World Journal of Medical Sciences 9 (3): 136-141, 2013
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2013.9.3.76204

# Cytogenetic and Embryotoxic Effects of Valdoxan (Agomelatine) on Female Mice and Their Embryos

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**Abstract:** Valdoxan (agomelatine) is a new-first-in-class antidepressant with a novel mode of action at melatonin and serotonin receptors. It is licensed for the treatment of major depression and anxiety. The safe use of valdoxan in human pregnancy has not been established. In order to evaluate the cytogenetic and embryo toxic effects of valdoxan (agomelatine) during pregnancy, Valdoxan was administrated orally to pregnant mice with a doses of (0.01, 0.02 and 0.03 mg/kg/day) from day 3 to 17 of pregnancy. Females were killed at day 18 of pregnancy and examined for evidence of embryotoxic and cytogenetic effects. The results showed that valdoxan caused a significant increases in the chromosomal aberrations, decrease in the fetal and maternal body weight and increase in the embryonic toxicity in all treated groups of pregnant females and their embryos compared with the control and these increases were dose-dependent. The embryo toxic effects as evidenced by increase in the total number of implantations, in the total number of dead embryos and decrease in the total number of live embryos were observed in all treated groups as compared with control. From the above results it was shown that valdoxan had maternal and embryo toxic effects on the female mice and their embryos when taken with a recommended and above the recommended dose during pregnancy. Therefore, we can conclude that valdoxan (agomelatine) should be taken during pregnancy under extreme medical control or restricted.

**Key words:** Valdoxan · Agomelatine · Chromosomal Aberrations · Embryos · Embryo Toxicity · Mice

## INTRODUCTION

Depression is a mental state or chronic mental disorder characterized by feelings of sadness, loneliness, low self-esteem and self-reproach; accompanying signs include psychomotor retardation, withdrawal from social contact and vegetative states such as loss of appetite and insomnia

There are several forms of depression (depressive disorders) [1].

Major depressive disorder and dysthymic disorder are the most common.

- Major depressive disorder is also known as major depression. The patient suffers from a combination of symptoms that undermine his ability to sleep, study, work, eat and enjoy activities. Experts say that major depressive disorder can be very disabling preventing the patient from functioning normally.
- Dysthymic disorder is also known as dysthymia or mild chronic depression. The patient suffers symptoms for along time perhaps many years. However, the symptoms are not severe as in major depression and the patient is not disabled by it. A person with dysthymia might also experience major depression during his life time.
- Another type of depression called postnatal depression is also known as post partum depression. It is not common as major depression or dysthymia a mother or a woman may feel depressed for a very short period during and after giving birth. Experts believe that about 10% to 15% of all women experience post natal depression during and after pregnancy [2].

Really we are still not sure what causes depression. Experts say depression is caused by a combination of factors, such as the person's genes, his biochemical

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environment, his personal experience and psychological factors. MRI (magnetic resonance imaging) has shown that the brain of a person with depression looks different, compared to the brain of a person who has never had depression. The areas of the brain that deal with thinking, sleep, mood, appetite and behavior do not appear to function normally. There are also indicators that neurotransmitters appear to be out of balance [3].

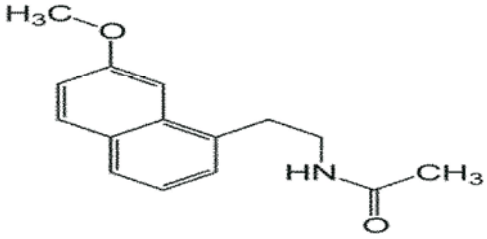
Depression is highly treatable even in its most sever forms, it can be treated with a number of methods, the most common are anti depressant drugs. The aim of an antidepressant drugs is to stabilize and normalize the neurotransmitters in our brain (naturally occurring brain chemicals) such as serotonin, dopamine and norepeniphrine. According to various studies, these neurotransmitters play vital role in regulating mood. SSRIS (selective serotonin reuptake inhibitors) and SNRIS (selective norepinephrine reuptake inhibitors) are the newest and the more popular to day than the older types of anti depressants, mainly because they have a fewer side-effects, MAOIS (monoamine oxidase inhibitors) and tricyclics are examples of older antidepressant drugs. Valdoxan (agomelatine) is classified as a (norepinephrine-dopamine disinhibitor (NDD) is a new medicine, with a unique pharmacological profile, as the first melatonergic antidepressant drug. Valdoxan acts on brain receptors for melatonin, a hormone that is important for regulating sleep, as well as serotonin receptors, also a new evidence establishes the efficacy of valdoxan (agomelatine) in the treatment of anxiety in depressed patients when compared with the other commonly antidepressant drugs [4].

