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Effect Of Famciclovir On The Testes, Spermes And Chromosomes Of Albino Rats; Histological And Cytogenetic Study

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Abstract

Back ground: Famciclovir is a widly used antiviral drug it has a potent and selective inhibitory effect on many human herpes viruses. Some side effects to the drug were reported By Food and Drug Administration.

Aim of the work: The aim of this study was to evaluate the histological effect of maximum therapeutic dose of famciclovir, antiviral drug, on the testes, sperms and chromosomes of albino rats.

Material and methods: Forty male albino rats have been divided into four groups, ten rats for each. The first was served as a control group; the second was treated for 2 weeks with135 mg/Kg B.wt/day. The third was treated for 4 week with the same dose; and the forth group was served as recovery group, where the animals were examined 4 weeks after stopping the drug. Rats were decapitated and testes specimens were taken and stained with Haematoxylin and Eosin. The sperms were examined for number, viability, motility and shape abnormalities. For Chromosomal study, rats from each group were anaesthetized and the bone marrow cells were obtained by Rabello-Gay and Ahmed method .

Result: Microscopic examination of the testicular specimens, revealed, disorganized germinal epithelium with abnormal mitotic figures and apoptotic cells. Sperm analysis showed that sperm count, viability and motility were decreased, and the sperm anomalies were increased. Chromosomal analysis of bone marrow cells showed many aberrations as chromosomal fragments, terminal chromatid deletions, ring chromosomes, chromosomal gaps, dicentric chromosomes, clumping of the chromosomes and polyploidy. All the former results were time dependent and reversible.

Conclusion: The maximum therapeutic dose of famciclovir affect spermatogenesis and alter normal sperm parameters. Their were also chromosomal aberrations which are time dependent and revirsable. So it is preferred to avoid the maximum therapeutic dose and prolonged intake of the drug.

Key words: Famciclovir, testes, chromosomes, sperms , histological.

Introduction

Famciclovir has a potent and selective inhibitor effect on many human herpes viruses. It has a selective inhibitory effect on herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) as it inhibits the DNA polymerase of these viruses. It has also proved that famciclovir is a selective inhibitor of Epstein Barr virus (EBV) in cell culture by inhibition of productive replication cycle (Bacon and Boyd, 1995). Series of HSV-1 and HSV-2 isolates were confirmed to be resistant to famciclovir in the plaque reduction assay. (Bacon *et al.*, 2003).

Therapeutically, famciclovir is used in the treatment of herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) (Sra and Tyring, 2004 and Tyring, 2001). It is also used in the treatment of hepatitisB (HBV) infection where it decreased HBV-DNA(Cirelli *et al.*,1996).

Oral famciclovir is well tolerated but may be associated with headache, diarrhea

and nausea (Saltzman *et al.*, 1994). Urticaria, rash, hallucinations and confusion, especially in elderly, have been reported (Hayden, 2001). Abdominal pain, fever, rarely granulocytopenia and thrombocytopenia have been reported in immunocompromised patients receiving famciclovir (Parfitt, 1999).

Some genotoxic effects after famciclovir intake as sister chromatid exchanges were reported (Denny, 2003). Famciclovir induces polyploidy in human lymphocytes in vitro in the absence of chromosomal damage. It was positive in L5187Y mouse lymphoma assay for gene mutation and chromosomal aberrations. It also causes an increase in the incidence of micronuclei formation in mouse bone marrow cells in vivo when administered intravenously at high toxic doses (500mg/Kg) (Olin *et al.*, 1994).

Toxic effects on the male reproductive system of male rats in the form of marked reduction in sperm count and motility were reported by (Sacks *et al.*, 1994).. Animal toxicity profiles for this drug indicate that it is carcinogenic for experimental animals at high doses. (Cassady and Whitly, 1997).

Material and Methods

Famciclovir, was obtained in the form of Famvir tablets (Smithkline Beecham, for Novartis Pharma AG, Basle, Switzerland), each tablet contains 125 mg famciclovir.

Forty adult male albino rats, weighing 300–350 gram, were housed with free access to food and water, and maintained on a 12 hour light/dark cycle. Animals were divided into 4 groups; ten rats for each.

The first group was served as a control group, the second was treated with the drug for 2 weeks, while the third was treated with the drug for 4 weeks. The forth group was the recovery group in which discontinuation of drug administration for 4 weeks for follow up. Each treated rat received 135 mg/Kg B.Wt famciclovir dissolved in distilled water by gavage once daily. The dose was calculated according to maximum therapeutic daily dose in rats, derived from the maximum therapeutic daily dose for human ,1500 mg/ day, according to Crumpacker (1996 b) using Paget table (Paget and Barns, 1964).

For Histological studies, rats were sacrificed by rapid decapitation, and samples from the testes were taken, fixed, and processed into paraffin sections of 5µm thickness. Haematoxylin and eosin staining (H&E) was done to demonstrate the morphological and histological changes in the testes.

For epididymal spermatozoal examination, spermatozoa collection was done as described by Blandau and Jordan (1941). Epididymal content of each rat was obtained immediately by cutting the tail of epididymis and squeezing it gently to obtain the fresh undiluted semen in a clean Petri dish. Sperm cell count was estimated according to the method reported by Blazak *et al.* (1993). The progressive motility of sperms and epididymal sperm viability and abnormalities were detected according to the method reported by Bearden and Flyquary (1980). The description of the sperm abnormal forms observed in this study was done according to Mori's classification (Mori *et al.*, 1991)

For Chromosomal study, rats from each group were anaesthetized with ether before sacrifice. The bone marrow was processed according to Rabello-Gay and Ahmed (1980). The data were checked and entered to Statistical Package of Social Science (SPSS) version 11.0 (Norusis, 1997).

Results

Histological examination:

Microscopic examination of the testicular specimens, stained with H& E of the treated rats revealed that the spermatogenesis was affected compared to control group(Fig.1). The germinal epithelium lining the tubules was disorganized with abnormal mitotic figures and apoptotic cells(Fig.2) .Further drug administration for another 2 weeks has resulted in aggravation of the previously mentioned histological changes with vacwles in tranucleen (Fig.3). In recovery group the histological changes in the seminiferous tubules were still present but

less than that present in treated groups (Figs. 4).

Semen analysis

The rats orally administrated with the maximum therapeutic doses of famciclovir for 2 weeks has resulted in a statistically significant decrease in the mean values of the sperm count when compared with those of the control group ($p < 0.01$). Further administration of the drug for another 2 weeks lead more reduction in the mean values of the sperm count when compared with those of the positive control group. These decreases that induced by drug treatment were progressive and time dependant as the difference between the mean values of sperm count in the rats of the treated groups by the end of the 2nd and the 4th weeks of treatment was highly significant ($p<0.001$). Recovery group sperm count was increased more than treated group but less than the recovery group. The same results were obtained as regard to sperm viability and motility.

As regard sperm abnormal forms percents, after 2 and 4 weeks of treatment, the mean values of the sperm abnormal forms percents of famciclovir treated rats showed a very highly statistically significant increase when compared with those of the control group ($p<0.001$). This increase was progressive and depended on the duration of treatment as there was a significant difference between the mean values of the sperm abnormal forms percents in the treated groups at the end of the 2nd week and those at the end of the 4th week of treatment ($p <0.001$). By the end of the follow up period, these mean values recorded a remarkable improvement and they showed a very highly statistically significant decrease when compared with those at the end of the 4th week of treatment ($p<0.001$). Figures 6, 7, 8, 9 and 10 showed examples for sperm abnormalities that detected in famciclovir group as compared to the normal sperm forms (Fig. 5). Figures 11, 12, 13 and 14 showed bar charts for different semen parameters.

