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Side effects of anastrozole in the experimental pre-menopausal mammary carcinogenesis

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The aim of this study was to assess side effects of aromatase inhibitor anastrozole in the prevention of N-methyl-N-nitrosourea – induced pre-menopausal mammary carcinogenesis in female Sprague-Dawley rats. This model mimicked situation in healthy, but from the point of view of the development of breast cancer, high-risk pre-menopausal women.

Aromatase inhibitor anastrozole was used as a chemopreventive agent taken by the animals in the food during the whole period of time of the experiment. Group 1 – the control group had taken food without anastrozole, the groups 2 and 3 with anastrozole in various concentrations – 0.05 mg/1 kg of food (ANA 0.05) and 0.5 mg/1 kg of food (ANA 0.5).

In anastrozole-treated animals in comparison with untreated animals, macroscopic changes of uterus and vagina were not found. The values of absolute and relative wet weight of uterus and vagina in the groups ANA 0.05 and ANA 0.5 were comparable with the control. Histological examination did not show atrophic changes in endometrium of uterus and in epithelium of vagina in anastrozole-treated animals. In the group ANA 0.5 myometrium was significantly grosser than in the group ANA 0.05 ($P<0.05$). Anastrozole neither affects parameters of plasma lipid metabolism (triacylglycerols, total cholesterol, low – density lipoprotein cholesterol and high – density lipoprotein cholesterol) nor serum levels of sex hormones (estradiol, testosterone, dehydroepiandrosterone). Compact bone thickness in the groups with anastrozole was significantly increased in comparison with untreated animals ($P<0.001$). A significant increase in body weight was found in the group ANA 0.5 compared with the control group ($P<0.01$). The significant increase in body weight gain was not attended by the significant increase in food intake.

The side effects of aromatase inhibitor anastrozole in the prevention of N-methyl-N-nitrosourea – induced pre-menopausal mammary carcinogenesis in female Sprague-Dawley rats on myometrium, compact bone thickness and body weight gain were observed.

Key words: pre-menopausal mammary carcinogenesis, chemoprevention, aromatase inhibitors, anastrozole, side effects, female rats

Hormonal therapy is used to treatment a hormone-receptor-positive breast cancer. Some of the hormonal therapies lower the amount of estrogen in the body, some block estrogen's ability to lock onto the estrogen receptor and some remove or shut down the major source of estrogen production.

The aromatase inhibitors deplete estrogen by inhibiting aromatase, the enzyme that synthesises estrogen from androgens. In estrogen-dependent breast tumours, estrogens induce the expression of growth factors responsible for cancer cell proliferation. *In situ* estrogen synthesis by aromatase is thought to play a key role in the promotion of breast cancer growth. Aromatase inhibitors provide new approaches for the prevention and treatment of breast cancer by inhibiting estrogen biosynthesis [1]. Clinical trials have shown the important benefits of aromatase inhibitors and more effectiveness than tamoxifen in post-menopausal women with hormone-receptor-positive breast cancer in the first-line therapy for advanced breast cancer [2, 3], in adjuvant therapy [4, 5, 6, 7, 8] and in neoadjuvant therapy [9, 10]. Today new

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aromatase inhibitors – non-steroidal letrozole, anastrozole and steroidal exemestane are considered to be the new standard of care for post-menopausal women with invasive hormone-receptor-positive breast cancer, both early and advanced-stage. Letrozole is approved as the drug for the first-line therapy of post-menopausal women with advanced receptor-positive breast cancer, also in adjuvant and neoadjuvant therapy of post-menopausal women with a receptor-positive early-stage breast cancer. Anastrozole is approved as the drug for the first-line therapy of post-menopausal women with advanced receptor-positive breast cancer, also in adjuvant therapy of post-menopausal women with a receptor-positive early-stage breast cancer. Exemestane is approved for the treatment of metastatic breast cancer in post-menopausal women with hormone-receptor-positive tumor.

