Original Article

Evaluation the Effect of Topiramate on the Induction Genotoxicity in Obesity Patients

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Abstract

Topiramate (sulfamate - substituted monosaccharide) a weight loss drug used a pharmacotherapeutic agent for obesity , a study was performed to evaluate the effect of the topiramate to induce chromosome aberrations (CA) and sister chromatid exchange (SCE) in lymphocytes of obesity patients . CA and SCE, a sensitive measure of chromosome damage , were counted in peripheral blood lymphocytes from 32 obesity patients treated with topiramate dose (6 months with 81mg/day , 12 months with 129 mg/day) and 16 healthy person as control group who had never received topiramate and other drugs during the period of the study. All of the treated patients with topiramate ,have cells with CA and abnormal SCE frequencies, in analysis ,obesity patients, was significantly increased CA in 129mg/day and 81mg/day topiramate dose compared with control (4.08±1.51 and 3.56±1.21) respectively, vs (1.40± 0.81),(P<0.01).Furthermore, a significantly higher SCE/Cell frequency (10.42 ±0.75and 8.75±0.38) in treated obesity patients with 129 mg/day ,81mg/day dose respectively comparison with their control group (5.91±0.31), (P<0.001).

The chromosome damage and genotoxics are related to the daily dose and may be determined by the duration of treatment .We conclude the patients treatment with topiramate may be associated with genetic toxicity according to byproducts of drug metabolism.

Key Words : Topiramate ,Sister chromatid exchange, Chromosome aberration, Obesity.

Introduction

Topiramate (Topamax, Janssen Pharmaceuticals, Inc, Titusville, NJ,USA) has a long and checkered history in clinical therapeutics (1-2).Topiramate is a sulfamate-substitute fructopyranose derivative with a unique pharmacodynamics profile (3).It was first approved for epilepsy and for migraine prophylaxis off-label use of topiramate includes adjunctive treatment of bipolar disorder(4-5) post-traumatic stress disorders(6) bulimia nervosa ,diabetes (7-8) bingeatin disorder (8-9)and obesity(10-11).

Topiramate marketed since 1996,and initially approved by Food and Drug Administration (FDA) for management of seizure disorders, it was first investigated as an anti- diabetic medication;as a fructose -1-6-diphosphate analog(sulfamate-substituted monosaccharide)that inhibit 1-6-bisphosphatase and thus inhibit gluconeogenesis(11-12) also it was eventually marketed for its Na+ and Ca+ channel blocking activity which is typical of antiepileptic drugs (1-2).

Topiramate has also shown benefit in reducing weight gain associated with a typical antipsychotics (9-12-13).In 2003,Ben-Menachem et all published the first prospective study f the weight loss effects of topiramate as well as investigating the major predictors of weight loss (14-15).

Topiramate, the first agent in more than 10 years to achieve regulatory approval Chronic management weight in obese patients (16) . In 2010 , the FAD rejected two proposed weight loss drugs, lorcaserin and phentermine/ topiramate extended release over safety and efficacy issues (17) .In 2012, the FAD reversed it position and Granted the approval of both lorcaserin and phentermine/topiramate at the same time the European Medicines Agency (EMA) rejected lorcaserin and phentermine/topiramate due to concerns over the potential cardiovascular and central nervous system effects associated with long term use, teratogenic potential, and use by patients for whom it is not indicated (18-19).(Topiramate –ER) trade name Qsymian (T.M) pharmacotherapeutic agent widely used for obesity (20). Obesity is now a major public health concern wide world prevalence and growing list of comorbidities and complication (21-22).

The place of pharmacotherapy in the management of obesity is a long and checkered on (23-24) in these study we examination the effect of topiramate to genotoxicity and mutagenicity on chromosome aberrations (CAs) and sister chromatid exchanges (SCEs) in obesity patients treated with topiramate.

Sister chromatid exchange, is a popular method in genetic toxicology and human population cytogenetic monitoring (25) SCE was first demonstrated in 1957 by Taylor et al.(26) SCE phenomenon is widely used as a reliable and sensitive indicator of chromosome (DNA) instability (27) . Since SCEs are consider to be sensitive indicators of genetic effects after exposure to mutagenic and carcinogenic agents (28- 29) , the SCE patterns can reveal a general genome instability , variation in(DNA) repair mechanisms or detoxifying enzymes have been implicated as causing genetic susceptibility associated with cancer (30-27).SCE in peripheral lymphocyte , has been widely used assess exposure to mutagens and carcinogens (31-32).

Our preliminary studies showed enhanced SCE and CA in human lymphocytes in *in Vivo* of obesity patients treated with topiramate.