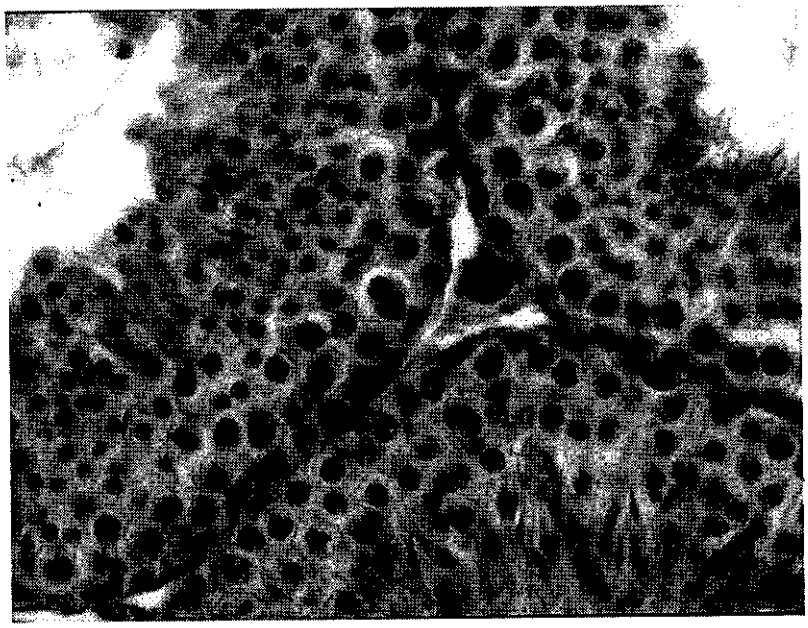

Fig.(1) A photomicrograph of a section from a rat's testis (control group) showing normal semineferous tubules lined by spermatogenic cells and showing normal spermatogenesis (H & E x400)

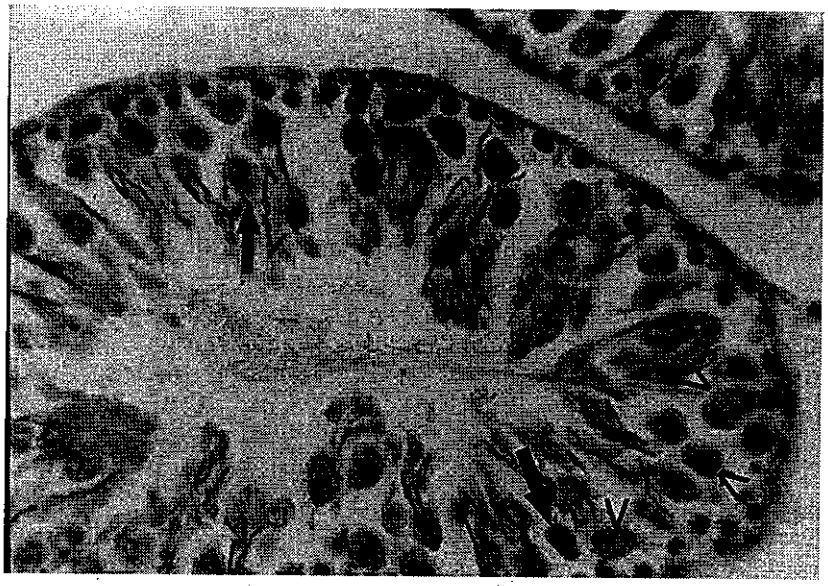

Fig. (2) A photomicrograph of a section from the testis of a rat orally gavaged with the maximum therapeutic dose of famciclovir daily for 2 weeks showing affected spermatogenic cells showed ,dark condensed nucleous (arrows), fragmented nucloei (arrow heads) (H & Ex 400)

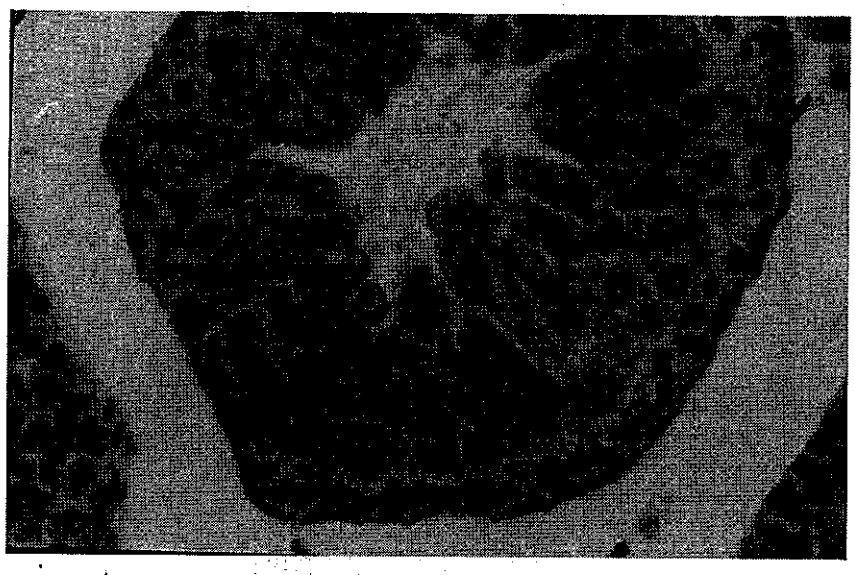

Fig. (3) A photomicrograph of a section from the testis of a rat orally gavaged with the maximum therapeutic dose of famciclovir daily for 4 weeks showing marked arrest of spermatogenesis, increased abnormal features in spermatogenic cells (arrows)(dark condensed nucleous, intranuclear vacuoles, fragmented nucloei) (H & Ex 400).

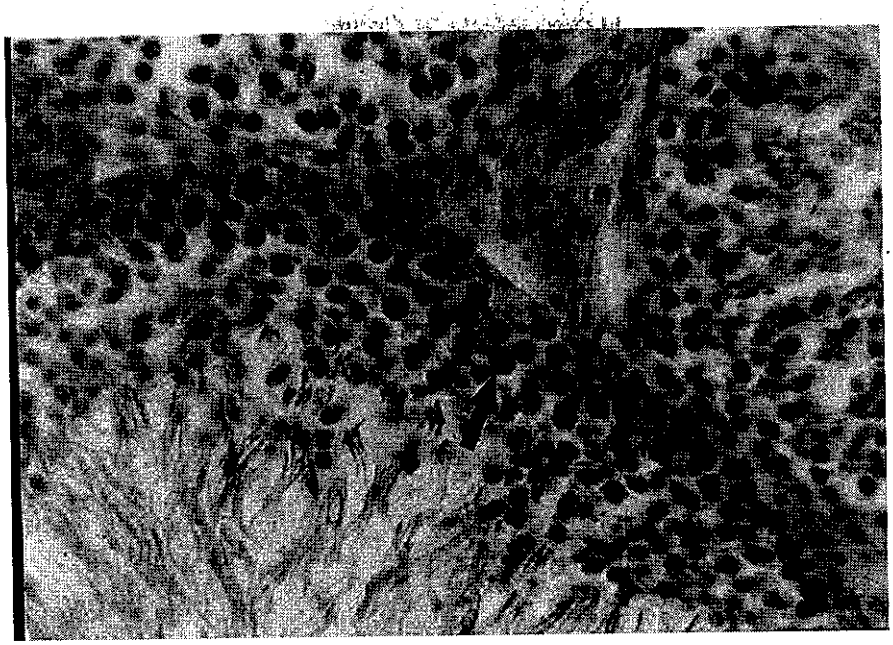

Fig. (4) A photomicrograph of a section from a rat's testis of famciclovir group after 4 weeks of stoppage of the drug showing partial recovery of spermatogenesis with fewer apoptotic cells with condensed chromatin (arrow). (H & Ex 400)