Valdoxan does not induce the side-effects typical of others antidepressants, such as selective serotonin reuptake inhibitors (i.e. gastrointestinal disorders, weight gain, serotonergic syndrome and insomnia). Therefore these properties give valdoxan a definite clinical advantage in the treatment of major depressive disorder (MDD) [5].

At present no adequate data is available that illustrates the safety use of valdoxan on the pregnant female and their embryos if given orally during pregnancy.So, in the present study we examined the cytogenetic and embryo toxic effects of valdoxan (a gomelatine) on pregnant females and their embryos if given orally at a recommended dose and over dose for 14 consecutive days during pregnancy.

## MATERIALS AND METHODS

**Drug:** Valdoxan (agomelatine) tablets produced by (Servier) and (Novartis) France is an oral melatonergic antidepressant drug. It is classified as norepinephrine-depamine disinhibitor (NDDI), each tablet contain 25mg of (agomelatine). Agomelatine has a molecular formula C15H17NO2. The chemical name is N-[2-(7-methoxynaphthalen-1-y) ethyl] acetamide and a molecular weight of 243.3. The structural formula is.




Valdoxan tablets, soluble in water and very soluble in ethanol. The recommended dose for human is 25 mg/once daily.

**Animals and Treatments:** Mature male and female swiss albino mice weighting 26-28gm were used; females mice were mated with males (3:1) over night and examined the next morning for copulatory plugs.The day on which a vaginal plug was found was designated day 1 of gestation.

Animals were housed and kept in a climate controlled animal facility at a temperature of 22 to ± 20°C and a 12-hr automatic light dark cycle with free access of food and tap water. On the evening of gestational day 1, females were divided into four groups. The first group of 10 pregnant females were administrated orally (by gavages) with a dose equal to the recommended human dose (0.01 mg/kg/day). The second group of 10 pregnant females were administrated orally with a dose equal to double the recommended human dose (0.02 mg/kg/day). The third group of 10 pregnant females were administrated orally with a dose equal to 3 times the recommended dose for human (0.03 mg/kg/day) and the fourth group served as control group were administrated orally with a distilled water.

All doses of (valdoxan) were modified to suit the small weight of swiss mice according to Pagat and Barnes [6].

(Valdoxan) was dissolved in distilled water and administrated orally once daily in the evening from day 3 to day 17 of gestation.

The general behaviour of the pregnant females was observed every day and on day 18 of gestation the pregnant females were sacrificed by cervical dislocation for studying developmental and cytogenetic effects of (valdoxan) on pregnant females and their embryos.

**Developmental Toxicity:** On day 18 of gestation, the females were sacrificed, the uterus contents were evaluated for the number of implantation sites, resorptions, dead and live fetuses. Also, the mean weight of mothers and embryos were recorded.

**Chromosomal Preparations in Bone Marrow Cells:** Chromosomes from bone marrow cells were prepared according to the method of Ford and Hamerton [7]. Bone marrow were collected in T.C. M199 culture media and colchicine was added to the tube (2ml of 0.05 colchicine), then the cells were incubated at 37°C for 90 minutes.

After centrifugation 5ml of hypotonic solution KCL (0.056%) was added and the pellet suspended and incubated at 37°C for 30 minutes, the cells were fixed in freshly prepared 3:1 methyl/acetic acid solution and then, two or three drops of cell suspension were dropped on a clean slide covered with cold ethanol and the slides were stained with 10% Giemsa stain for 25 minutes.

**Chromosomal Preparations in Embryonic Cells:** At day 18 of gestation embryos were prepared cytogenetically according to the method of Romagnano *et al.* [8] with minor modifications. Embryonic livers were incubated in 5ml TCM 199 media containing 0.1 mg/mL colcemid for 90 min at 37°C then an amount of 5mL of hypotonic solution of 0.56% KCl was added to the pellet and the cells were incubated at 37°C for 20 minutes, 5mL of fresh fixative (3 methyl alcohol: 1 acetic acid) were added to the cells, two or three drops of the cell suspension were dropped on the surface of clean slides, air-dried and stained with 5% Giemsa stain and examined for chromosomal aberrations. 50 metaphase spreads were examined from each pregnant female and embryo, scoring the different type of chromosomal aberrations.

**Statistical Analysis:** The incidences of resorption, dead and live embryos between experimental and control values were calculated non-parametrically using wilxocon's rank sum test Siegal [9]. The data of chromosomal aberrations in the females and embryos were subjected to analysis of variance (ANOVA) according to Snedecor and Cochran [10].