In the pre-menopausal population with hormone receptor positive disease, research on the use of aromatase inhibitors is only beginning to emerge. Available research to date regarding efficacy and toxicity of aromatase inhibitors in the treatment of pre-menopausal breast cancer and future research directions are also discussed [11, 12].

In this study the side effects of non-steroidal aromatase inhibitor third generation anastrozole in the experimental pre-menopausal mammary carcinogenesis were evaluated.

Materials and methods

In our experiment, 60 intact female Sprague-Dawley rats (AnLab, Prague, Czech Rep.) 31 – 35 days old, weighing 130 – 170 grams were used. The animals were adapted to the standard conditions of vivarium (temperature 23 +/- 2 şC, relative humidity 50 – 60 %, artificial light regimen, light: dark/12: 12). The animals were taken standard food for rats (Kocanda Mlyn, Prague, Czech Rep.) and water *ad libitum*. All procedures were carried out according to EU directives and reviewed by Ethical Committee of the Comenius University.

The animals were divided into 3 groups (20 animals in 1 group). Aromatase inhibitor anastrozole was used as a chemopreventive agent. Chemoprevention with anastrozole began 7 days before carcinogen administration and lasted till the end of the experiment, i.e. 14 weeks after the application of carcinogen. Group 1 – the control group, animals were given food without anastrozole, the groups 2 and 3 with anastrozole in various concentrations – 0.05 mg/1 kg of food (ANA 0.05) and 0.5 mg/1 kg of food (ANA 0.5).

The N-methyl-N-nitrosourea (NMU) as carcinogen (Sigma, Deisenhofen, Germany) was used to induce mammary carcinogenesis. NMU was dissolved in saline (0.5 ml/1 animal) and then injected intraperitoneally on the 42nd day in the dose of 50 mg/kg of the animal‘s body weight. This model mimicked situation in healthy, but from the point of view of the development of breast cancer, high-risk pre-menopausal women.

Once a week the rats were weighed and palpated. The body weight of animals was evaluated and the local mammary tumors were assessed in terms of their presence, number, place and size. In the 7th and 11th weeks of the experiment water and food intake were measured. At the end of the experiment, i.e. 14 weeks after the application of NMU, the animals were killed by quick decapitation. Their blood was taken to examine biochemical parameters of plasma lipid metabolism – total cholesterol, high – density lipoprotein cholesterol (HDL – cholesterol), low – density lipoprotein cholesterol (LDL – cholesterol) and triacylglycerols (TAG) (Institute of the laboratory diagnostics Alpha Medical a.s. Ružomberok) and serum levels of sex hormones – estradiol, testosterone, dehydroepiandrosterone (Department of Physiology, Faculty of Medicine, Comenius University, Bratislava). Parameters of plasma lipid metabolism were measured by automatic biochemical analyser AU 640 (Olympus) and serum levels of sex hormones using ELISA kits with intra- and interassay coefficients of variations < 5 %.