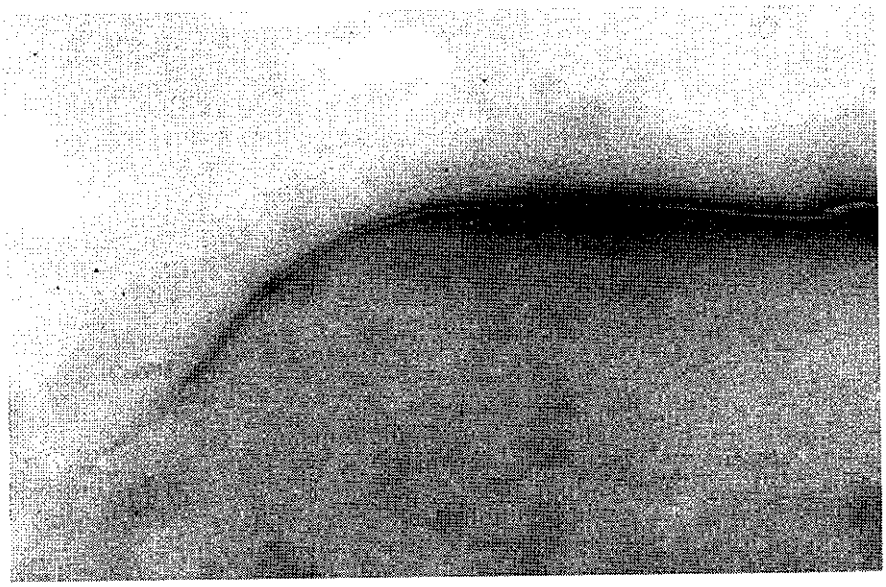

Fig. (5) A photomicrograph of a sperm with normal shape obtained from the semen of an adult male albino rat of the control group. (Nigrosin and Eosin x400)

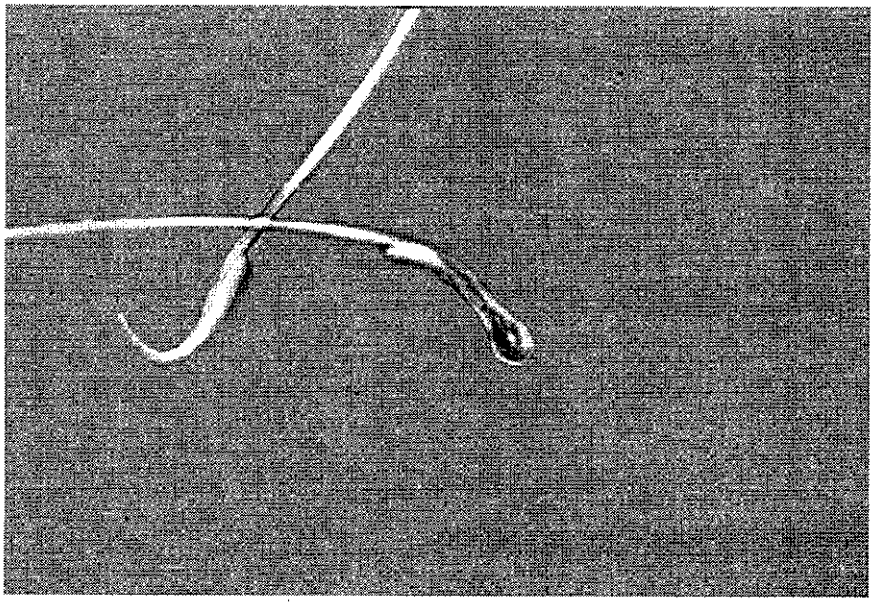

Fig. (6) A photomicrograph showing sperm anomaly in the form of pear shaped head The semen obtained from an adult male albino rat of famciclovir treated group (group2) (Nigrosin and Eosin x400)

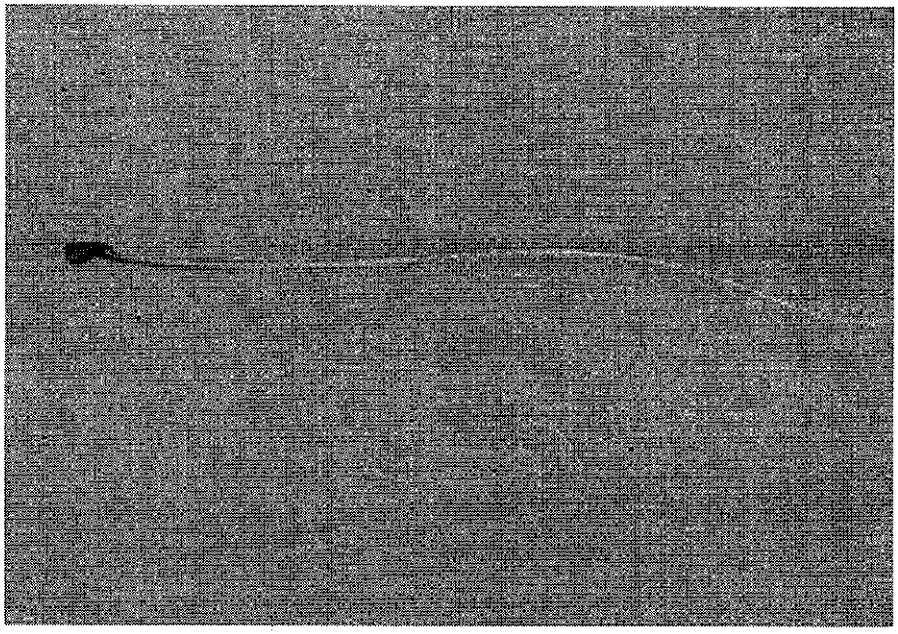

Fig.(7) A photomicrograph showing a sperm with pin head obtained from the semen of an adult male albino rat orally gavaged with the maximum therapeutic dose of famciclovir for 4 weeks. (Nigrosin and Eosin x400)

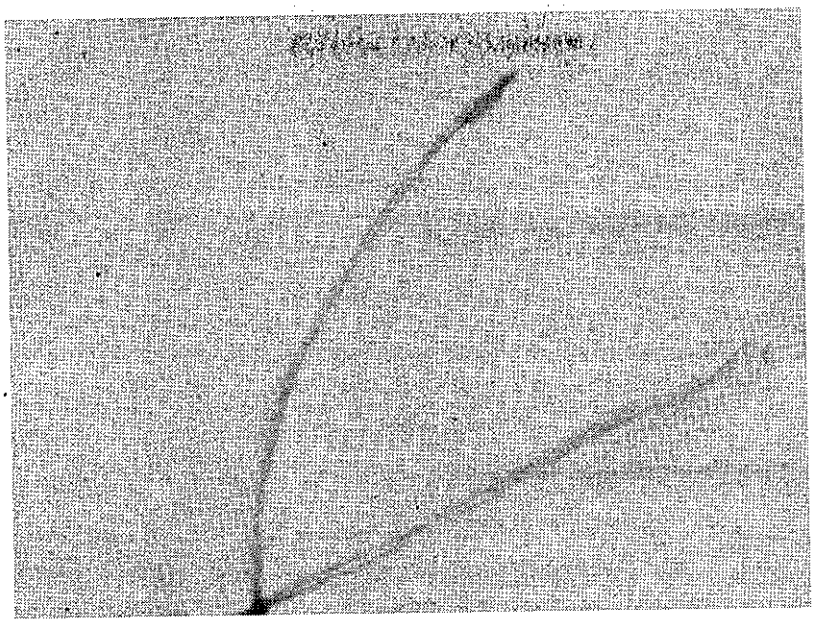

Fig. (8) A photomicrograph showing two sperms, the upper one showing flattened head obtained from the semen of an adult male albino rat orally gavaged with the maximum therapeutic dose of famciclovir for 4 weeks. (Nigrosin and Eosin x400)