Patients and Methods:

Patients : This study was conducted between July 2019 and continued through March 2020 in Al - Diwaniah Teaching Hospital ,the study included 48individuls , 32 obesity patients (12 males and 20 females) with age (20-30 years) were treated with topiramate at the time of the study , 16 were being topiramate treated since 6^{th} months and 16 being were treated with topiramate for more than 12^{th} months, the mean dose of the drug was 81mg/day before 6^{th} months and 129 mg/day after 6^{th} months .The control group 16 healthy persons (6 males and 10 females) , with same ages range of the patients ,who had never received topiramate and another cytotoxic drugs .The hospital Ethical committee approved the human study.

Sister chromatid exchanges estimation : From each individual a peripheral venous blood samples was collected in a heparinized tube under aseptic condition . Whole blood culture was done in RPM I -1640 medium supplemented with fetal calf serum (20%) ,phytohaemagglutinin M(3%),L-glutamine(0.03%), penicillin(100 IU/ml),Streptomycin(100 *M*g/ml), $5^{/}$-bromo-2'-deoxy- uridine (5Mg/ml),and blood (0.3 ml) culture vials were wrapped with aluminum foil and incubated at $37C^0$ in a 5% CO_2 atmosphere.

Cultures were harvested at 48 hours to study (CA) (30-33)and at 72 hours for (SCE) analysis .Three hours before harvesting , colchicine (0.1 Mg/ml) treatment was given to arrest the cells in metaphase . The culture was centrifuged at 1200 rpm for0 minutes . The supernatant was discarded and pellets were re suspended in 0.075 M KCI and fixed in methanol : acetic (3:1). Slides were prepared and stained by fluorescence plus Giemsa technic (32-33). SCEs and CA ,from one hundred well spread metaphase were scored for CA and 50 well spread metaphase with good differentiation were scored for SCE analysis for each individual (34). Statistical analysis carried out by SPSS version 15 ,comparison by (ANOVA-LSD) and correlation by spearman correlation.

Results:

Chromosomal aberrations:

The cultures of human lymphocyte obesity patients treated with topiramate as that shown in (Table 1 and Figure 1) the aberrant metaphase percentage was significantly higher ($P<0.01$) in obesity patients treated with topiramate dose 81mg/day and 129 mg/day with mean (3.56 ± 1.21) and (4.08 ± 1.51) respectively in comparison with their control group with mean (1.40 ± 0.81) .Chromosomal aberrations were of included chromatid gap and break types, mitotic index , was low though not significantly so in both patients and control groups.

Table1: Comparison chromosomal aberration in obesity patients treated with topiramate and control group.

Subjects	Duration of treated (m; Mean+- SD)	Chromosomal aberration				
		No.of cells Scored	Mitotic index (Mean± SD)	Aberrant Metaphase (%Mean SD)	Chromatid Gap %(Mean SD)	Chromatid Break (%Mean SD)
Topiramate treated (129 mg/day) n=16	12± 0.3	800	2.14 ± 0.82	4.08±1.51*	2.03± 1.20	2.05± 1.2
Topiramate treated n=1)(81mg/day	06± 0.4	800	2.90± 0.71	3.56± 1.21*	1.77± 1.00	1.77± 0.9
Control n=16	0	800	3.94± 0.25	1.40± 0.81	0.60± 0.4	0.80± 07

*** Significant at P < 0.01.**

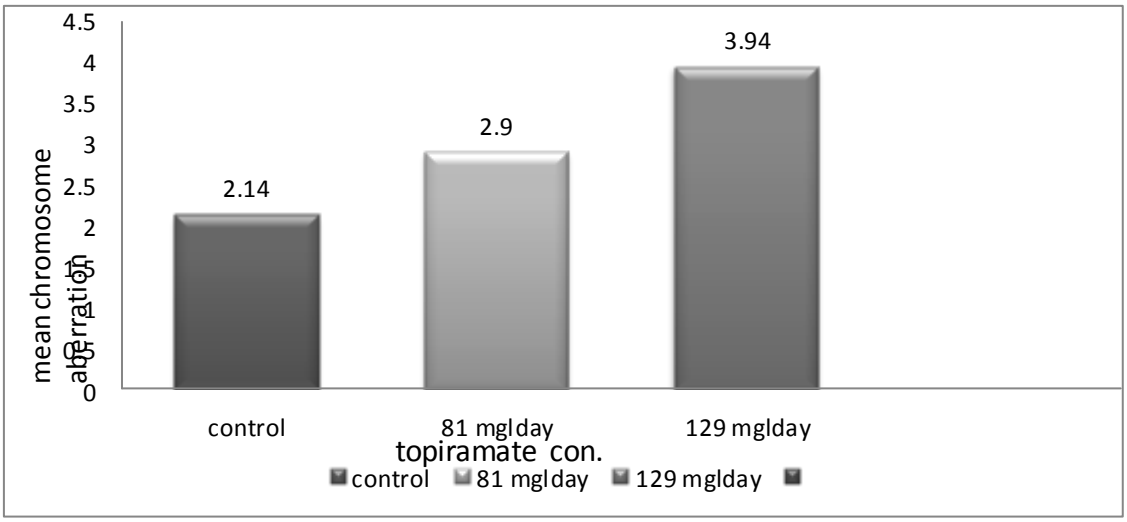

Figure 1: Comparison mean chromosome aberration in obesity patients treated with topiramate and control group.