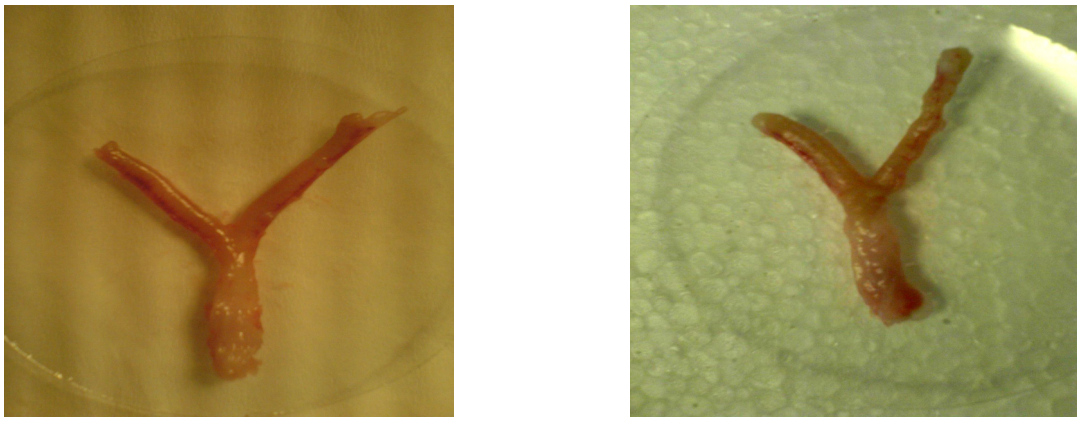
During autopsy, mammary tumors, uterus, vagina and femurs were excised. The samples (uterus, vagina) were weighed and together with the other samples sent for histological analysis. Samples of mammary tumors, uteri and vaginas were fixed in 10% buffered formalin; 3-mm long specimens of femori taken from the middle of diaphysis were decalcificated. Then all samples were embedded in paraffin using conventional automated systems. The blocks were cut to obtain 4 to 5 μm thick sections and were stained with hematoxylin-eosin. Histopathologic examination was performed by light microscopy (Department of Pathological Anatomy, Jessenius Faculty of Medicine, Comenius University in Martin).

The tumor incidence was assessed by Mann-Whitney U-test, the other parameters by one-way variance analysis (ANOVA) or Kruskal-Wallis test.

Results

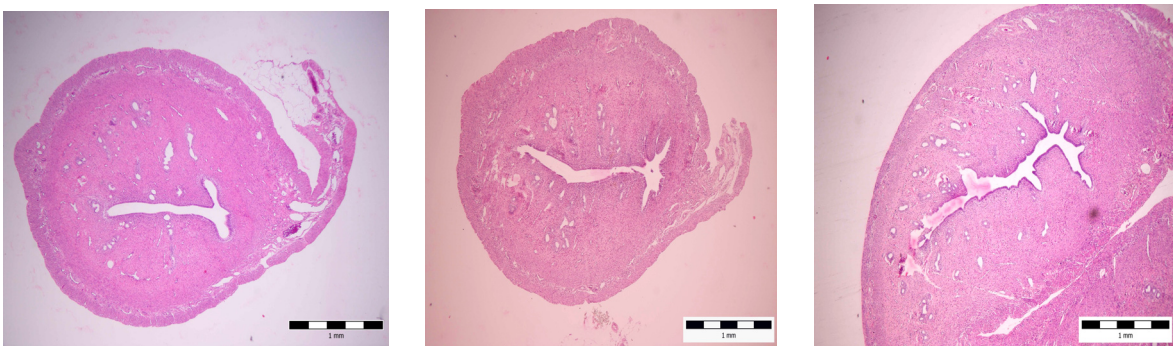
In our experiment a preventive tumor suppressive effect of anastrozole in the model of pre-menopausal mammary carcinogenesis in female Sprague-Dawley rats was observed. In the group ANA 0.5 anastrozole significantly suppressed tumor incidence ($P<0.05$) and tumour frequency per group ($P<0.01$) in comparison with control group. Altogether 119 mammary tumor samples were histological analysed. All tumors were malignant adenocarcinomas. The tumours were classified according to the criteria for classification of rat mammary tumors [13].

The side effects of anastrozole were evaluated in this experiment. In anastrozole – treated animals in comparison with untreated animals, macroscopic changes of uterus and vagina were not found (Figure 1). The values of absolute and relative wet weight of uterus and vagina in the groups ANA 0.05 and ANA 0.5 were comparable with the control. Histological examination did not show atrophic changes in endometrium of uterus and in epithelium of vagina in anastrozole – treated animals. In the group ANA