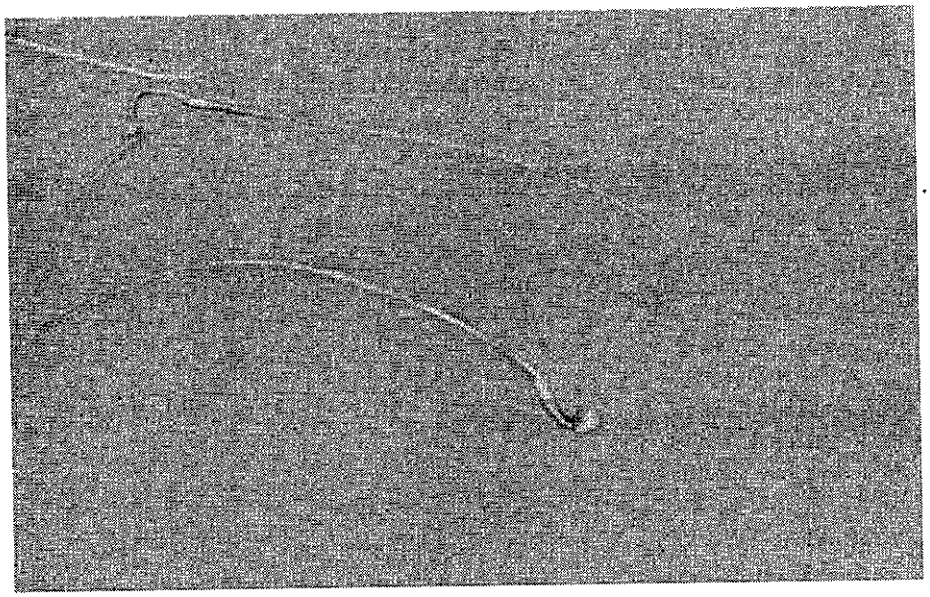

Fig. (9) A photomicrograph of two abnormal sperms with bent tail obtained from the semen of an adult male albino rat orally gavaged with the maximum therapeutic dose of famciclovir for 4 weeks. (Nigrosin and Eosin x400)

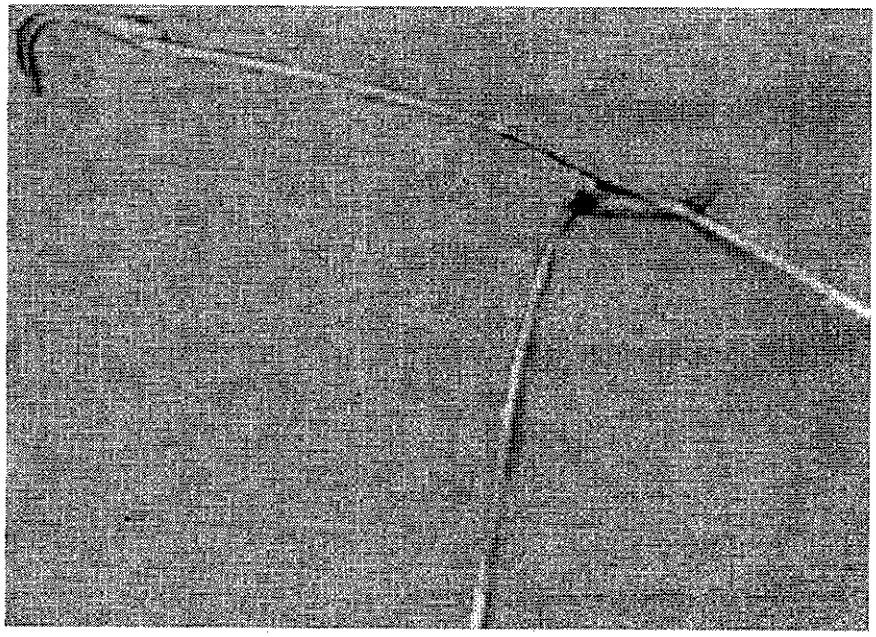

Fig. (10) A photomicrograph of a deformed sperm (bent neck) obtained from the semen of an adult male albino rat orally gavaged with the maximum therapeutic dose of famciclovir for 4 weeks. (Nigrosin and Eosin x400)

Table (1): changes of the mean values of sperm count (10^6/mm^3) that induced by the daily oral administration of the maximum therapeutic doses of famciclovir in adult male albino rats at the end of the 2nd and 4th weeks of treatment and the 4th week of drug withdrowal by ANOVA test.

Groups / Periods	Control group	Famciclovir group	P
X±SD x10^6 After 2 weeks of treatment	25.65±2.49	21.57±3.93	<0.001 ***
X±SD x10^6 After 4 weeks of treatment	26.23±2.52	10.19±2.64	<0.001 ***
X±SD x10^6 After 4 weeks of follow up	26.26±2.79	21.90±3.14	<0.001 ***

* **: means Highly Significant ($P < 0.01$).

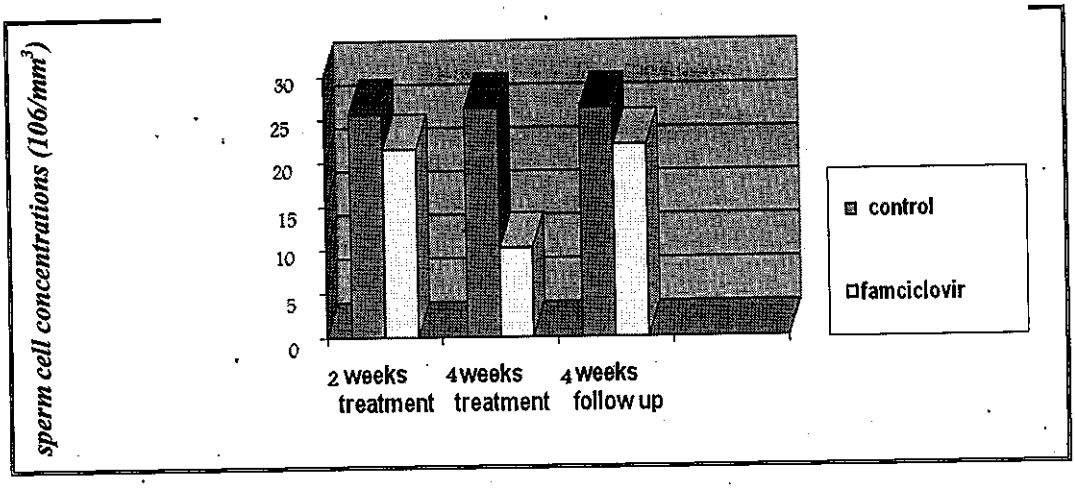

Fig. (11) Bar chart shows the mean values of the sperm count ($106/mm^3$) of the adult male albino rats treated daily with the maximum therapeutic doses of famciclovir for 2 and 4 weeks and those after 4 weeks of follow up as compared to the control group.

Table (2): Statistical analysis of the changes in the percents (%) of sperm motility and viability that induced by the daily oral administration of the maximum therapeutic dose of famciclovir in adult male albino rats at the end of the 2nd and 4th weeks of treatment and the 4th week of drug withdrowal ANOVA test.

