ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

EFFECT OF ANTI-KALA-AZAR DRUG MILTEFOSINE ON OVARIAN ASCORBIC ACID LEVEL IN ALBINO RATS

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Manuscript Info

Manuscript History:

Received: 25 March 2014
Final Accepted: 26 April 2014
Published Online: May 2014

Key words:
Anti-kala-azar drug, Miltefosine, Ovarian Ascorbic Acid, Estrogen Agonist

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Abstract

Female healthy cyclic albino rats of body weight (100-170g) groups were treated with different dose and duration of orally effective anti-kala-azar drug miltefosine (hexadecylphosphocholine),registered as Impavido (R), a highly significant ($p < 0.001$) increased level of ovarian ascorbic acid were observed in different dose and duration treated experimental rat groups in comparison to control rat groups. All such findings might be possible due to the antineoplastic activity of drug miltefosine which exerts its effect as an estrogen agonist on ovarian tissue which may be causative factors for sterility in female albino rats.

INTRODUCTION:

Pharmacodynamically drugs may be divided into two broad classes- agonist and antagonist. Most agonist caused a receptor to maintain its confirmation in the active state, whereas antagonist prevents activation of the receptor by agonists. The anti-kala-azar (Leishmaniasis) drug miltefosine (hexadecylphosphocholine) registered as Impavido (R) has become the first orally effective, affordable and acceptable drug for combating the serious disease kala-azar. Urbina (2006)studied the mechanism of action of this drug and reported that its action is associated with a variety of subcellular structures and enzymes, particularly associated with cellular membranes. This drug inhibits the growth of a wide variety of cancer cells and wide range of cellular processes such as the modulation of calcium homeostasis (Henke et al., 1999), the alteration of phospholipase activity (Lucas, Hemandez – Alcoceba, Penalva& Local, 2001), affect signal transduction (Arthur and Bittman, 1998,Ruiter et al., 2001)may arrest cell proliferation by interfering with biosynthesis of phosphatidylcholine (PC) (Beekovic, 1998), Sindermann& Engel (2006) reported that miltefosine induced testicular changes of the sertoli cell type and caused an impairment in fertility during treatment. But, whether it affects ovarian physiology or not, this present proposed investigation has been undertaken.

Materials & Methods:

30 cyclic female albino rats of Charl's Foster strain of (100-170g) body weight groups were employed in this investigation. All rats were divided into 5 groups of six rats. Their regular estrous cycle was studied by vaginal smear technique of Long & Evans, (1922). One group of six rats were considered as control group and other four were as experimental groups.

All the experimental rats as well as control groups were maintained at uniform animal husbandry conditions of food, water, light and temperature throughout the experimental period. The dose and duration of miltefosine was administered to experimental rats as follows:-

Exptl.rat Group – I	:	1.4mg/kg body wt. for 7 days
Exptl.rat Group – II	:	1.2mg/kg body wt. for 14 days
Exptl.rat Group – III	:	01mg/kg body wt. for 21 days
Exptl.rat Group – IV	:	0.8mg/kg body wt. for 28 days

Control rats were treated with glass distilled water till the experimental period.

After completion of treatment, the rats of experimental groups were killed by cervical dislocation and their ovary was dissected. The ovarian tissue were macerated separately in 10 ml of glass distilled water to prepare homogenate and further processed for the estimation of ovarian ascorbic acid by the titrimetric method of Haris& Ray (1932). Results were analysed by student't' test.

Results and Discussion:-

The kinetics of follicular growth, follicular cell function and its metabolic activities are under the control of pituitary gonadotropins (F.S.H. & L.H.) and ovarian steroids (estrogen & progesterone). Ovarian follicular cells like granulosa and theca contains receptor for F.S.H. & L.H. The intracellular increase and decreaseof various substances affect the cellular events necessary for the process of reproduction (Williams, 1999). Earlier report of Mills and Schwartz (1961)indicated that ovarian ascorbic acid as an endogenous and exogenous assay for cyclic proestrus release in rats.

As indicated in Table.-1, it was observed a highly significant increased level of ascorbic acid after the various doses and duration of miltefosine treated experimental rats in comparison to control rats. This increased level of ascorbic acid in the ovarian tissue of the drug treated experimental rats might have been possible due to the surfactant effect of drug. As earlier report of Stafford et al., (1989) indicated that due to the amphiphilic nature of drug, it showed a nonspecific cytotoxic effect. It might be possible that this cytotoxic effect induces stress in the ovarian tissue, which ultimately increased the level of ascorbic acid to control toxic condition of cell through the process of detoxification. On the other hand, the increased serum LH level in drug treated rats also in accordance with our findings that increased ovarian ascorbic acid caused a rise in serum LH in miltefosine treated experimental rats.

Table – 1: Ovarian ascorbic acid levels at different dose and duration

Sl. No.	Status of rat	Dose of Drug	Duration of treatment	Level of ovarian ascorbic acid (in µg/mg of ovarian tissue Mean ± SEof 6 rats
1.	Normal	0.5 ml G.D.W.	Throughout experimentation period	0.74 ± 0.03^{a}
2.	Exptl. I	1.4 mg/kg body wt.	7 days	2.80 ± 0.116^{b}
3.	Exptl. II	1.2 mg/kg body wt.	14 days	8.70 ± 0.179^{c}
4.	Exptl. III	1 mg/kg body wt.	21 days	2.80 ± 0.179^{d}
5.	Exptl. IV	0.8 mg/kg body wt.	28 days	2.80 ± 0.237^{e}

P value:-a to b, a to c, a to d and a to e = ($p < 0.001$)

b to c = ($p < 0.01$) c to d = ($p < 0.02$)

Acknowledgements:

Authors are thankful to Dr. K. N. Tiwari, Head, P.G. Dept. of Zoology, H.D. Jain College, V.K.S. University, Ara for providing laboratory facilities.

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