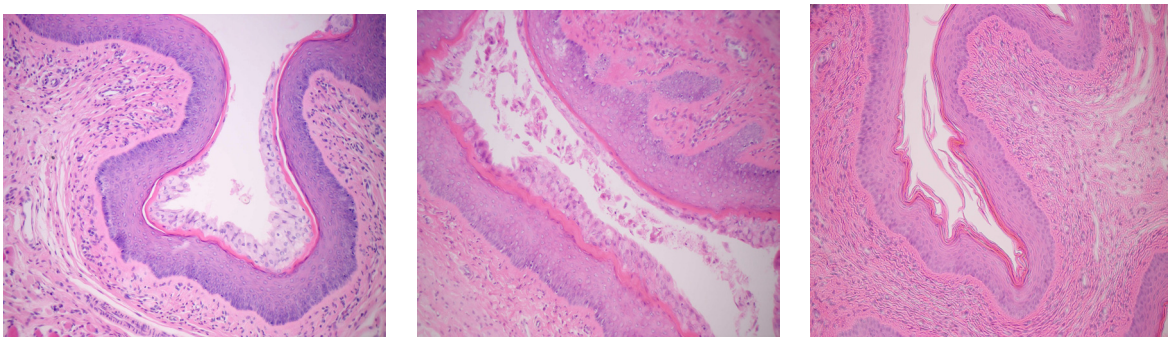
CONTROL ANA 0.5

Figure 1. Uterus and vagina macroscopically after 14 weeks of anastrozole administration. Macroscopic differences between CONTROL and ANA 0.5 were not found.
CONTROL – control group without anastrozole, ANA 0.5 – group with anastrozole in concentration 0.5 mg/1 kg of food.



CONTROL ANA 0.05 ANA 0.5

Figure 2. Uterus microscopically after 14 weeks of anastrozole administration. In the group ANA 0.5 myometrium was significantly grosser than in the group ANA 0.05.
CONTROL – control group without anastrozole, ANA 0.05 – group with anastrozole in concentration 0.05 mg/1 kg of food, ANA 0.5 – group with anastrozole in concentration 0.5 mg/1 kg of food.



CONTROL ANA 0.05 ANA 0.5

Figure 3. Vagina microscopically after 14 weeks of anastrozole administration. Microscopic differences between anastrozole – treated animals in comparison with untreated animals were not found.
CONTROL – control group without anastrozole, ANA 0.05 – group with anastrozole in concentration 0.05 mg/1 kg of food, ANA 0.5 – group with anastrozole in concentration 0.5 mg/1 kg of food.

Table 1. Effects of anastrozole on uterine and vaginal weights and on uterine endometrium and myometrium.

Group	Uterine wet weight		Uterine		Vaginal wet weight	
	absolute (g)	relative* (%)	**endometrium** (μm)	**myometrium** (μm)	absolute (g)	relative *(%)
CONT	0.617±0.031	0.225±0.010	747.75±37.77	378.90±18.86	0.206±0.009	0.075±0.004
ANA 0.05	0.675±0.058	0.234±0.020	753.05±49.69	357.15±22.31	0.223±0.007	0.078±0.003
ANA 0.5	0.574±0.029	0.202±0.011	678.50±42.50	432.05±21.54[a]	0.220±0.009	0.077±0.003

Data are expressed as means±SEM. *Relative organ weight (%) = [absolute organ weight (g) / body weight (g)] x 100. Significantly different, [a] P<0.05 vs ANA 0.05.

Table 2. Effects of anastrozole on plasma lipid metabolism.

Group	Triacylglycerols (mmol/l)	Total cholesterol (mmol/l)	LDL- cholesterol (mmol/l)	HDL- cholesterol (mmol/l)
CONT	1.26±0.13	2.30±0.12	0.18±0.02	0.68±0.03
ANA 0.05	1.32±0.10 (+ 5 %)	2.11±0.11 (- 8.5 %)	0.18±0.01 (0 %)	0.63±0.03 (- 7.5 %)
ANA 0.5	1.13±0.12 (- 10.5 %)	2.15±0.09 (- 6.5 %)	0.21±0.01 (+ 16.5 %)	0.61±0.03 (- 10.5 %)

Data are expressed as means±SEM. Values in brackets are calculated as %-ual deviation from the 100% of non-influenced control group.