Duration	Groups / Parameter	Control group	Famciclovir group	P
After 2 weeks of treatment	sperm motility Percent X±SD (%)	82.60±5.66	29.75±4.09	<0.001 ***
	sperm viability Percent X±SD (%)	90.30±4.97	41.13±8.93	<0.001 ***
After 4 weeks of treatment	sperm motility Percent X±SD (%)	84.00±7.36	12.00±3.33	<0.001 ***
	sperm viability Percent X±SD (%)	91.96±4.43	18.68±4.44	<0.001 ***
After 4 weeks Of follow up	sperm motility Percent X±SD (%)	83.50±8.29	50.75±15.75	<0.001 ***
	sperm viability Percent X±SD (%)	92.30±2.26	61.83±17.38	<0.001 ***

***: means Very Highly Significant (p>0.001).

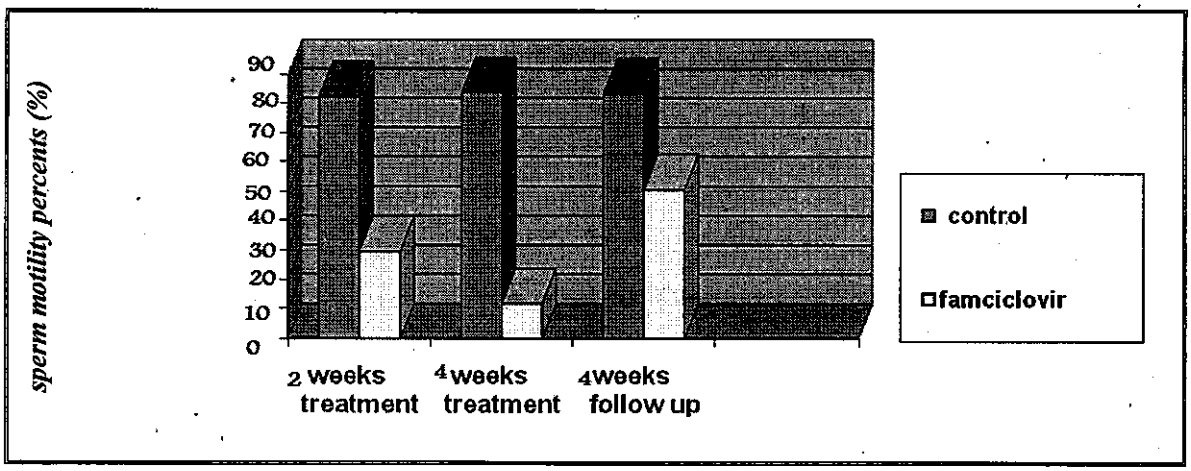

Fig.(12): Bar chart shows the mean values of the sperm motility percents (%) of the adult male albino rats treated daily with the maximum therapeutic doses of famciclovir for 2 and 4 weeks and those after 4 weeks of follow up as compared to the control group.

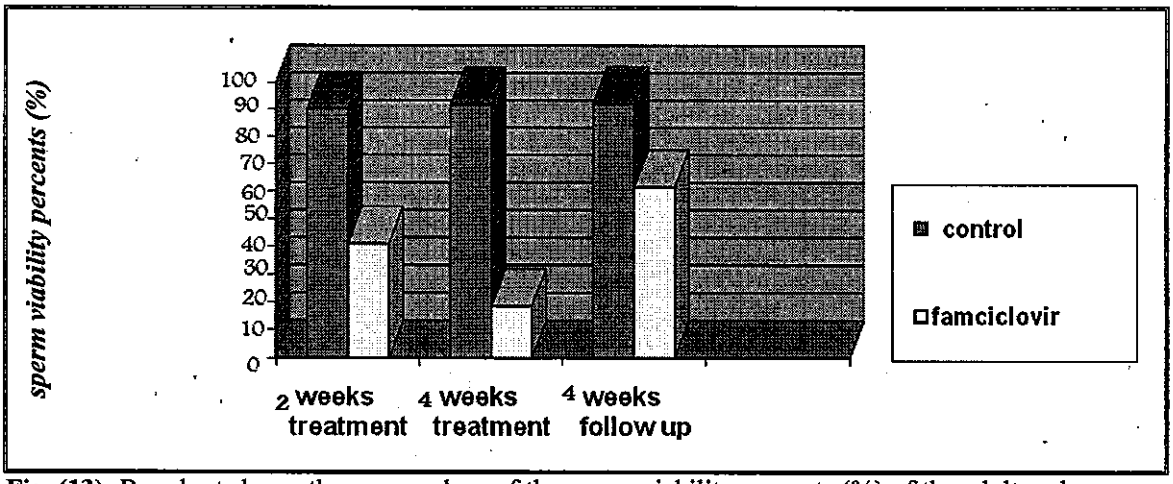

Fig. (13): Bar chart shows the mean values of the sperm viability percents (%) of the adult male albino rats treated daily with the maximum therapeutic doses of famciclovir for 2 and 4 weeks and those after 4 weeks of follow up as compared to the control group.

Table (3): Statistical analysis of the changes in the percents of the sperm abnormal forms (%) that induced by the daily oral administration of the maximum therapeutic dose of famciclovir in adult male albino rats at the end of the 2nd and 4th weeks of treatment and the 4th week of drug withdrowal by ANOVA test.

Groups / Periods	Control group	Famciclovir group	P
X±SD (%) After 2 weeks of treatment	2.08±0.10	8.08±2.26	<0.001 ***
X±SD (%) After 4 weeks of treatment	2.20±0.11	13.23±4.25	<0.001 ***
X±SD (%) After 4 weeks of follow up	1.98±0.11	5.00±1.60	<0.001 ***

***: means Very highly significant (P <0.001).

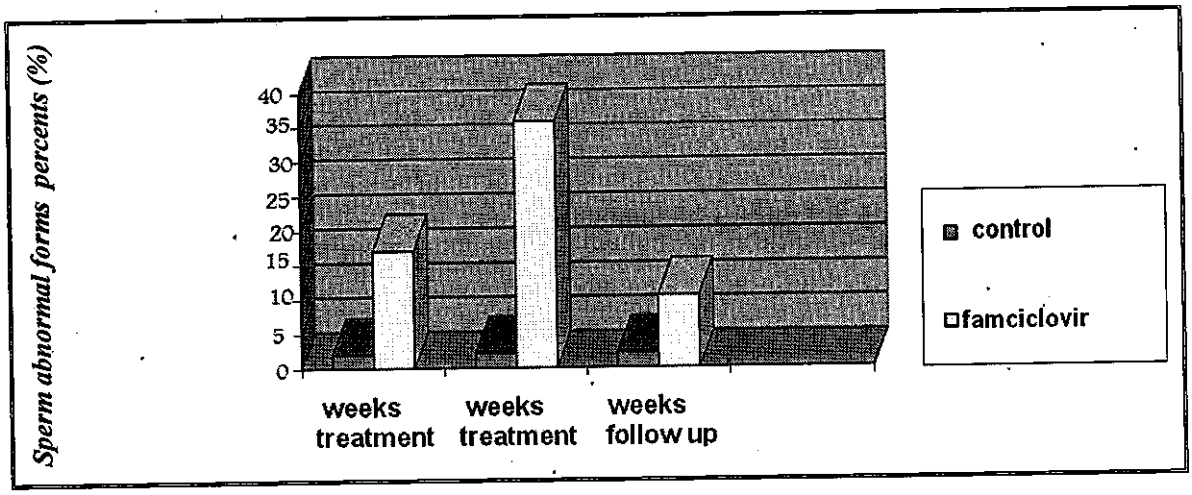

Fig. (14): Bar chart shows the mean values of the sperm abnormal forms percent (%) of the adult male albino rats treated daily with the maximum therapeutic doses of famcilovir for 2 and 4 weeks and those after 4 weeks of drug withdrowal as compared to the control group.

In Cytogenic study the bone marrow cells of the control groups showed normal metaphase spread having 42 chromosomes (Fig.15) While bone marrow cells of rats gavaged with the maximum therapeutic dose of famciclovir once daily for 2 weeks showed chromosomal aberrations increased by the end of the 4th week. These changes were in the form of chromosomal fragments, terminal chromatid deletions, ring chromosomes, chromosomal gaps, dicentric chromosomes, clumping of the chromosomes and polyploidy (Figs.16, 17, 18and 19).