Least significant differences were used to compare between means according to Waller and Duncan [11] at probability 5%.

## RESULTS

**Maternal Effects:** The data are summarized in Table (1). There were no maternal death in any treatment groups during the experiment. Also there was a significant dose-dependent decrease in the average female body weights compared with the controls.

**Embryonic Effects:** The data are summarized in Table (1). The administration of valdoxan to the pregnant females from day 3 to day 17 of gestation resulted in an increase in the number of resorption and in the number of dead embryos with the increase of the dose level of valdoxan, while the number of implantations and the number of live embryos were decreased with the increase of valdoxan dose. Also the treatment with valdoxan caused a decrease in the mean fetal weight and these decreases were dose dependent.

**Chromosomal Aberration in the Pregnant Females:** The data are summarized in Table (2). The administration of valdoxan to the pregnant female mice during pregnancy from day 3 to 17 of gestation caused a significant increases in the frequencies of chromosomal aberrations (structural and numerical) in all valdoxan treated groups when comparing with control group and these increases were dose dependent. The total structural and numerical aberrations in valdoxan treated groups (0.01, 0.02 and 0.03mg/kg/day) were (36.7, 50 and 64.7) and (12.3, 19.7 and 25) respectively as compared with control group (19.0 and 5.3). Chromosomal aberration in the embryos:

The data are summarized in Table (3). The frequencies of the total number of structural and numerical aberrations in all embryo groups treated with different doses of valdoxan (0.01, 0.02 and 0.03mg/kg/day) were increased significantly compared with the control group and these increases were dose-dependent.

The frequencies of the total number of structural and numerical aberrations in the embryo treated groups (0.01, 0.02 and 0.03 mg/kg/day) were (26.3, 36 and 48.7) and (7.7, 14.7 and 19) respectively compared with control group (11 and 3).

**Comparison Between Pregnant Females (Mother) Groups and (Embryo) Groups:** When comparing the results of cytogenetic examination between mothers and embryos

Table 1: The effect of valdoxan on the fertility and off spring development in mice at (day 18 of gestation)

| | | Dose/mg/kg day | | |
|---|---|---|---|---|
| Parameters | Control | 0.01 | 0.02 | 0.03 |
| No of pregnant females | 10 | 10 | 10 | 10 |
| Total number of implantations | 70 | 65 | 59 | 53 |
| Total number of resorptions | 3 | 5 | 7 | 7 |
| % | 4.3% | 7.8% | 11.9% | 13.2% |
| Total number of dead fetuses | 0 | 2 | 3 | 5 |
| % | 0% | 3.1% | 5.1% | 9.4% |
| Total number of live fetuses | 67 | 60 | 49 | 41 |
| % | 95.7% | 92.3% | 83.1% | 77.4% |
| Mean fetal body weight | 3.81 | 3.60 | 3.55 | 3.40 |
| Mean maternal body weight | 30.00 | 28.00 | 27.50 | 26.55 |

Table 2: The effect of oral administration of valdoxan on pregnant females at day 18 of gestation.

| | Structural aberrations | | | | | | | Numerical aberrations | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatments | Chromatid gap | Chromosomal gaps | Chramatid break | Deletion | Fragment | Endo-metosis | Centromeric attenuation | T.S. A | <40 | >40 | Poly- ploidy | T.N. A |
| Control | 3.3±0.6$^{a}$ | 2.0±.0$^{a}$ | 1.3±1.2$^{a}$ | 2.0±1.0$^{a}$ | 2.0±0.0$^{a}$ | 4.3±0.6$^{a}$ | 4.0±1.0$^{a}$ | 19.0±2.6$^{a}$ | 3.3±0.6$^{a}$ | 0.0±0.0$^{a}$ | 0.0±0.0$^{a}$ | 5.3±0.6$^{a}$ |
| Low 0.01 | 6.0±1.0$^{b}$ | 3.3±0.6$^{b}$ | 43±0.6$^{b}$ | 4.7±0.6$^{b}$ | 5.7±0.6$^{b}$ | 6.7±0.6$^{b}$ | 6.0±1.0$^{b}$ | 36.7±3.2$^{b}$ | 6.0±1.0$^{b}$ | 2.3±0.6$^{b}$ | 2.3±0.6$^{b}$ | 12.3±1.5$^{b}$ |
| Medium 0.02 | 9.0±1.0$^{c}$ | 5.0±0.05$^{c}$ | 6.0±0.0$^{c}$ | 6.0±1.0$^{c}$ | 6.7±0.6$^{c}$ | 9.0±0.0$^{c}$ | 8.3±0.6$^{c}$ | 50.0±0.0$^{c}$ | 8.3±0.6$^{c}$ | 5.0±1.0$^{c}$ | 5.0±1.0$^{c}$ | 19.7±1.5$^{c}$ |
| High 0.03 | 13±1.0$^{d}$ | 6.3±0.6$^{d}$ | 7.7±0.6$^{d}$ | 8.0±1.0$^{d}$ | 9.0±0.0$^{d}$ | 11±1.0$^{d}$ | 9.7±0.6$^{d}$ | 64.7±1.5$^{d}$ | 10.3±0.0$^{d}$ | 7.0±1.0$^{d}$ | 7.0±1.0$^{d}$ | 25±1$^{d}$ |