0.5 myometrium was significantly grosser than in the group ANA 0.05 (P<0.05) (Table 1, Figure 2, 3). Anastrozole neither affect parameters of plasma lipid metabolism – triacylglycerols, total cholesterol, LDL – cholesterol and HDL – cholesterol (Table 2) nor serum levels of sex hormones – estradiol, testosterone, dehydroepiandrosterone (Table 3). Compact bone thickness in the groups with anastrozole was significantly increased in comparison with untreated animals (P<0.001). The significant increase in body weight gain was found in the group ANA 0.5 compared with the control group (P<0.01) (Table 4) but was not attended by the significant increase in food intake.

Table 3. Serum levels of estradiol, testosterone and dehydroepiandrosterone after anastrozole treatment in female rats.

Group	Estradiol (pg/ml)	Testosterone (ng/ml)	Dehydroepiandrosterone (ng/ml)
CONT	22.296±0.609	0.267±0.026	0.390±0.074
ANA 0.05	25.468±2.235	0.307±0.041	0.549±0.067
ANA 0.5	24.626±2.180	0.253±0.032	0.351±0.074

Data are expressed as means±SEM.

Discussion

Our experimental model of pre-menopausal mammary carcinogenesis in female Sprague-Dawley rats showed preventive tumor suppressive effect of anastrozole (submitted for publication by Kubatka et al., 2008). Non-steroidal aromatase inhibitor anastrozole significantly suppressed tumor incidence and tumor frequency per group in the group with higher concentration of anastrozole. The daily average dose of anastrozole was 7.32 μg per rat in the group ANA 0.5. This dose of anastrozole used in our experiment was equivalent to daily clinical dose of anastrozole in Arimidex administered in post-menopausal women with breast cancer. Similar tumor suppressive effect in the model of pre-menopausal mammary carcinogenesis was observed with non-steroidal aromatase inhibitor letrozole in our previous study [14, 15, 16]. Despite of that, in the study with steroidal aromatase inhibitor exemestane the tumor suppressive effect of exemestane in the model of pre-menopausal mammary carcinogenesis was not proved (submitted for publication by Kubatka et al., 2008). Observed different effects on pre-menopausal mammary carcinogenesis of aromatase inhibitors could be of their non-steroidal of letrozole and anastrozole and steroidal of exemestane chemical structure dependent.

Table 4. Effects of anastrozole on compact bone thickness and body weight of animals.

Group	Compact bone thickness	Body weight		
	(mm)	initial (g)	final (g)	gain (g)
CONT	0.459±0.007	145.90±1.92	274.35±4.96	128.45±3.72
ANA 0.05	0.515±0.009 [a] (+ 12 %)	153.35±1.63 [b]	287.90±3.64 [c]	134.55±3.16
ANA 0.5	0.520±0.007 [a] (+ 13 %)	146.00±1.56	290.60±4.33 [c]	144.60±3.93 [b]

Data are expressed as means±SEM. Values in brackets are calculated as %-ual deviation from the 100% of non-influenced control group. Significantly different, [a]P < 0.001 vs CONT, [b]P < 0.01 vs CONT, [c]P < 0.05 vs CONT.

Except the effect of anastrozole on parameters of mammary carcinogenesis, the side effects of anastrozole were evaluated in our experiment. Aromatase inhibitors block the effects of aromatase enzyme; it catalyzes conversion of androgens, androstenedione and testosterone into estrogens, estrone and estradiol in peripheral tissues including the breast, muscle, liver, and fat tissue. The suppression of estrogen production lowers the risk of development and progression of hormone-dependent breast cancer but can give rise to side effects or adverse effects.