After 2 and 4 weeks of treatment there was a very highly significant increase in the chromosomal aberrations of marrow cells of the rats of the treated groups when compared with those of the control group ($p<0.001$).

After 4 weeks of follow up the number of chromosomal aberration significantly decreased compared to those after 4 weeks of treatment but still there were very high significant difference between them and those of control group ($p<0.001$).

Fig 20 showed the relation of sperm abnormalities in treated and recovery group in relation to control group.

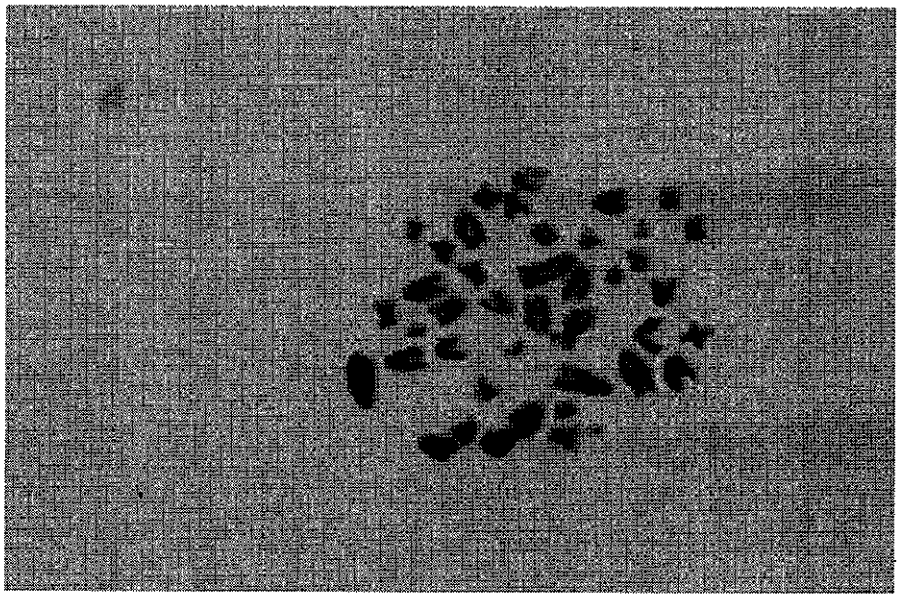

Fig. (15): A photomicrograph of a metaphase spread prepared from the bone marrow cells of an adult male albino rat of control group, showing a normal chromosomal pattern (Geimsa stain x 1000)

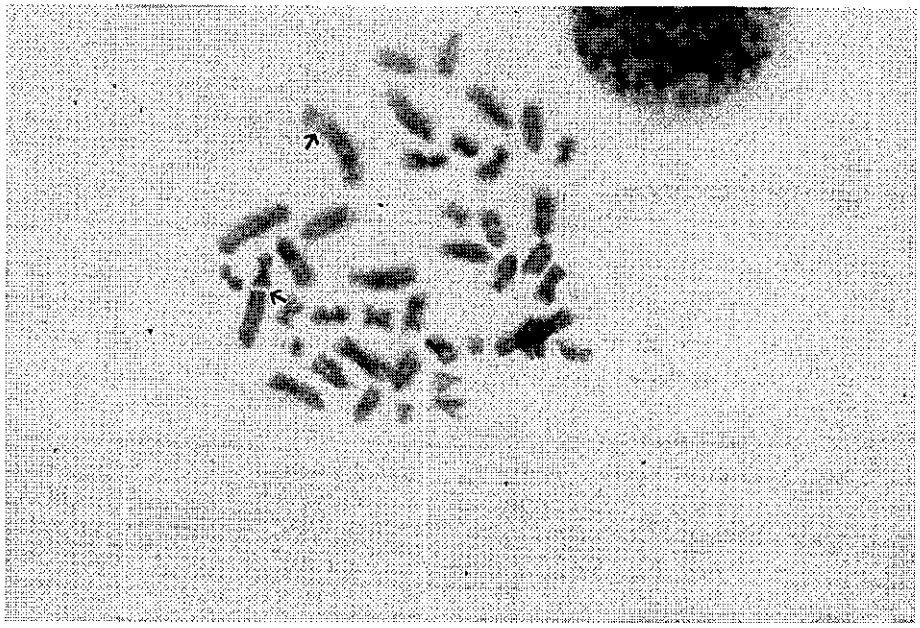

Fig. 16: A photomicrograph of a metaphase spread prepared from the bone marrow cells of an adult male albino rat given famciclovir at the maximum therapeutic dose orally once daily for 2 weeks showing a chromatid deletion, and a chromosomal gap .
(Geimsa stain x 1000)

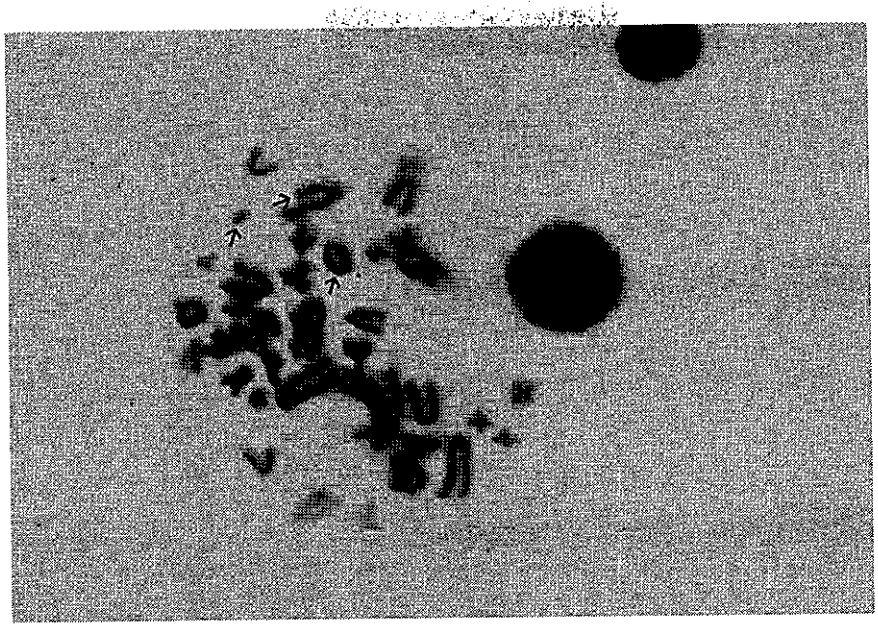

Fig. 17: A photomicrograph of a metaphase spread prepared from the bone marrow cells of an adult male albino rat given famciclovir at the maximum therapeutic dose orally once daily for 2 weeks showing an isochormosome , chorosomal fragments , a terminal chromatid deletion and a ring chromosome(arrows) . (Geimsa stain x 1000)