* Means of different letters (A,b,c,d) in the same column are significantly different.

* The column with the same letters is not significant

* 50 metaphase were examined from each animals.

Table 3: The effect of oral administration of valdoxan on embryos at day 18 of gestation

| | Structural aberrations | | | | | | | Numerical aberrations | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatments | Chromatid gap | Chromosomal gaps | Chramatid break | Deletion | Fragment | Endo-metosis | Centromeric attenuation | T.S. A | <40 | >40 | Poly- ploidy | T.N. A |
| Control | 1.7±0.6$^{a}$ | 1.3±1.2$^{a}$ | 0.7±0.6$^{a}$ | 1.0±0.0$^{a}$ | 1.3±0.6$^{a}$ | 2.3±0.6$^{a}$ | 2.7±0.6$^{a}$ | 11±2.6$^{a}$ | 1.7±0.6$^{a}$ | 1.3±0.6$^{a}$ | 0.0±0.0$^{a}$ | 3.0±0.0$^{a}$ |
| Low 0.01 | 3.7±0.6$^{b}$ | 3.0±0.0$^{b}$ | 3.0±0.0$^{b}$ | 3.3±0.6$^{b}$ | 3.7±0.6$^{b}$ | 5.0±0.0$^{b}$ | 4.7±0.6$^{b}$ | 26.3±0.6$^{b}$ | 4.0±1.0$^{b}$ | 2.7±0.6$^{b}$ | 1.0±1.0$^{b}$ | 7.7±2.7$^{b}$ |
| Medium 0.02 | 6.3±0.6$^{c}$ | 3.0±1.0$^{c}$ | 4.0±1.0$^{c}$ | 5.0±1.0$^{c}$ | 5.3±0.6$^{c}$ | 6.0±1.0$^{c}$ | 6.3±0.6$^{c}$ | 36.0±2.6$^{c}$ | 6.3±0.0$^{c}$ | 5.0±0.0$^{c}$ | 3.3±0.6$^{c}$ | 14.7±0.6$^{c}$ |
| High 0.03 | 9.0±1.0$^{d}$ | 4.7±0.6$^{d}$ | 5.7±0.6$^{d}$ | 7.0±0.0$^{d}$ | 6.3±0.6$^{d}$ | 8.0±1.0$^{d}$ | 8.0±0.0$^{d}$ | 48.7±1.5$^{d}$ | 8.0±0.0$^{d}$ | 6.3±0.6$^{d}$ | 4.7±0.6$^{d}$ | 19.0±1.0$^{d}$ |

* Means of different letters (A,b,c,d) in the same column are significantly different.

* The column with the same letters is not significant

* 50 metaphase were examined from each animals.

treated with different doses of valdoxan showed that the mothers had increases in the frequencies of the total aberrations (structural and numerical) than embryo groups and these increases were dose-dependent. The frequencies of the total number of (structural and numerical) in mother groups were (36.7, 12.3, 50, 19.7 and 64.7, 25) compared with that of embryo groups (20.3, 7.7, 36, 14.7 and 48.7, 19) and also it can be seen that all types of chromosomal aberrations were more frequent in mothers than in embryos in all treated groups.

## DISCUSSION

Depression is a serious and pervasive mood disorder. It causes feelings of sadness, hopelessness, helplessness and worthlessness. Depression can be mild to moderate with symptoms of apathy, little appetite, difficulty sleeping, low self-esteem and low-grade fatigue. In the world, about 15 million people experience depression each year. The majority of them are women. In fact, women are twice as likely to develop clinical depression as men up to one in four women is likely to have an episode of major depression at some point in life. Some experts believe that the increased chance of depression in women may be related to changes in hormone levels that occur throughout a woman's life. These changes are evident during puberty pregnancy and menopause, as well as often giving birth or experiencing a miscarriage. According to the National Institutes of the Health, factors that increase the risk of depression in women include reproductive, genetic, or other biological factors, interpersonal factors and certain psychological and personality characteristics [12].

