in a study on the association of antidepressants with cancers, medline has been searched for relevant articles published. Four human studies and nine experimental models have been found. Human studies showed transiently statistically positive association between amitriptyline and liver cancer and a negative association with pancreatic cancer; and the antidepressants amitriptyline, nortriptyline, desipramine, and phenelzine may increase breast cancer. Amitriptyline was found to promote tumour growth, fluoxetine and clomipramine were reported to be both tumour promoters and antineoplastic agents, and imipramine and citalopram both demonstrated antineoplastic properties (13).

In contrast to the studies above, the effects of SSRI on the developing fetus during pregnancy and lactation has been explored reviewing the relevant animal and human studies. Animal studies were inconclusive while human investigations indicated no relationship between in utero exposure to fluoxetine and teratogenic effects. It has been reported that SSRI's use during pregnancy do not increase teratogenic risk when used in recommended dosages (14-16). It has been reported that the maternal fluoxetine use during the third trimester does not result in significant postnatal complications (17). In an investigation, it has been found that the rates of major malformations in children exposed in utero fluoxetine, tricyclic antidepressants and non-teratogenic drugs did not differ from the rates in general population (18). Addis and Koren examined all published and unpublished reports and made meta analysis. As a result, they reported that the use of fluoxetine during the first trimester of pregnancy is not associated with measurable teratogenic effects in human (19).

SCE is a reciprocal exchange of DNA segments between sister chromatids at identical loci (20). This phenomenon occurs during DNA synthesis. The detailed mechanism underlying SCE formation is not clear; however, it has been related to the processes of replication and repair (21). During the past years, quantitative analysis of SCEs has been used as a sensitive method of detecting damage to the DNA, thereby evaluating the mutagenic and carcinogenic potential of various agents (22,23). According to various reports, a variation in SCE frequency exist among healthy individuals (24). Variation is associated with different experimental conditions in different laboratories. However, it still exists when conditions are kept constant. Age, sex, different physiologic parameters, as well as different genomes may affect the frequency of SCEs (25). Increased SCE frequency may occur following exposure to chemicals, irradiation and drugs (26,27). Physiological factors that may affect SCE frequency are reproductive hormones; evaluation of SCE frequencies during a normal menstrual cycle demonstrated a higher rate around ovulation and in the luteal phase as compared to the early follicular phase (28). In our study, All the subject (patients and the control group) were at the same phase of the menstrual cycle (within 20th and 27th days following the beginning of menstrual cycle) at the time of sampling.

Although there is not enough data in the literature that the fluoxetine is associated with teratogenity and cancerogenesis, the mean frequency of SCE in patients receiving fluoxetine for a long time was found significantly higher than that of the control group. As all the factors that may have influence on the SCE frequencies (e.g., age, sex, race, nutrition, environment etc.) were similar in both groups, we suggest that the difference in the SCE frequencies was induced by the use of fluoxetine.

As these preliminary data based on few subjects and etiological and pathological mechanism remain obscure, further large-scale experimental and clinical studies are needed.

Corresponding address:
Dr. Ruşen Dündaröz
Bağ-Kur blk. 4. Blk. No: 69/14
06010 Etlik / Ankara

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