Sister chromatid exchanges estimation:

Topiramate induces a highly significant increased frequency SCE in the obesity treated patients compared with the control group (P<0.001) Table 2,Figure 2a, shows the significantly increased mean in both treated group without affecting mitotic index.

A significantly higher SCE/cell mean ± SD (8.42 ± 0.38) and (10.42 ± 0.75) in treated obesity patients with 81mg/day and 129 mg/day dose respectively when compared with their control group mean ± SD (5.91 ±0.31).

Table 2: Comparison SCE frequency in second division metaphases in obesity in patients treated with topiramate and control group.

Subjects	Duration of treated (m ; Mean ± SD)	Sister chromatid exchange		
		No. of cells Scored	SCE / cell (Mean ± SD)	SCE Rang
Topiramate treated (129 mg/day) n=16	12± 0.3	800	10.42 ± 0.75**********	(8-14)
Topiramate treated (81mg/day) n=16	06 ± 0.4	800	8.75± 0.38**	(8-14)
Control n=16	0	800	5.91± 0.31	(3-6)

*** * Significant at P < 0.001.**

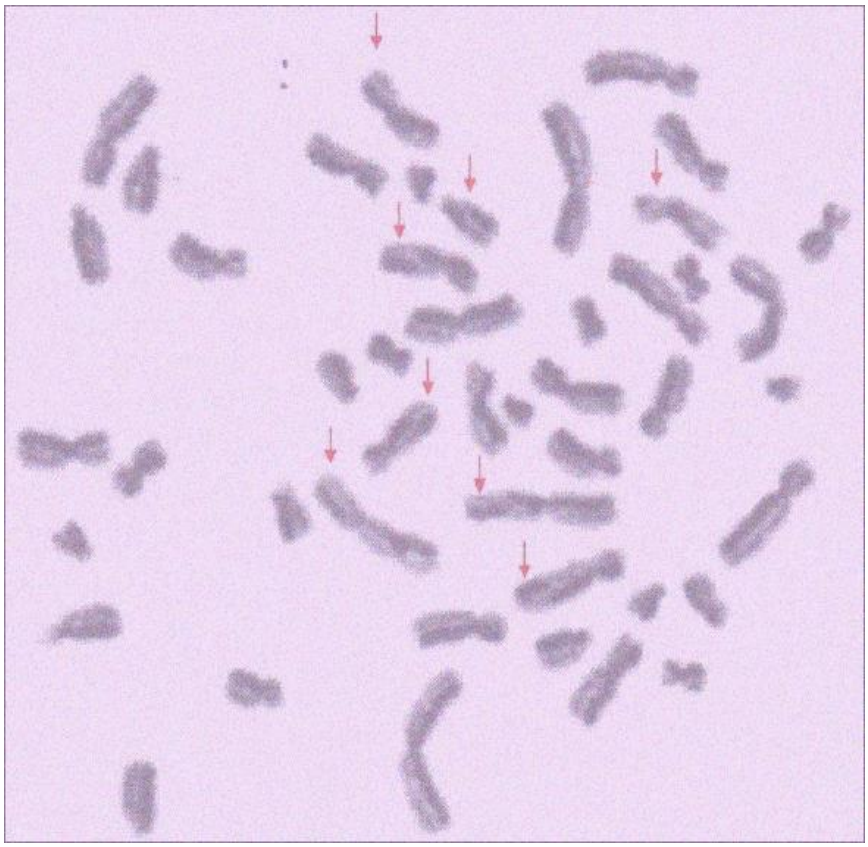

Figure 2 a : sister chromatid exchanges in lymphocytes cell of obesity patient treated with topiramate

As shown in results Figure 2 b, the SCE frequencies in the second division metaphase in obesity patients treated with topiramate significant there was a increase ($P<0.001$) the mean ± SD with increased duration and the concentration dose of drug when compared the patients groups with 81mg/day for six months and 129 mg/day treated for 12 months.