Pregnancy has long been viewed as a period of well-being that protected women against psychiatric disorders. But depression in women occurs almost as commonly in pregnant women as it does in those who are not pregnant. In fact, untreated depression during pregnancy can put both mother and infant at risk [13].

There are a variety of methods used to treat depression, including medications such as antidepressants, brain stimulation techniques and psychotherapy. Valdoxan (Aagomelatine) is a new antidepressant drug. It is classified as a norepinephrine disinhibitor (NDD). Agomelatine acts on brain receptors for melatonin, a hormone that is important for regulating sleep, as well as serotonin receptors. Its antidepressant efficacy has been demonstrated in the treatment of major depressive disorder [14]. Due to the risk associated with untreated depressive women (Valdoxan) therapy is generally continued during pregnancy. For (Valdoxan) no clinical data are available that illustrates the safety use for pregnant females and their embryos.

Our results showed that there was a marked increase in the embryonic toxicity (in the number of resorption and dead embryos) and decrease in the number of live embryos and fetal body weight when compared with the control group and this effect was dose dependent.

This result was agreement with Papp *et al*. [15] who reported that when valdoxan (agomelatine) administrated orally to the pregnant rats during pregnancy, it passes into the placenta and fetuses of pregnant rats and there were a maternal and fetal body weight reduction after a repeated dose of valdoxan. Also positive results were observed by Steven *et al*. [16] who found that maternal toxicity was seen at high doses in rats.

However, negative results were observed by Kennedy *et al*. [17] who reported that reproduction studies in the rat and the rabbit showed no effect of valdoxan (agomelatine) on fertility embryo foetal development and pre-and postnatal development.

Also, in the present study we found that there were a significant increases in the chromosomal aberrations in maternal bone marrow cells and in the embryonic cells in all three doses groups (0.01, 0.02 and 0.03mg/kg/day) of valdoxan which corresponding to the (1 x, 2 x and 3x) the therapeutic dose for human respectively and these increases were dose dependent.

This result was agreement with Huiling [18] who found that in carcinogenicity studies agomelatine induced an increase in the incidence of liver tumors in the rat and the mouse, at a dose at least 11 0-fold higher than the therapeutic dose. Liver tumors are most likely related to enzyme induction specific to rodents and also positive results were observed by Emilio *et al*. [19] at high doses of agomelatine a chromosomal aberration was found in human lymphocytes. However, negative results were obtained by Karakus *et al*. [20] who observed that no hepatotoxicity was observed in rodents and monkeys in the repeat dose toxicity studies.

Also, negative results were obtained by Elyacoubi *et al*. [21] who found that *in vitro* and *in vivo* standard genotoxicity assays had no mutagenic or clastogenic potential of agomelatine.

Also, the present study showed that the maternal bone marrow cells treated with valdoxan had more increases in the chromosomal aberrations than embryonic cells and this result is in agreement with that of Russell [22] who reported that levels of chemicals and drugs in the blood steam in the systemic circulation can be used to approximate somatic cell exposure, but are not necessarily accurate for germ cells exposure since the gonads are protected from the general circulation by what are referred to as blood/gonadal barriers. As a result of this, the gonadal barriers probably reduced the risk of exposure of the germ cells if compared to the somatic cells.

## CONCLUSION

In conclusion, valdoxan (agomelatin) had a mutagenic effect on the chromosomes of both mothers and embryos and also had embryo toxic effect on the total number of dead, resorped and live embryos when administrated orally in a therapeutic dose, 2 x and 3x the therapeutic dose (0.01, 0.02 and 0.03 mg/kg/day) from day 3 to17during pregnancy and these mutagenic and toxic effects were dose dependent. This may be as a result that valdoxan (agomelatine) acts on melatonin receptors and melatonin hormone may cause DNA damage if given orally at a higher doses.

Also, from the above results we found that valdoxan (agomelatine) affected maternal cells more than fetal cells. This may be as a result of the direct injection of valdoxan to the pregnant female during pregnancy which reached directly to the mothers bone marrow cells and indirectly through the placenta to the fetal cells. Therefore, valdoxan is considered not to be safe to the mothers and embryos and it should be used during pregnancy only under medical control and after careful consideration of the risk/benefit.

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