We followed the side effects of anastrozole on genital organs (uterus and vagina), biochemical parameters of plasma lipid metabolism (total cholesterol, HDL – cholesterol, LDL – cholesterol and TAG), serum levels of sex hormones (estradiol, testosterone and dehydroepiandrosterone), compact bone thickness and body weight of animals. Several side effects of anastrozole were observed in our experiment.

The significant increase in body weight gain was found in the group ANA 0.5 compared with the control group. Actions of estradiol on many aspects of physiological and behavioural regulation of energy balance are well – known [17, 18]. A hypothesis about the role of estradiol in mediating leptin‘s effects on body weight exists. This effect of anastrozole is also known in anastrozole treated post-menopausal women with hormone-receptor-positive breast cancer. In our previous experiment, a significant increase of food intake in letrozole – treated rats characterized by increase in body weight and body fat content was observed [14, 15, 16]. Similarly, exemestan caused an increase in food consumption and body weight gain of rats (submitted for publication by Kubatka et al., 2008).

Low plasma estrogen levels caused by treatment of aromatase inhibitors can lead to bone demineralization. Bones can become thinner and weaker and finally it can result to osteoporosis. Compact bone thickness in the groups with anastrozole was significantly increased in comparison with untreated animals in our experiment.

In addition to bone changes, other side effects are seen more often in post-menopausal women taking aromatase inhibitors. All three aromatase inhibitors have been shown to result in increase in complaints of sore muscles or joint pain and to increase blood cholesterol levels. High cholesterol levels are associated with an increased risk of cardiovascular problems. Anastrozole did not affect parameters of plasma lipid metabolism – triacylglycerols, total cholesterol, LDL – cholesterol and HDL – cholesterol in our experimental pre-menopausal mammary carcinogenesis. In our previous study with letrozole a significant increase in serum triacylglycerols and no significant changes in total cholesterol, in LDL – cholesterol and HDL – cholesterol were found [14, 15, 16]. In exemestane study, exemestane had beneficial effects on lipid metabolism in rats. The triacylglycerols, total cholesterol, LDL – cholesterol and HDL – cholesterol were decreased (submitted for publication by Kubatka et al., 2008).

In anastrozole – treated animals in comparison with untreated animals, macroscopic changes of uterus and vagina were not found. Moreover, histological examination did not show atrophic changes of the uterus and vagina in anastrozole – treated animals. In the group ANA 0.5 myometrium was significantly grosser than in the group ANA 0.05. There are evidences about the effects of anastrozole on endometrium and myometrium uteri but its effects are antiestrogenic. Some clinical works showed efficacy of anastrozole in the treatment of endometriosis [19, 20], endometrial hyperplasia [21], endometrial carcinoma [22], uterine leiomyoma [23] or uterine leiomyosarcoma [24]. In the experiments with exemestane, changes in weights and histology of uterus and vagina were not found (submitted for publication by Kubatka et al., 2008). Some other experimental studies in rats with letrozol found out antiestrogenic effects on rat genital system resulting in atrophic changes [14, 15, 16, 25, 26].

In the groups with anastrozole the serum levels of sex hormones – estradiol, testosterone and dehydroepiandrosterone were not lower in comparison with control animals. Anastrozole blocked *in situ* estrogen synthesis without its influence on serum levels of sex hormones. Similar effect on sex hormones was found in the study with exemestane (submitted for publication by Kubatka et al., 2008). The key role of *in situ* estrogen synthesis via aromatase in the mammary gland tissue in the development and progression of breast cancer was also proved in other experimental works [27, 28, 29]. On the other side the results of our experiments with anastrozole in the pre-menopausal mammary carcinogenesis model could cause low dose of anastrozole administered in the food.

Generally, the aromatase inhibitors have relatively few serious or unmanageable side effects. The number of people, who have side effects due to the aromatase inhibitors, and particularly anastrozole, is low. It is necessary to assess the benefit/risk ratio of aromatase inhibitors application in women with hormone receptor positive breast cancer. The use of aromatase inhibitors in pre-menopausal breast cancer patients is area of next exploration.

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