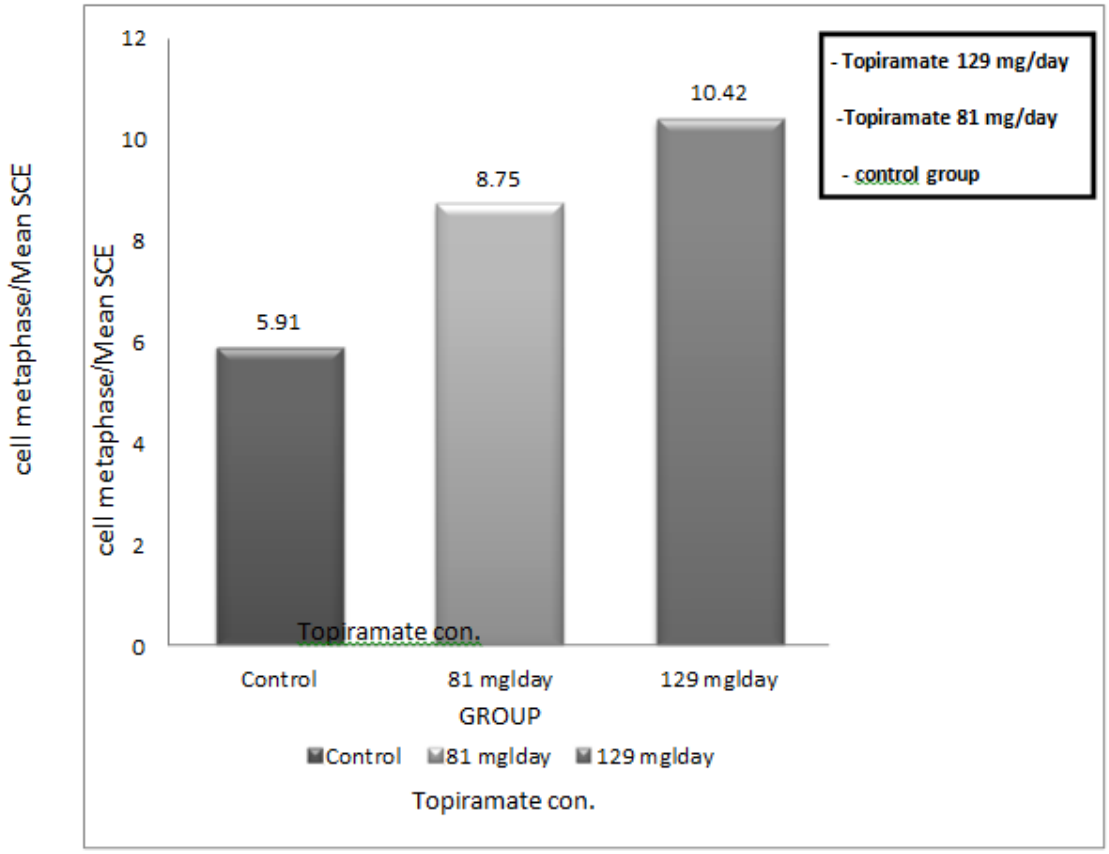

Figure 2 b: Comparison mean SCE frequency in second division metaphases in obesity patients treated with topiramate and control group.

The study of correlation of CA and SCEs in obesity patients treated with topiramate reveals a positive significant between CA , SCEs and dose concentration ,duration ($P= 0.757$, $r = 0.040$) .In comparing cells obtained from patients and control groups, non-significant differences in SCE and CA mean occurrence was observed in relation to gender.

Discussion:

Damage to genetic materials can be cytologically observed as chromosome aberration and sister chromatid exchange suggests exposure to genotoxicity and possibly carcinogens (35) . These observations show that SCE analysis is a very sensitive measure of chromosome damage induced by topiramate used as antiobesic treatment the ex-tent of chromosome damage is closely related to present daily dose , and although the analysis of the results is complicated by the drug regimens that are used for determination by the total dose received or the duration of treatment.

The SCE frequencies increased with the duration of treatment , these observation suggest that chromosome CA and SCE frequencies induced by topiramate cumulative is, these result are conventional with other work indicated many side effects, topiramate have grave risks including addiction, myocardial toxicity and sudden death (15),caused pulmonary hypertension and valve heart disease (37-38), also EMA rejected topiramate due to concern over the potential cardiovascular and central nervous system effects , associated with long term use , teratogenic potential in pregnant women (37-39) teratogenesis associated with gastrulation itself disrupted by genetic abnormalities and toxic insults , regarding the potential risk of development of orofacial clefts if patients are exposed to medication during the first trimester of pregnancy (39 – 40). When CA , SCE in obesity patients it may be possible to identify those who are most at risk of drug induced the potential risk for tumor such as other obesity ages an phentermineanalogs an sympathomimetic (41- 3).Topiramate have adverse side effects including factor

analysis of genetic variant associated with response to those pharmacotherapies (39).The safety of topiramate is still a matter of debate , and there appears to be scientific evidence pointing in both direction efficacy and safety. The results, obtained in the present study shows the topiramate may associated with genotoxic effects and chromosome damage is related to dose dependent and cumulative with duration of treatment.

Conclusion:

The patients treated with topiramate may associated with genetic toxicity according to toxic byproducts of drug metabolism.

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