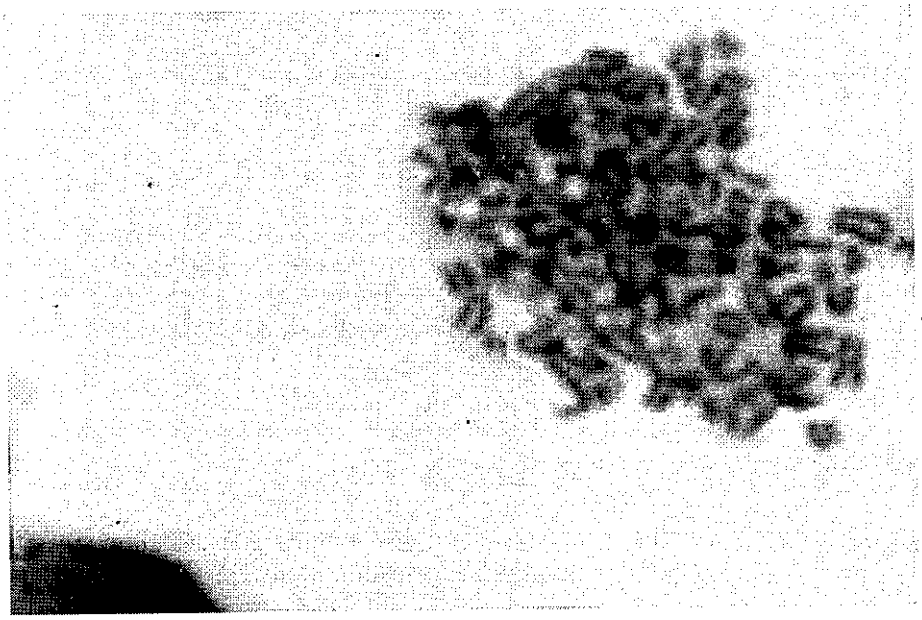

Fig. 18 : A photomicrograph of a metaphase spread prepared from the bone marrow cells of an adult male albino rat given famciclovir at the maximum therapeutic dose orally once daily for 4 weeks showing ploypliody . (Geimsa stain x 1000)

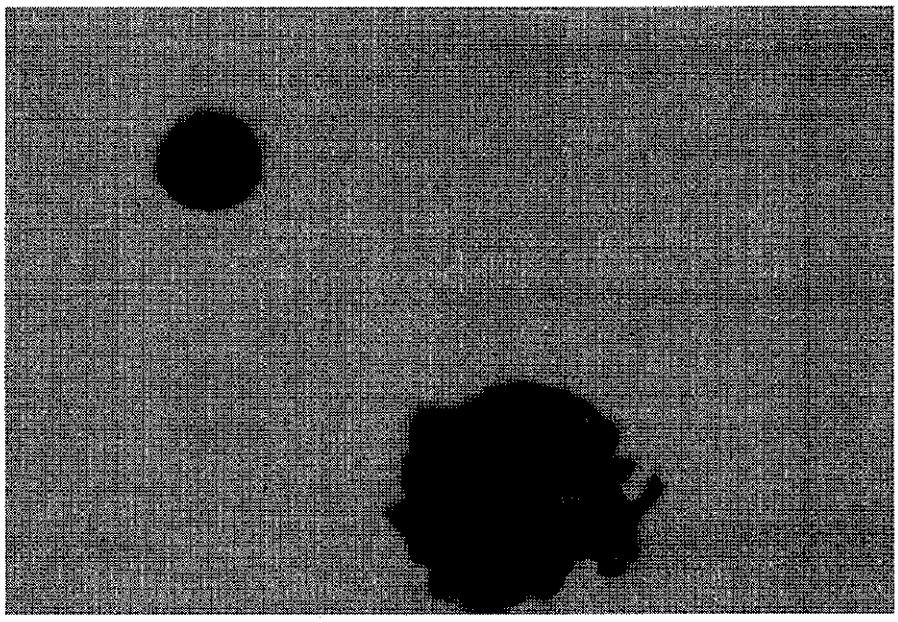

Fig. (19): A photomicrograph of a metaphase spread prepared from the bone marrow cells of an adult male albino rat given famciclovir at the maximum therapeutic dose orally once daily for 4 weeks showing chorosomal clumping . (Geimsa stain x 1000)

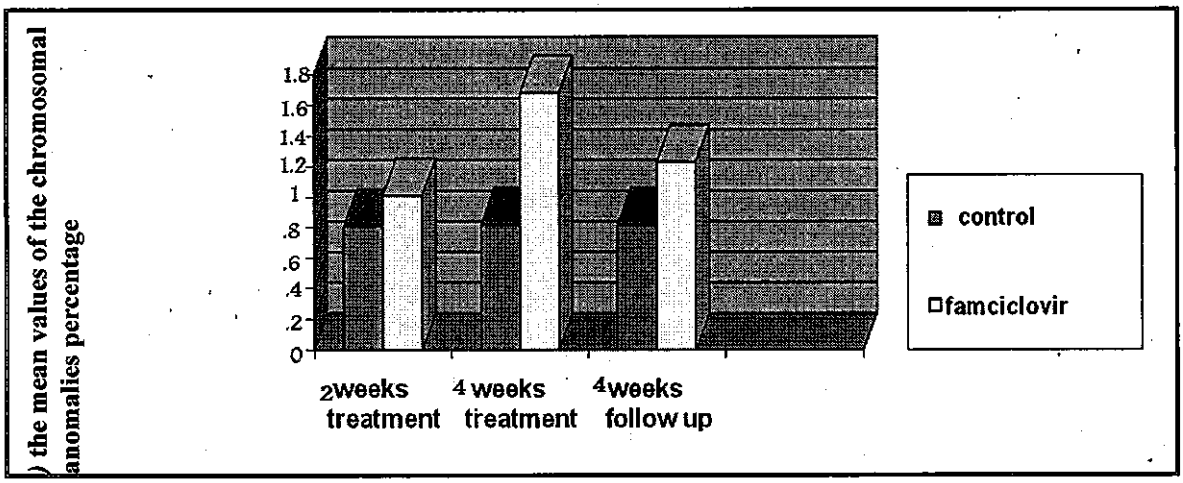

Fig.(20): Bar chart shows the mean values of the chromosomal anomalies percentage (%) of the adult male albino rats treated daily with the maximum therapeutic doses of famciclovir for 2 and 4 weeks and those after 4 weeks of follow up compared to the control group.

Discussion

Famciclovir is an antiviral drug that shown to be effective and safe for the treatment of the first episode and recurrent genital herpes. It is also useful as suppressive therapy for individuals with frequent genital herpes recurrences. High doses of famciclovir have been used to speed the healing of herpes zoster (Colgan *et al.*, 2003 and Moomaw *et al.*, 2003). Famcicloveir has also potential effect in cancer gene therapy (suicide gene therapy) (Tomicic *et al.*, 2002).

The increasing wide use of these apparently safe drugs making them an interesting subject to investigate their possible adverse effects on the human being. So the aim of this study was to evaluate the toxic effects of famciclovir at the maximum therapeutic doses on the testes, sperms and chromosomes of adult male albino rats.

The time of drug administration to rats is determined by the fact that one month administration in rats is equivalent to 24 months in humans (Bentiz, 1970).

It was observed that, the mean values of the semen analysis parameters (sperm count, sperm motility, and viability) in famciclovir treated rats after 2 and 4 weeks of treatment were significantly reduced when compared with those of the control group. These parameters were increased in recovery group but still less than that of control group. The abnormal forms increased in treated groups. In the recovery group the abnormal forms percent was less than the treated groups but more than that of control group

Semen analysis results of the present work were consistent with Saltzman et al. (1994) who stated that; famciclovir had been associated with adverse effects on testicular functions.

Moomaw *et al*, (2003) reported that, penciclovir and famciclovir can produce testicular toxicity in experimental animal treated with them for long periods. Also a report by FDA (1997) has mentioned that, these testicular toxicities included: atrophy of semineferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility.

The findings of this study could be attributed to the mechanism of action of famciclovir that inhibit viral DNA synthesis (Moomaw *et al.*, 2003).

Genotoxic agents that cause DNA damage could damage the rapidly dividing normal cells, including the mucosal cells of the gastrointestinal tract, germ cells and the hematopoietic cells within the bone marrow (Boyonoski *et al.*, 2000).

Cells in the testis are, especially, vulnerable to destruction by DNA damaging agents since they undergo numerous processes (e.g. mitosis, meiosis, and morphogenesis) that are targeted by different clastogens (Ghosh and Das gupta, 1999; Hsu *et al.*, 1998 and Stanely and Akbrsha, 1994).

The testes and sperms were affected by famciclovir may be due to the high concentration of the drug in the semen, similar to acyclovir the structurally related drug. (Douglas *et al.* 1988)

The toxic effect of famciclovir was also proved by histological examination of testes where rates treated with the maximum therapeutic doses for 2 and 4 weeks had many toxic effects on the testis of the adult male albino rats, these toxic effects were evident by light microscopical examination of H&E stained sections in the form of semineferous tubules that were lined with disorganized hypo-cellular germinal epithelium with frequent abnormal mitotic figures and apoptotic cells. These toxic effects appeared to be time dependent as it aggravated at the end of the 4th week of treatment, where testicular examination revealed that the majority of the semineferous tubules were lined by few spermatogenic cells.

Ahtianen *et al.* (2004) explain the toxic effect of famciclovir on testes by giving famciclovir in a dose of 200 mg/Kg per day for 4 weeks to adult transgenic mice expressing herpes simplex virus thymidine kinase. This enzyme monophosphorylates famciclovir with subsequent production of its cytotoxic triphosphate form which could

incorporated in the elongating DNA of the proliferating cells, resulting in termination of replication and cell death.

In the present work it was noticed that, the most sensitive cells to the toxic effects of famciclovir treatment were the spermatogenic cells, while Sertoli cells appeared to be less vulnerable to this effect This was explained by Ahtianen *et al.* (2004) who stated that, spermatogenic cells are characterized by active DNA replication making it more vulnerable to the toxic effects of DNA damaging drugs. While adult Sertoli cells are terminally differentiated non dividing cells (Moore *et al.* 1992)

Microscopic examination of H&E stained testicular specimens of the rats of treated groups revealed that, many spermatogenic cells were undergoining apoptosis. These cells were pyknotic, other cells showed karyorrkexis .

These results were in accordance with Tomicic *et al.* (2002) who stated that, famciclovir is shown to be strong inducers of apoptosis which characterized to be concentration- and time-dependant.

These abnormal findings was explained by Halloran and Fenton (1998) who stated that, irreversible cell cycle arrest with G2-metaphase damage checkpoint represents a general mechanism of cytotoxicity of these nucleoside analogues.

Chromosomal aberrations in bone marrow cells obtained from rats' femurs were another findings in famciclovir toxicity. The most frequent changes in treated rats were clumping, chromosomal fragment, ring chromosomes and terminal chromatid deletion. All chromosomal aberrations in the rats were time dependant, the recovery group showed the same anomalies but less than that of treated group.

Wutzler and Thust, 2001 stated that most nucleoside analogue antiviral drugs induce chromosomal aberrations but are inactive in gene mutation assays. The possible mechanisms by which these agents may cause damage in the genetic information are still largely hypothetical

The mechanism of genotoxic effect of famciclovir were studied by Thust *et al.* (2000), they studied the genotoxic effects of the three antiviral dugs; acyclovir, ganciclovir and penciclovir in metabolically competent cells (Chinese Hamester Ovary cells (CHO) with stable transfection of HSV thymidine kinase gene) that will permit high concentrations of these drugs. They found that acyclovir induced an increase in sister chromatid exchange (SCE) frequency immediately after exposure and reached a peak of ~72 SCEs/cell at 28 h post-exposure. Fourteen hours later, the SCE values declined to the range of background rates in CHO cells surviving treatment with high concentrations of acyclovir. They also added that acyclovir induced clastogenicity was dose-dependent and the dominant aberration types were chromatid breaks and translocations. They suggest that the clastogenic effects of acyclovir are due to chain termination, whereby attempts to bypass the sites of incorporation causing DNA replication blockage that may lead to the formation of SCEs or cause DNA strand breaks leading to structural chromosomal aberrations. As regard famciclovir, they found that, it was less genotoxic than acyclovir, inducing sister chromatid exchanges only at cytotoxic/apoptotic concentrations, and is only weakly clastogenic.

The former study which proved that famciclovir is genotoxic in toxic concentration only, has supported by the study done by Sacks *et al.* (1994) who studied the effects of chronic administration of famciclovir at a dose of 250 mg twice daily for 18 weeks on semen parameters of men with recurrent genital herpes infection. They concluded that famciclovir is well tolerated and has no significant effects on semen. This results were in consisted with the present study which can be explained on the base that the former study was carried out for shorter duration and using smaller doses as compared with the present study.

So the toxic effects of the maximum therapeutic dose of famciclovir which proved in this study can be avoided by using the drug in lower doses and shorter periods

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تأثير عقار فامسيكلوفير علي الخصيتين والحيوانات المنوية والصبغيات الوراثية في الجرذان البيضاء : دراسة هستولوجية, ووراثة خلوية

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قسم الهستولوجى بكلية الطب جامعة بنها* قسمى الهستولوجى والتشريح بكلية الطب جامعةالأزهر

** قسم الهستولوجى بكلية الطب جامعةالزقازيق***

يستخدم عقار فامسيكلوفير فى علاج كثير من الفيروسات المسببة لمرض الحلأ النطاقى والتناسلى، وقد وجد لهذا العقار بعض الأثار الجانبية ولذلك تمت هذه الدراسة لمعرفة الأثار الضارة لعقار فامسيكلوفير "أقصى جرعة علاجية للإنسان" .وقد استخدمت فى هذه الدراسة أربعون من الجرذان البيضاء حيث قسمت إلى أربع مجموعات ،كل مجموعة مكونة من عشرة فئران بالغة ،استخدمت المجموعة الأولى كمجموعة ضابطة ،وأعطيت المجموعة الثانية العقار لمدة أسبوعين بجرعة 135/ مجم لكل كجم ، وللمجموعة الثالثة نفس الجرعة لمدة أربعة أسابيع وفي المجموعة الرابعة تم وقف العلاج لمدة أربعة اسابيع أخرى لمعرفة مدى تأثير توقف العقار على الأثار الجانبية .

وفى نهاية كل فترة تم أخذعددا من الفئران، و اخذت الخصيتاين وتم دراسة قطاعاتها بصبغة الهيماتوكسلين والأيوسين ، كما تم اخذ الحيوانات المنوية من الوعاء الناقل لعدد أخر من الفئران وتمت دراسة الحيوانات المنوية من حيث العدد والنشاط والحركة وكذلك العيوب الخلقية فى الحيوانات المنوية .

كما تم تخدير بعض الفئران وأخذ خلايا النخاع العظمى ودراسة الصبغيات الوراثية بها . وقد وجد بالخصيتين عدة آثار ضارة ، و قد كانت هذه الأضرار في صورة إختلال فى النسيج الطلائى المبطن للأنبيبيات البرزية (المنوية) مع ظهور خلايا ميتة موتا مبرمجا. أما فحص النطف المنوية فقد أظهر نقص عددها وكذلك حركتها ونشاطها مع زيادة النطف الشاذة فى تركيبها. وبالنسبة للصبغيات الوراثية فقد وجد بها شذوذات تركيبية و عددية . ولقد اشتملت هذه الشذوذات على كسور وفجوات كروماتيدية وكروموزومات حلقية و خلايا بها تكتل بالكروموزومات.

وقد كانت هذه التأثيرات تزداد بازدياد فترة التعرض وتقل تدريجيا مع التوقف عن إعطاء هذين العقارين.

ولذلك: لتجنب الأثار الضارة الناتجة من إستخدام العقار لفترة زمنية طويلة بأقصى جرعة مسموح به ، ينصح باستخدام هذا العقار لفترة زمنية قصيرة وعدم الوصول بالجرعة إلى أقصى جرعة مسموح بها.